DISEASES OF THE BREAST

FIFTH EDITION

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To the many talented and dedicated laboratory and translational investigators and clinical researchers who have been committed to the breast cancer problem and have contributed to the substantial progress made in recent decades in fighting this disease.

In memory of Jonathan Pine, our highly esteemed editor, who left all of us much too soon.

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PREFACE TO THE FIFTH EDITION

The previous four editions of *Diseases of the Breast* were intended as up-to-date, single-source multidisciplinary compilations of important knowledge on breast diseases, with a focus on breast cancer, presented in a form accessible to practicing clinicians. We have been gratified by the success of this effort and, for the fifth edition, we have similarly invited a diverse and distinguished group of experts to summarize the current knowledge about breast diseases, including its biology and epidemiology, clinical features, and management. The underlying premise for this book has been that multidisciplinary care of the breast cancer patient is critical to obtaining best outcomes and that effective communication between pathologists, breast imagers, medical geneticists, experts in nursing, psychosocial support, and rehabilitation as well as surgical, medical and radiation oncologists is essential.

This fifth edition comes at a time when considerable progress has been made in the treatment of breast cancer. In the United States and in Western Europe, there has been a substantial decrease in the death rate from the disease, attributable to early detection with screening mammography and increasingly effective systemic treatment. Also, it is now established that effective local treatment is essential to decreasing breast cancer mortality. A key contributor to this decrease in breast cancer mortality has been the willingness of many thousands of women with breast cancer who have participated in clinical trials. Of importance as well to this progress are the many talented and dedicated laboratory and translational investigators and clinical researchers who have been committed to the breast cancer problem. This edition is dedicated to them.

Efforts have also been made to understand and improve the quality of life of breast cancer patients. The widespread use of sentinel node biopsy as an alternative to axillary lymph node dissection is a prominent example. Systemic therapy is increasingly targeted and less toxic and advances in the molecular characterization of breast cancers have begun to explain the heterogeneity of the disease and allow for individualization of treatments. Radiation treatment has advanced by better incorporation of imaging modalities and more sophisticated irradiation techniques also allowing for more targeted, less toxic, and, in many cases, abbreviated courses of treatments. While there has been progress in the treatment of breast cancer, we are very aware that there are still many patients who die of the disease and that much more progress is needed.

We hope that the fifth edition of *Diseases of the Breast* will be a useful resource for both clinicians and translational investigators and will foster the understanding and communication necessary to provide optimal patient care and to help foster advances in managing diseases of the breast, especially breast cancer.

Jay R. Harris, MD
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PREFACE TO THE FIRST EDITION

Interest in, and knowledge about, breast diseases, especially breast cancer, have increased greatly in recent years. A number of factors have contributed to this, the foremost of which are the high occurrence of breast cancer in westernized countries and the dramatic upswing in this incidence during the past few decades. Clinical investigators have also helped define various benign diseases of the breast and have described their management and relation to subsequent breast cancer development. Moreover, clinical trials performed throughout the world have contributed considerable information about the early detection and management of breast cancer using surgery, radiation therapy, and systemic therapies, including chemotherapy and hormonal interventions. Finally, rapid advances in the understanding of the molecular biology and genetics of both normal tissues and cancers have raised optimism that new, more specific methods can be developed to identify a woman's risk for breast cancer, to prevent, or at least detect, the disease at an earlier stage, and, failing this, to cure it with minimal toxicity. Ultimately a source of hope, these factors have nevertheless caused considerable anxiety in the population, as well as provided a proliferation of information important for clinicians dealing with diseases that strike the breast.

Diseases of the Breast is intended as a single-source compilation of the new knowledge on breast diseases presented in a form accessible to practicing clinicians. Although it is widely recognized that multidisciplinary interaction and information sharing are essential to effective clinical management of diseases of the breast, new developments are rapidly demonstrating that clinicians also need to be knowledgeable about advances in basic science. A prominent example of how advances in basic science can rapidly enter the clinical arena is the discovery of the first genetic mutations at specific loci shown to be associated with a high risk of breast cancer. Clinicians are now faced with patient questions about the nature and meaning of such testing as well as its risks and benefits. We believe that other advances in basic science will quickly be reflected in clinical practice.

For *Diseases of the Breast,* we invited a large, diverse, and distinguished group of experts to summarize the current knowledge about breast diseases, including clinical features, management, and underlying biologic and epidemiologic factors. In assembling these contributions, we have tried to make the book comprehensive and timely, as well as accessible to practicing clinicians. We believe that this book will also be an aid to basic and translational scientists concerned about a breast cancer problem by providing clinical information that can help focus their energies and talents. We hope that *Diseases of the Breast* will be a useful resource for both clinicians and scientists and will foster the understanding and communication necessary to provide optimal patient care and to rapidly achieve advances in managing diseases of the breast, especially breast cancer.

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SECTION I

Breast Anatomy and Development

CHAPTER 1

Breast Anatomy and Development

Michael P. Osborne and Susan K. Boolbol

CHAPTER CONTENTS

Mammary glands are a distinguishing feature of mammals. Nursing of the young in the animal kingdom has many physiologic advantages for the mother, such as aiding postpartum uterine involution, and for the neonate, in terms of the transfer of immunity and bonding. It has become increasingly apparent that the advantages of nursing are substantial for both mother and child.

An understanding of the morphology and physiology of the breast, and the many endocrine interrelationships of both, is essential to the study of the pathophysiology of the breast and the management of benign, preneoplastic, and neoplastic disorders.

EMBRYOLOGY

During the fifth week of human fetal development, the ectodermal primitive milk streak, or "galactic band," develops from axilla to groin on the embryonic trunk (1). The ectoderm over the thorax invaginates into the surrounding mesenchyme, with subsequent epithelial budding and branching (2). In the region of the thorax, the band develops to form a mammary ridge, whereas the remaining galactic band regresses. Incomplete regression or dispersion of the primitive galactic band leads to accessory mammary tissues, found in 2% to 6% of women in the form of accessory nipples or axillary breast tissue.

At 7 to 8 weeks' gestation, a thickening occurs in the mammary anlage (milk hill stage), followed by invagination into the chest wall mesenchyme (disc stage) and tridimensional growth (globular stage). Further invasion of the chest wall mesenchyme results in a flattening of the ridge (cone stage) at 10 to 14 weeks' gestation. Between 12 and 16 weeks' gestation, mesenchymal cells differentiate into the smooth muscle of the nipple and areola. Epithelial buds develop (budding stage) and then branch to form 15 to 25 strips of epithelium (branching stage) at 16 weeks' gestation; these strips represent the future secretory alveoli (3). The secondary mammary anlage then develops, with differentiation of the hair follicle, sebaceous gland, and sweat gland elements, but only the sweat glands develop fully at this time. Phylogenetically, the breast parenchyma is believed to develop from sweat gland tissue. In addition, apocrine glands develop to form the Montgomery glands around the nipple. The developments described thus far are independent of hormonal influences.

During the third trimester of pregnancy, placental sex hormones enter the fetal circulation and induce canalization of the branched epithelial tissues (canalization stage) (4). This process continues from the 20th to the 32nd week of gestation. At term, 15 to 25 mammary ducts have been formed, with coalescence of approximately 10 major ducts and sebaceous glands near the epidermis (5). Parenchymal differentiation occurs at 32 to 40 weeks with the development of lobuloalveolar structures that contain colostrum (end-vesicle stage). A fourfold increase in mammary gland mass occurs at this time, and the nipple–areolar complex develops and becomes pigmented. Externally the nipple is small and flattened, although rudimentary sebaceous glands and Montgomery tubercles are present. The circular smooth muscle fibers that lead to the erectile function of the nipple are developed by this stage.

In the neonate, the stimulated mammary tissue secretes colostral milk (sometimes called *witch's milk*), which can be expressed from the nipple for 4 to 7 days postpartum in most neonates of either sex. At birth, the withdrawal of maternal steroids results in the secretion of neonatal prolactin. It is this hormone that stimulates newborn breast secretion. In the newborn, colostral secretion declines over a 3- to 4-week period owing to involution of the breast after

withdrawal of placental hormones. During early childhood, the end vesicles become further canalized and develop into ductal structures by additional growth and branching.

After birth, the male breast undergoes minimal additional development and remains rudimentary. In the female, the breasts undergo extensive further development, which is regulated by hormones that influence reproduction. The breast has reached its major development by 20 years of age and will usually begin to undergo atrophic changes in the fifth decade of life.

DEVELOPMENTAL ABNORMALITIES

The developmental abnormalities may be unilateral or bilateral and involve both the nipple and the breast or both. These abnormalities are usually isolated to the breast, but there are reports of being associated with a variety of other abnormalities. The most common association is with upper limb and urinary tract abnormalities.

Congenital Abnormalities

Polythelia and Polymastia

The most frequently observed abnormality seen in both sexes is an accessory nipple (polythelia). Ectopic nipple tissue may be mistaken for a pigmented nevus, and it may occur at any point along the milk streak from the axilla to the groin. The reported incidence of polythelia varies greatly in the literature. In a prospective study, Mimoumi et al. (6) found the incidence of polythelia to be 2.5%. Urbani and Betti (7) evaluated the association between polythelia and kidney and urinary tract malformations. These data indicate a significantly higher frequency of kidney and urinary tract malformations in patients with polythelia. This is a controversial issue, and many studies in the literature do not find any connection between polythelia and renal anomalies (8,9).

Rarely, accessory true mammary glands develop; these are most often located in the axilla (polymastia). During pregnancy and lactation, an accessory breast may enlarge; occasionally, if it has an associated nipple, the accessory breast may function.

Hypoplasia and Amastia

Hypoplasia is the underdevelopment of the breast; congenital absence of a breast is termed *amastia*. When breast tissue is lacking but a nipple is present, the condition is termed *amazia*. A wide range of breast abnormalities have been described and can be classified as follows (10,11):

Unilateral hypoplasia, contralateral normal
Bilateral hypoplasia with asymmetry
Unilateral hyperplasia, contralateral normal
Bilateral hyperplasia with asymmetry
Unilateral hypoplasia, contralateral hyperplasia
Unilateral hypoplasia of breast, thorax, and pectoral muscles (Poland's syndrome)

Most of these abnormalities are not severe. The most severe deformity, amastia or marked breast hypoplasia, is associated with hypoplasia of the pectoral muscle in 90% of cases (12), but the reverse does not apply. Of women with pectoral muscle abnormalities, 92% have a normal breast (13). Congenital abnormalities of the pectoral muscle are usually manifested by the lack of the lower third of the muscle and an associated deformity of the ipsilateral rib cage. The association among absence of the pectoral muscle, chest wall deformity, and breast abnormalities was first recognized by Poland in 1841. The original description, however, did not note the concomitant abnormalities of the hand (symbrachydactyly, with hypoplasia of the middle phalanges and central skin webbing) (14), and considerable controversy has evolved concerning the validity of the eponym for this congenital syndrome (15,16).

Athelia

The congenital absence of the nipple areolar complex is a rare entity and is usually associated with absence of the breast. This condition is typically associated with other anomalies.

Acquired Abnormalities

The most common—and avoidable—cause of amastia is iatrogenic. Injudicious biopsy of a precociously developing breast results in excision of most of the breast bud and subsequent marked deformity during puberty. The use of radiation therapy in prepubertal girls to treat either hemangioma of the breast or intrathoracic disease can also result in amastia. Traumatic injury of the developing breast, such as that caused by a severe cutaneous burn, with subsequent contracture, can also result in deformity.

NORMAL BREAST DEVELOPMENT DURING PUBERTY

Puberty in girls begins at the age of 10 to 12 years as a result of the influence of hypothalamic gonadotropin-releasing hormones secreted into the hypothalamic–pituitary portal venous system. The basophilic cells of the anterior pituitary release follicle-stimulating hormone and luteinizing hormone. Follicle-stimulating hormone causes the primordial ovarian follicles to mature into Graafian follicles, which secrete estrogens, primarily in the form of 17-estradiol. These hormones induce the growth and maturation of the breasts and genital organs (17). During the first 1 to 2 years after menarche, hypothalamic–adenohypophyseal function is unbalanced because the maturation of the primordial ovarian follicles does not result in ovulation or a luteal phase. Therefore, ovarian estrogen synthesis predominates over luteal progesterone synthesis. The physiologic effect of estrogens on the maturing breast is to stimulate longitudinal growth of ductal epithelium. Terminal ductules also form buds that precede formation of breast lobules. Simultaneously, periductal connective tissues increase in volume and elasticity, with enhanced vascularity and fat deposition. These initial changes are induced by estrogens synthesized in immature ovarian follicles, which are anovulatory; subsequently, mature follicles ovulate, and the corpus luteum releases progesterone. The relative role of these hormones is not clear. In experimental studies, estrogens alone induce a pronounced ductular increase, whereas progesterone alone does not. The two hormones together produce full ductular–lobular–alveolar development of mammary tissues (17). The marked individual variation in development of the breast makes it impossible to categorize histologic changes on the basis of age (4). Breast development by age has been described by external morphologic changes. The evolution of the breast from childhood to maturity has been divided into five phases by Tanner (18), as shown in Table 1-1.

MORPHOLOGY

Adult Breast

The adult breast lies between the second and sixth ribs in the vertical axis and between the sternal edge and the midaxillary line in the horizontal axis (Fig. 1-1). The average breast

TABLE 1-1

Phases of Breast Development

Phase I	
Age: puberty	Preadolescent elevation of the nipple with no palpable glandular tissue or areolar pigmentation.
Phase II	
Age: 11.1 ± 1.1 yr	Presence of glandular tissue in the subareolar region. The nipple and breast project as a single mound from the chest wall.
Phase III	
Age: 12.2 ± 1.09 yr	Increase in the amount of readily palpable glandular tissue with enlargement of the breast and increased diameter and pigmentation of the areola. The contour of the breast and nipple remains in a single plane.
Phase IV	
Age: 13.1 ± 1.15 yr	Enlargement of the areola and increased areolar pigmentation. The nipple and areola form a secondary mound above the level of the breast.
Phase V	
Age: 15.3 ± 1.7 yr	Final adolescent development of a smooth contour with no projection of the areola and nipple.

From Tanner JM. *Wachstun und Reifung des Menschen*. Stuttgart: Georg Thieme Verlag, 1962, with permission.

measures 10 to 12 cm in diameter, and its average thickness centrally is 5 to 7 cm. Breast tissue also projects into the axilla as the axillary tail of Spence. The contour of the breast varies but is usually dome-like, with a conical configuration in the nulliparous woman and a pendulous contour in the parous woman. The breast is comprised of three major structures: skin, subcutaneous tissue, and breast tissue, with the last comprising both parenchyma and stroma. The parenchyma is divided into 15 to 20 segments that converge at the nipple in a radial arrangement. The collecting ducts that drain each segment are 2 mm in diameter, with subareolar lactiferous sinuses of 5 to 8 mm in diameter. Approximately 10 major collecting milk ducts open at the nipple (5).

The nomenclature of the duct system is varied. The branching system can be named in a logical fashion, starting with the collecting ducts in the nipple and extending to the ducts that drain each alveolus, as shown in Table 1-2. Each duct drains a lobe made up of 20 to 40 lobules. Each lobule consists of 10 to 100 alveoli or tubulosaccular secretory units (5,19). The stroma and subcutaneous tissues of the breast contain fat, connective tissue, blood vessels, nerves, and lymphatics.

The skin of the breast is thin and contains hair follicles, sebaceous glands, and eccrine sweat glands. The nipple, which is located over the fourth intercostal space in the nonpendulous breast, contains abundant sensory nerve endings, including Ruffini-like bodies and end bulbs of Krause. Moreover, sebaceous and apocrine sweat glands are present, but not hair follicles. The areola is circular and pigmented, measuring 15 to 60 mm in diameter. The Morgagni tubercles, located near the periphery of the areola, are elevations formed by openings of the ducts of the Montgomery glands. The Montgomery glands are large sebaceous glands capable of secreting milk; they represent an intermediate stage between sweat and mammary glands. Fascial tissues envelop the breast; the superficial pectoral fascia envelops the breast and is continuous with the superficial abdominal fascia of Camper. The undersurface of the breast lies on the deep pectoral fascia, covering the pectoralis major and anterior serratus muscles. Connecting these two fascial layers are fibrous bands (Cooper suspensory ligaments) that represent the "natural" means of support of the breast.

Vascular Anatomy of the Breast

The principal blood supply to the breast is derived from the internal mammary and lateral thoracic arteries. Approximately 60% of the breast, mainly the medial and central parts, is supplied by the anterior perforating branches of the internal mammary artery. Approximately 30% of the breast, mainly the upper, outer quadrant, is supplied by the lateral thoracic artery. The pectoral branch of the thoracoacromial artery; the lateral branches of the third, fourth, and fifth intercostal arteries; and the subscapular and thoracodorsal arteries all make minor contributions to the blood supply.

The principal veins involved in the venous drainage of the thoracic wall and the breast are the perforating branches of the internal thoracic vein, tributaries of the axillary vein, and perforating branches of posterior intercostal veins.

Lymphatic Drainage of the Breast

Lymph Vessels

The lymphatic drainage of the breast is of great importance in the spread of malignant disease of the breast. The subepithelial or papillary plexus of the lymphatics of the breast is confluent with the subepithelial lymphatics over the surface of the body. These valveless lymphatic vessels communicate with subdermal lymphatic vessels and merge with the Sappey subareolar plexus. The subareolar plexus receives lymphatic vessels from the nipple and areola and communicates by way of vertical lymphatic vessels equivalent to those that connect the subepithelial and subdermal plexus elsewhere (20). Lymph flows unidirectionally from the superficial to deep plexus and from the subareolar plexus through the lymphatic vessels of the lactiferous ducts to the perilobular and deep subcutaneous plexus. The periductal lymphatic vessels lie just outside the myoepithelial layer of the duct wall (21). Flow from the deep subcutaneous and intramammary lymphatic vessels moves centrifugally toward the axillary and internal mammary lymph nodes. Injection studies with radiolabeled colloid (22) have demonstrated the physiology of lymph flow and have countered the old hypothesis of centripetal flow toward the Sappey subareolar plexus (23). Approximately 3% of the lymph from the breast is estimated to flow to the internal mammary chain, whereas 97% flows to the axillary nodes (24).

New insight into lymphatic anatomy and the physiology of lymph flow has been gained from sentinel lymph node studies. It has been observed that the dermal and parenchymal lymphatics drain to the same axillary lymph nodes that are the main basin for lymph draining from the breast (25–30). This might be expected considering the embryology of the breast described earlier in this chapter.

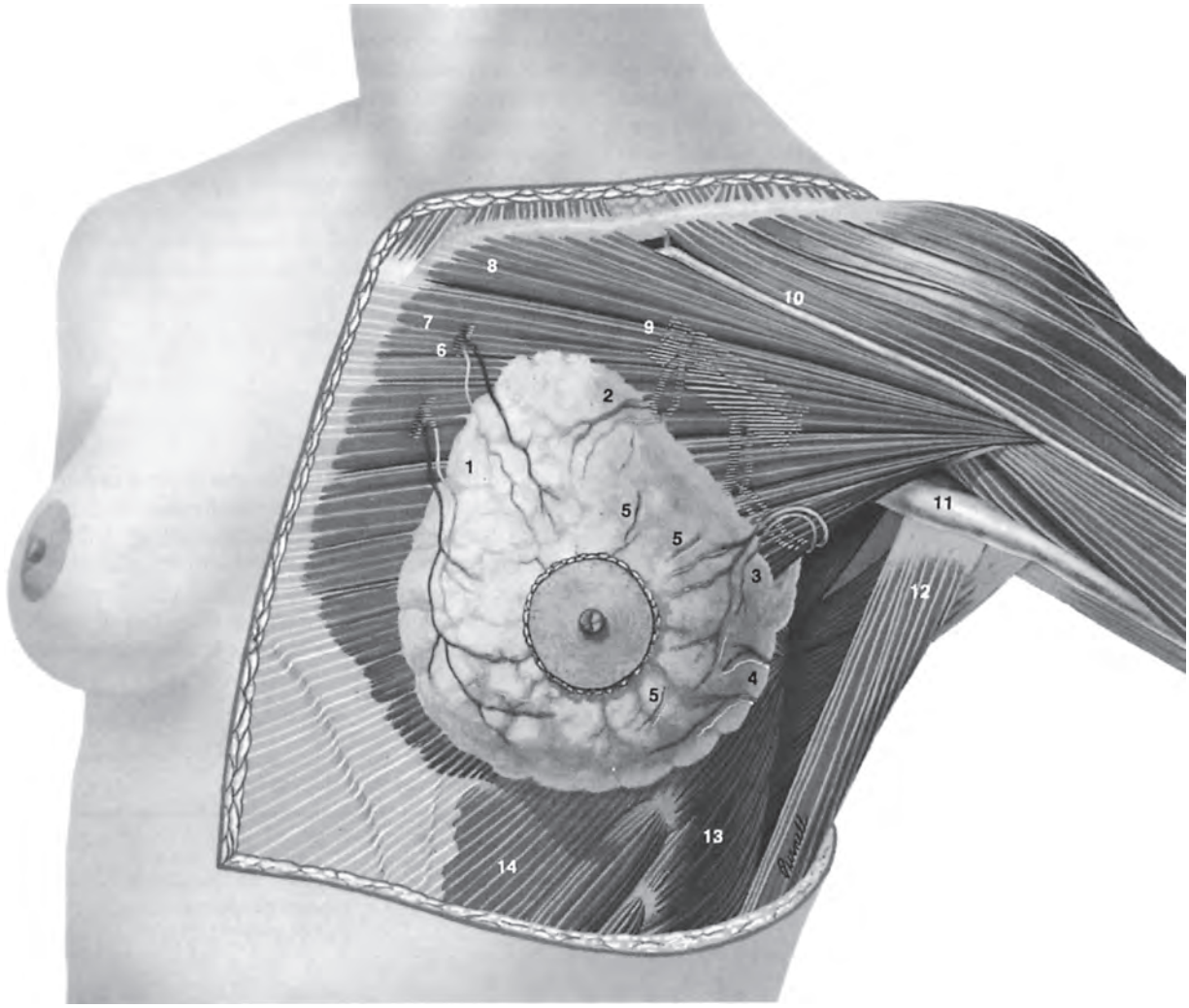

FIGURE 1-1 **Normal anatomy of the breast and pectoralis major muscle.** 1. Perforating branches from internal mammary artery and vein; 2. Pectoral branches from thoracoacromial artery and vein; 3. External mammary branch from lateral thoracic artery and vein; 4. Branches from subscapular and thoracodorsal arteries and veins; 5. Lateral branches of third, fourth, and fifth intercostal arteries and veins; 6. Internal mammary artery and veins; 7. Sternocostal head of pectoralis major muscle; 8. Clavicular head of pectoralis major muscle; 9. Axillary artery and vein; 10. Cephalic vein; 11. Axillary sheath; 12. Latissimus dorsi muscle; 13. Serratus anterior muscle; 14. External abdominal oblique muscle.

Lymphoscintigraphic studies have also shown that deeper parenchymal or retromammary lymphatics preferentially drain to the internal mammary lymph nodes when compared to intradermal or subdermal injection (31–35). There has been controversy over the direction of parenchymal lymph flow in relation to the subareolar plexus. Isotope injection of technetium-99m–labeled sulfur colloid into the subareolar region results in localization of isotope in the axillary sentinel lymph node (36–38). A detailed isotope study of subareolar injection and the lymphatic channels leading to the sentinel lymph node showed that in 90% of cases a single channel exited the areolar margin superiorly or laterally and terminated in an axillary sentinel lymph node (39). Secondary lymphatic channels exited the areola in 75% of cases. None entered the internal mammary lymph node chain.

Suami et al. (40) studied 24 breasts in 14 fresh human cadavers to examine the lymphatic drainage. Lymph collecting vessels were found evenly spaced at the periphery of the anterior upper torso draining radially into the axillary nodes. As identified in cross-section analysis, as these collecting vessels reached the breast some passed over and some through the breast parenchyma. Perforating lymph vessels that coursed beside the branches of the internal mammary vessels and drained into the ipsilateral internal mammary

TABLE 1-2

Nomenclature of the Breast Epithelial System

Major ducts	Terminal ducts
Collecting ducts	Extralobular
Lactiferous sinuses	Intralobular
Segmental ducts	Lobules
Subsegmental ducts	Alveoli
Terminal duct–lobular unit	

lymphatics were also found. Some of these findings are discordant with current knowledge and may explain some of the false-negative rates of sentinel lymph node biopsy.

Axillary Lymph Nodes

The topographic anatomy of the axillary lymph nodes has been studied as the major route of regional spread in primary mammary carcinoma. The anatomic arrangement of the axillary lymph nodes has been subject to many different classifications. The most detailed studies are those of Pickren (41), which show the pathologic anatomy of tumor spread. Axillary lymph nodes can be grouped as the apical or subclavicular nodes, lying medial to the pectoralis minor muscle, and the axillary vein lymph nodes, grouped along the axillary vein from the pectoralis minor muscle to the lateral limit of the axilla; the interpectoral (Rotter) nodes, lying between the pectoralis major and minor muscles along the lateral pectoral nerve (42,43); the scapular group, comprising the nodes lying along the subscapular vessels; and the central nodes, lying beneath the lateral border of the pectoralis major muscle and below the pectoralis minor muscle (Fig. 1-2). Other groups can be identified, such as the external mammary nodes lying over the axillary tail, intramammary lymph nodes, which are found in 28% of breasts (44), and the paramammary nodes located in the subcutaneous fat over the upper, outer quadrant of the breast.

An alternative method of delineating metastatic spread, for the purposes of determining pathologic anatomy and metastatic progression, is to divide the axillary lymph nodes into arbitrary levels (45). Level I lymph nodes lie lateral to the lateral border of the pectoralis minor muscle, level II nodes lie behind the pectoralis minor muscle, and level III nodes are located medial to the medial border of the pectoralis minor muscle (Fig. 1-3). These levels can be determined accurately only by marking them with tags at the time of surgery.

Internal Mammary Lymph Nodes

The internal mammary nodes lie in the intercostal spaces in the parasternal region. The nodes lie close to the internal mammary vessels in extrapleural fat and are distributed in the intercostal spaces, as shown in Figure 1-3. From the second intercostal space downward, the internal mammary nodes are separated from the pleura by a thin layer of fascia in the same plane as the transverse thoracic muscle. The number of lymph nodes described in the internal mammary chain varies. The nodes lie medial to the internal mammary vessels in the first and second intercostal spaces in 88% and 76% of cases, respectively, whereas they lie lateral to the vessels in the third intercostal space in 79% of cases. The prevalence of nodes in each intercostal space is as follows: first space, 97%; second space, 98%; third space, 82%; fourth space, 9%; fifth space, 12%; and sixth space, 62% (46). The pathologic anatomy of this route of lymphatic drainage in the spread of breast disease has been described by Handley and Thackray (47) and Urban and Marjani (48).

In the presence of nodal metastases, obstruction of the physiologic routes of lymphatic flow may occur, and alternative pathways may then become important. The alternative routes that have been described are deep, substernal, cross-drainage to the contralateral internal mammary chain (49,50); superficial presternal crossover, lateral intercostal, and mediastinal drainage (51); and spread through the rectus abdominis muscle sheath to the subdiaphragmatic and subperitoneal plexus (the Gerota pathway). This last route allows the direct spread of tumor to the liver and retroperitoneal lymph nodes. Substernal crossover is demonstrable by isotope imaging of the lymph nodes and may be of significance in early breast cancer (52).

Muscular and Neural Anatomy

The important muscles in the region of the breast are the pectoralis major and minor, serratus anterior, and latissimus dorsi muscles, as well as the aponeurosis of the external oblique and rectus abdominis muscles (Fig. 1-2).

The pectoralis minor muscle arises from the outer aspect of the third, fourth, and fifth ribs and is inserted into the medial border of the upper surface of the coracoid process of the scapula. The muscle is usually prefixed, rather than postfixed, and is innervated by the medial pectoral nerve, which arises mainly from the medial cord of the brachial plexus (cervical vertebra number, or C8, T1 segmental origin) and descends posteriorly to the muscle crossing the axillary vein anteriorly. The nerve enters the interpectoral space, passing through the muscle itself in 62% of cases and around the lateral border as a single branch in 38% of cases (53). Varying numbers of branches passing through the muscle provide motor supply to the lateral part of the pectoralis major muscle. The terms *medial* and *lateral* pectoral nerves are confusing: The standard terminology refers to their brachial plexus origin rather than their anatomic positions. Changes in terminology have been proposed but have not yet been generally accepted. The arrangement of these nerves is of particular importance in performing an axillary dissection.

The serratus anterior muscle stabilizes the scapula on the chest wall. The muscle arises by a series of digitations from the upper eight ribs laterally; its origin from the first rib is in the posterior triangle of the neck. At its origin from the fifth, sixth, seventh, and eighth ribs, the serratus anterior muscle interdigitates with the origin of the external oblique muscle. The muscle inserts into the vertebral border of the scapula on its costal surface and is supplied by the long thoracic nerve of Bell (the nerve to the serratus anterior muscle). The origin of this important nerve is the posterior aspect of the C5, C6, and C7 roots of the brachial plexus. It passes posteriorly to the axillary vessels, emerging on the chest wall high in the medial part of the subscapular fossa. The nerve lies superficial to the deep fascia overlying the anterior serratus muscle and marks the posterior limit of dissection of the deep fascia. Preservation of the nerve to the serratus anterior muscle as it passes downward is essential to avoid "winging" of the scapula and loss of shoulder power.

The latissimus dorsi muscle, the largest muscle in the body, is characterized by a wide origin from the spinous processes and supraspinous ligaments of the seventh thoracic vertebra downward, including all the lumbar and sacral vertebrae. The muscle inserts, by a narrow tendon forming the posterior axillary fold, into a 2.5-cm insertion in the bicipital groove of the humerus. As the muscle spirals around the teres major muscle, the surfaces of the muscle become reversed to the point of insertion. The muscle is supplied by the thoracodorsal nerve (the nerve to the latissimus dorsi muscle), which arises from the posterior cord of the brachial plexus, with segmental origin from C6, C7, and C8. The nerve passes behind the axillary vessels, approaches the subscapular vessels from the medial side, and then crosses anterior to these vessels to enter the medial surface of the muscle. As the nerve passes through the axilla it is intimately involved in the scapular group of lymph nodes. Resection of the nerve does not result in any important cosmetic or functional defect; nevertheless, it should be preserved when possible.

An important landmark in the apex of the axilla is the origin of the subclavius muscle, which arises from the costochondral junction of the first rib. At the tendinous part of the lower border of this muscle, two layers of the clavipectoral fascia fuse together to form a well-developed

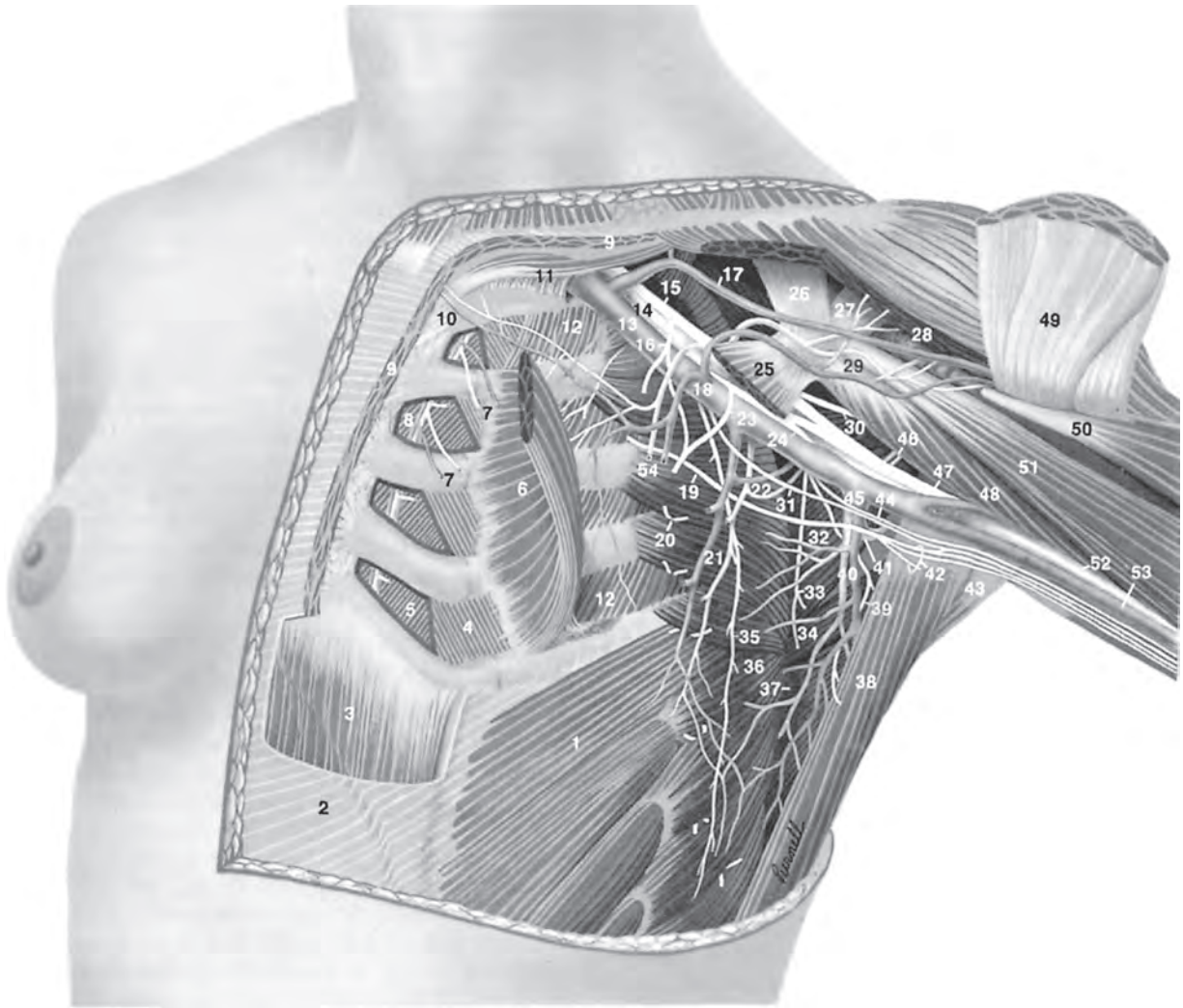

FIGURE 1-2 **Chest wall muscles and vascular anatomy.** 1. External abdominal oblique muscle; 2. Rectus sheath; 3. Rectus abdominis muscle; 4. Internal intercostal muscle; 5. Transverse thoracic muscle; 6. Pectoralis minor muscle; 7. Perforating branches from internal mammary artery and vein; 8. Internal mammary artery and vein; 9. Cut edge of pectoralis major muscle; 10. Sternoclavicular branch of thoracoacromial artery and vein; 11. Subclavius muscle and Halsted ligament; 12. External intercostal muscle; 13. Axillary vein; 14. Axillary artery; 15. Lateral cord of brachial plexus; 16. Lateral pectoral nerve (from the lateral cord); 17. Cephalic vein; 18. Thoracoacromial vein; 19. Intercostobrachial nerve; 20. Lateral cutaneous nerves; 21. Lateral thoracic artery and vein; 22. Scapular branches of lateral thoracic artery and vein; 23. Medial pectoral nerve (from medial cord); 24. Ulnar nerve; 25. Pectoralis minor muscle; 26. Coracoclavicular ligament; 27. Coracoacromial ligament; 28. Cut edge of deltoid muscle; 29. Acromial and humeral branches of thoracoacromial artery and vein; 30. Musculocutaneous nerve; 31. Medial cutaneous nerve of arm; 32. Subscapularis muscle; 33. Lower subscapular nerve; 34. Teres major muscle; 35. Long thoracic nerve; 36. Serratus anterior muscle; 37. Latissimus dorsi muscle; 38. Latissimus dorsi muscle; 39. Thoracodorsal nerve; 40. Thoracodorsal artery and vein; 41. Scapular circumflex artery and vein; 42. Branching of intercostobrachial nerve; 43. Teres major muscle; 44. Medial cutaneous nerve of forearm; 45. Subscapular artery and vein; 46. Posterior humeral circumflex artery and vein; 47. Median nerve; 48. Coracobrachialis muscle; 49. Pectoralis major muscle; 50. Biceps brachii muscle, long head; 51. Biceps brachii muscle, short head; 52. Brachial artery; 53. Basilic vein; 54. Pectoral branch of thoracoacromial artery and vein.

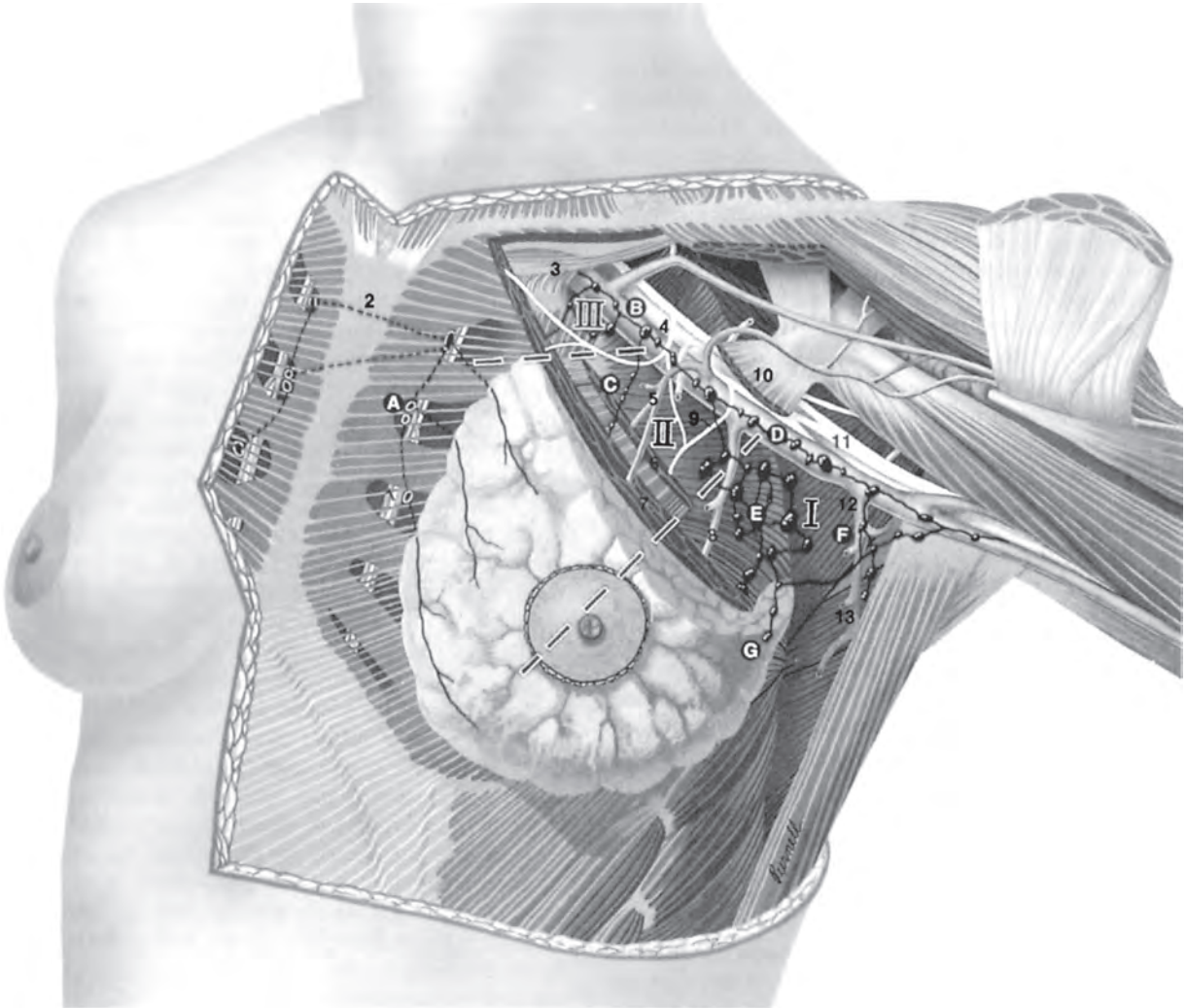

FIGURE 1-3 **Lymphatic drainage of the breast showing lymph node groups and levels.** 1. Internal mammary artery and vein; 2. Substernal cross-drainage to contralateral internal mammary lymphatic chain; 3. Subclavius muscle and Halsted ligament; 4. Lateral pectoral nerve (from the lateral cord); 5. Pectoral branch from thoracoacromial vein; 6. Pectoralis minor muscle; 7. Pectoralis major muscle; 8. Lateral thoracic vein; 9. Medial pectoral nerve (from the medial cord); 10. Pectoralis minor muscle; 11. Median nerve; 12. Subscapular vein; 13. Thoracodorsal vein; A. Internal mammary lymph nodes; B. Apical lymph nodes; C. Interpectoral (Rotter) lymph nodes; D. Axillary vein lymph nodes; E. Central lymph nodes; F. Scapular lymph nodes; G. External mammary lymph nodes; Level I lymph nodes: lateral to lateral border of pectoralis minor muscle; Level II lymph nodes: behind pectoralis minor muscle; Level III lymph nodes: medial to medial border of pectoralis minor muscle.

band, the costocoracoid ligament, which stretches from the coracoid process to the first costochondral junction (the Halsted ligament). At this point, the axillary vessels (the vein being anterior and inferior to the artery) enter the thorax, passing over the first rib and beneath the clavicle. Many unnamed small branches enter the axillary vein at its lower border. Near the apex, a small artery, the highest thoracic artery, arises from the axillary artery and lies on the first and second ribs.

Muscular Abnormalities

Congenital absence of the sternocostal head of the pectoralis major muscle and its associated abnormalities (Poland's syndrome) have been described earlier in this chapter. In 5% of cadavers, a sternalis muscle can be found lying longitudinally between the sternal insertion of the sternocleidomastoid muscle and the rectus abdominis muscle. The pectoralis minor muscle is inserted into the head of the humerus as well as the coracoid process of the scapula in 15% of cases. Part of the tendon then passes between the two parts of the coracoacromial ligament to insert into the coracohumeral ligament. Rarely, the axillopectoral muscle arises as a separate part of the latissimus dorsi muscle and inferolaterally crosses the base of the axilla superficially, passing deep to the pectoralis major muscle to join its insertion or to continue to the coracoid process (the axillohumeral arch of Langer). This anatomic arrangement can cause compression of the axillary vessels (54) and difficulty in orientation during axillary dissection.

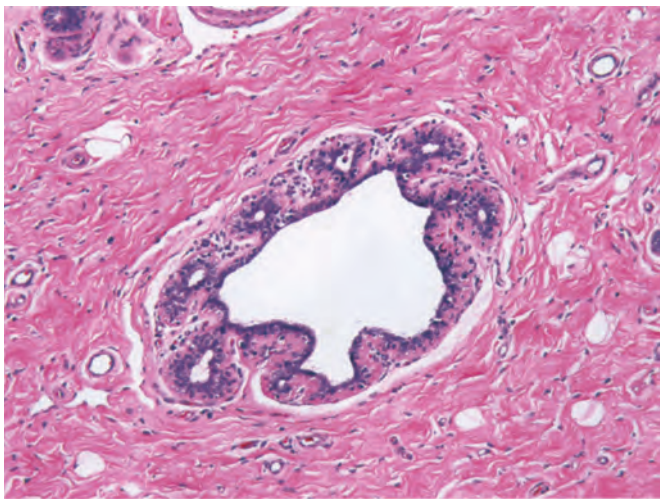

FIGURE 1-4 **Normal duct in adolescent female breast.** Rudimentary lobules are seen to be "budding" from the parent duct. Hematoxylin and eosin (H&E) stain. (Photomicrograph courtesy of Dr. Syed Hoda.)

Microanatomy of Breast Development

The developing breast at puberty has been described in detail by Russo and Russo (55) as growing and dividing ducts that form club-shaped terminal end buds. Growing terminal end buds form new branches, twigs, and small ductules termed *alveolar buds* (Fig. 1-4). Alveolar buds subsequently differentiate into the terminal structure of the resting breast, named the *acines* by German pathologists or the *ductule* by Dawson (4). The term *alveolus* is best applied to the resting secretory unit, and *acines* to the fully developed secretory unit of pregnancy and lactation (55).

Lobules develop during the first few years after menarche. The alveolar buds cluster around a terminal duct and form type I (virginal) lobules, comprising approximately 11 alveolar buds lined by two layers of epithelium. Full differentiation of the mammary gland proceeds through puberty, takes many years, and may not be fully completed if interrupted by pregnancies.

Detailed microanatomic studies of the breast have shown the presence of three distinct types of lobules (55). Type I lobules, previously described, are the first generation of lobules that develop just after the menarche. The transition to type II and type III gradually results from continued sprouting of new alveolar buds. The characteristics of the four lobular types are described in Tables 1-3 and 1-4.

Russo et al. (56) recently determined that the breast tissue of women with invasive cancer and those with a familial pattern of breast cancer have an architectural pattern different from the control group of normal tissue. They also found that the *BRCA1* or related genes may have a functional role in the branching pattern of the breast during lobular development. This is seen mainly in the epithelial stroma interaction.

Microscopic Anatomy of the Adult Breast

In the immature breast, the ducts and alveoli are lined by a two-layer epithelium that consists of a basal cuboidal layer and a flattened surface layer. In the presence of estrogens at puberty and subsequently, this epithelium proliferates, becoming multilayered in the adult breast (Figs. 1-5 and 1-6). Three alveolar cell types have been observed: superficial (luminal) A cells, basal B cells (chief cells), and myoepithelial cells.

Superficial, or luminal, A cells are dark, basophilic-staining cells that are rich in ribosomes. Superficial cells undergo intercellular dehiscence, with swelling of the mitochondria, and become grouped, forming buds within the lumen. Basal B cells, or chief cells, are the major cell type in mammary epithelium. They are clear, with an ovoid nucleus without nucleoli. Where the basal cells are in contact with the lumen, microvilli occur on the cell membrane. Intracytoplasmic filaments are similar to those in myoepithelial cells, suggesting their differentiation toward that cell type. Myoepithelial cells are located around alveoli and small excretory milk ducts between the inner aspect of the basement membrane and the tunica propria. Myoepithelial cells are arranged in a branching, star-like fashion. The sarcoplasm contains filaments that are 50 to 80 nm in diameter; these myofilaments are inserted by hemidesmosomes into the basal membrane. These cells are not innervated but are stimulated by the steroid hormones prolactin and oxytocin.

Anatomy of the Nipple and Breast Ducts

Recent advances exploring ductal lavage (57) and direct visualization of the ducts with breast endoscopy (58) have made the anatomy of the nipple clinically relevant. Utilizing six different approaches to examine the ductal anatomy, Love and Barsky (59) found that more than 90% of all nipples examined contained five to nine ductal orifices, generally arranged as a central group and a peripheral group. The central ducts did not extend in a radial fashion from the nipple as previously thought but traveled back from the nipple toward the chest wall. They also found that each nipple orifice communicated with a

TABLE 1-3

Characteristics of Human Breast Lobules

Lobule Type	*Lobule Area (mm^2)*	*Component Structures*	*Component Area ($\times 10^{-2}/mm^2$)*	*No. of Components/ Lobule*	*No. of Components/mm^2*	*No. of Cells/Area Section*
I	0.048 ± 0.0444	Alveolar bud	0.232 ± 0.090	11.20 ± 6.34	253.8 ± 50.17	32.43 ± 14.07
II	0.060 ± 0.026	Ductule	0.167 ± 0.035	47.0 ± 11.70	682.4 ± 169.0	13.14 ± 4.79
III	0.129 ± 0.049	Ductule	0.125 ± 0.029	81.0 ± 16.6	560.4 ± 25.0	11.0 ± 2.0
IV	0.250 ± 0.060	Acini	0.120 ± 0.050	180.0 ± 20.8	720.0 ± 150.0	10.0 ± 2.3

From Russo J, Russo IH. Development of human mammary gland. In: Neville MC, Daniel CW, eds. *The mammary gland*. New York: Plenum, 1987:67, with permission.

TABLE 1-4

Proliferative Activity of Human Breast Terminal Duct–Lobular Unit Components as Measured by DNA-Labeling Index

Structure	*Index*
Terminal end bud	15.8 ± 5.2
Type I lobule	5.5 ± 0.5
Type II lobule	0.9 ± 1.2
Type III lobule	0.25 ± 0.3
Terminal duct	1.2 ± 0.5

From Russo J, Russo IH. Development of human mammary gland. In: Neville MC, Daniel CW, eds. *The mammary gland.* New York: Plenum, 1987:67, with permission.

separate, nonanastomosing ductal system, which extended to the terminal duct lobular unit. Rusby et al. (60) prospectively examined nipples from mastectomy specimens. The median number of ducts was 23, but they found far fewer ductal orifices on the nipple surface. This study demonstrates that many ducts share a few common openings on the nipple surface and explains the discrepancy between the number of ductal openings on the nipple and the number of actual ducts.

There is evidence to suggest that both ductal and lobular carcinoma arises in the terminal duct lobular unit. Stolier and Wang (61) examined 32 nipples of mastectomy specimens. In 29 of the specimens, there were no terminal duct lobular units identified. Three of the 32 specimens were found to have terminal duct lobular units. All terminal duct lobular units were found at the base of the nipple as opposed to near the tip. As interest in intraductal approaches and treatment increases, so too will knowledge of ductal and nipple anatomy.

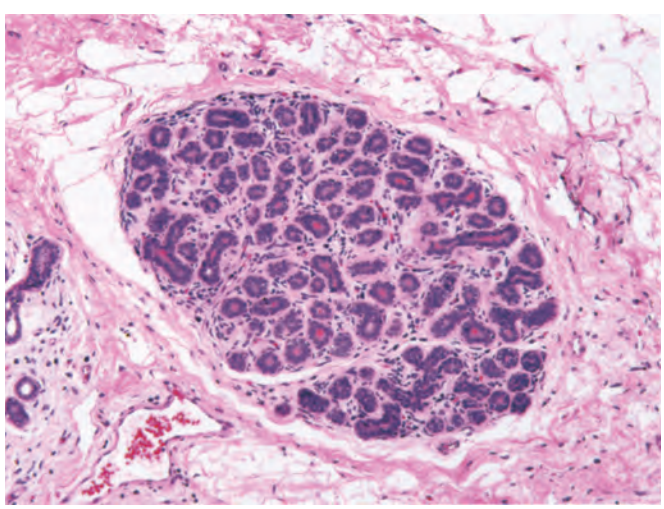

FIGURE 1-5 **Normal lobule in adult female breast.** The lobule is the functional unit of the breast. It is lined by two cell layers: inner epithelial layer and outer myoepithelial layer. The latter are inconspicuous on routine hematoxylin and eosin (H&E) stain such as this. (Photomicrograph courtesy of Dr. Syed Hoda.)

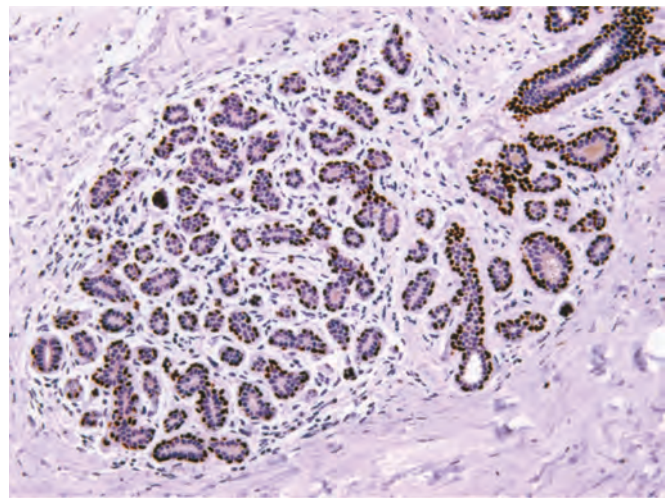

FIGURE 1-6 **Normal lobule in adult female breast.** p63 immunostain highlights the nuclei of the outer myoepithelial cell layer of the lobule. (Photomicrograph courtesy of Dr. Syed Hoda.)

PHYSIOLOGY

Microscopy, Morphology, and the Menstrual Cycle

Histologic changes in the normal breast have been identified in relation to the endocrine variations of the menstrual cycle (62). Normal menstrual cycle–dependent histologic changes in both stroma and epithelium have been observed.

Cyclic changes in the sex steroid hormone levels during the menstrual cycle profoundly influence breast morphology. Under the influence of follicle-stimulating hormone and luteinizing hormone during the follicular phase of the menstrual cycle, increasing levels of estrogen secreted by the ovarian graafian follicles stimulate breast epithelial proliferation. During this proliferative phase, the epithelium exhibits sprouting, with increased cellular mitoses, RNA synthesis, increased nuclear density, enlargement of the nucleolus, and changes in other intercellular organelles. In particular, the Golgi apparatus, ribosomes, and mitochondria increase in size or number. During the follicular phase, at the time of maximal estrogen synthesis and secretion in midcycle, ovulation occurs. A second peak occurs in the midluteal phase, when luteal progesterone synthesis is maximal. Similarly, progestogens induce changes in the mammary epithelium during the luteal phase of the ovulatory cycles. Mammary ducts dilate, and the alveolar epithelial cells differentiate into secretory cells, with a partly monolayer arrangement. The combination of these sex steroid hormones and other hormones results in the formation of lipid droplets in the alveolar cells and some intraluminal secretion.

The changes in breast epithelium in response to hormones are mediated through either intracellular steroid receptors or membrane-bound peptide receptors. The presence of steroid receptors for estrogen and progestogens in the cytosol of normal mammary epithelium has been demonstrated (63). Through the binding of these hormones to specific receptors, the molecular changes, with their observed morphologic effects, are induced as physiologic changes. Similarly, membrane receptors are present to mediate the actions of prolactin. Increases in endogenous estrogen can also exert a histamine-like effect on the mammary microcirculation (64), resulting in an increased blood flow 3 to 4 days

before menstruation, with an average increase in breast volume of 15 to 30 cm^3. Premenstrual breast fullness is attributable to increasing interlobular edema and enhanced ductular–acinar proliferation under the influence of estrogens and progestogens. With the onset of menstruation, after a rapid decline in the circulating levels of sex steroid hormones, secretory activity of the epithelium regresses.

Postmenstrually, tissue edema is reduced, and regression of the epithelium ceases as a new cycle begins, with concomitant rises in estrogen levels. Minimum breast volume is observed 5 to 7 days after menstruation. The cyclic changes in breast cellular growth rates are related to hormonal variations in the follicular and luteal phases of the menstrual cycle. Measurement of these changes can be made by observation and measurement of a variety of cellular and nuclear parameters:

- Histologic pattern
- Cellular morphology
- Nuclear morphology
- Mitoses
- Tritiated thymidine uptake
- Image cytometry
  - Nuclear area
  - Circumference
  - Boundary fluctuation
  - Chromatin granularity
  - Stain intensity
- Proliferation markers
  - Ki-67
  - Proliferating cell nuclear antigen
  - MIB1

Most observations have been made from surgical specimens, which are usually from women with breast abnormalities, or from autopsy specimens, which may have resulted in inconsistent and contradictory results.

Most studies have shown that breast epithelial cell proliferation increases in the second half (luteal phase) of the menstrual cycle (65–71).

A study of nuclear tritiated thymidine uptake in surgically excised breast tissue showed that peak uptake was during the luteal phase on days 22 to 24, coinciding with an increase in circulatory progesterone levels and a second peak of estrogen. The role of estrogen was considered unimportant because the preovulatory peak of estrogen was not associated with an increase in tritiated thymidine uptake (67). The possibility of a synergistic action between estrogen and progesterone would therefore be unlikely.

The role of estrogen and progesterone was subsequently studied in explants of human breast tissue implanted subcutaneously in nude mice (72). An increase in epithelial cell growth was observed 7 days after exposure to estrogen; progesterone had no effect, and a combination of estrogen and progesterone neither enhanced nor diminished the proliferative effect of estrogen. These observations may explain why proliferation increases during the luteal phase subsequent to the preovulatory estrogen peak.

Breast Changes during Pregnancy

During pregnancy, marked ductular, lobular, and alveolar growth occurs as a result of the influence of luteal and placental sex steroids, placental lactogen, prolactin, and chorionic gonadotropin (Fig. 1-4B). In experimental studies, these effects are observed when estrogen and progesterone cause a release of prolactin by reducing the hypothalamic release of prolactin-inhibiting factor (PIF) (69). Prolactin in humans is also released progressively during pregnancy and probably stimulates epithelial growth and secretion (70,71). Prolactin increases slowly during the first half of pregnancy; during the second and third trimesters, blood levels of prolactin are three to five times higher than normal, and mammary epithelium initiates protein synthesis.

In the first 3 to 4 weeks of pregnancy, marked ductular sprouting occurs with some branching, and lobular formation occurs under estrogenic influence. At 5 to 8 weeks, breast enlargement is significant, with dilatation of the superficial veins, heaviness, and increasing pigmentation of the nipple–areolar complex. In the second trimester, lobular formation exceeds ductular sprouting under progestogenic influence. The alveoli contain colostrum but no fat, which is secreted under the influence of prolactin. From the second half of pregnancy onward, increasing breast size results not from mammary epithelial proliferation but from increasing dilatation of the alveoli with colostrum, as well as from hypertrophy of myoepithelial cells, connective tissue, and fat. If these processes are interrupted by early delivery, lactation may be adequate from 16 weeks of pregnancy onward.

At the beginning of the second trimester, the mammary alveoli, but not the milk ducts, lose the superficial layer of A cells. Before this, as in the nonpregnant woman, the two-layer structure is maintained. In the second and third trimesters, this monolayer differentiates into a colostrum–cell layer and accumulates eosinophilic cells, plasma cells, and leukocytes around the alveoli. As pregnancy continues, colostrum, composed of desquamated epithelial cells, accumulates. Aggregations of lymphocytes, round cells, and desquamated phagocytic alveolar cells (foam cells) may be found in colostrum; these are termed the *Donné corpuscles*.

Lactation

After parturition, an immediate withdrawal of placental lactogen and sex steroid hormones occurs. During pregnancy, these hormones antagonize the effect of prolactin on mammary epithelium. Concomitant to the abrupt removal of the placental hormones, luteal production of the sex steroid hormones also ceases. A nadir is reached on the fourth to fifth day postpartum; at this time, the secretion of PIF from the hypothalamus into the hypothalamoadenohypophyseal portal system decreases. This reduction in PIF secretion allows the transmembrane secretion of prolactin by pituitary lactotrophs. Sex steroid hormones are not necessary for successful lactation, and physiologic increases, such as may occur with postpartum ovulatory cycles, do not inhibit it.

Prolactin, in the presence of growth hormone, insulin, and cortisol, converts the mammary epithelial cells from a presecretory to a secretory state. During the first 4 or 5 days after giving birth, the breasts enlarge as a result of the accumulation of secretions in the alveoli and ducts (Fig. 1-7). The initial secretion is of colostrum, a thin, serous fluid that is, at first, sticky and yellow. Colostrum contains lactoglobulin, which is identical to blood immunoglobulins. The importance of these immunoglobulins is unknown; many maternal antibodies cross the placenta, transferring passive immunity to the fetus *in utero*. Fatty acids such as decadienoic acid, phospholipids, fat-soluble vitamins, and lactalbumin in colostrum have considerable nutritional value. After colostrum secretion, transitional milk and then mature milk are elaborated.

Mechanisms of Milk Synthesis and Secretion

The effects of prolactin are mediated through membrane receptors in the mammary epithelial cells. The release of prolactin is maintained and stimulated by suckling, as is the release of corticotrophin (adrenocorticotropic hormone). The mammary cells are cuboidal, depending on the degree of intracellular accumulation of secretions. The DNA and RNA of the nuclei increase, and abundant mitochondria,

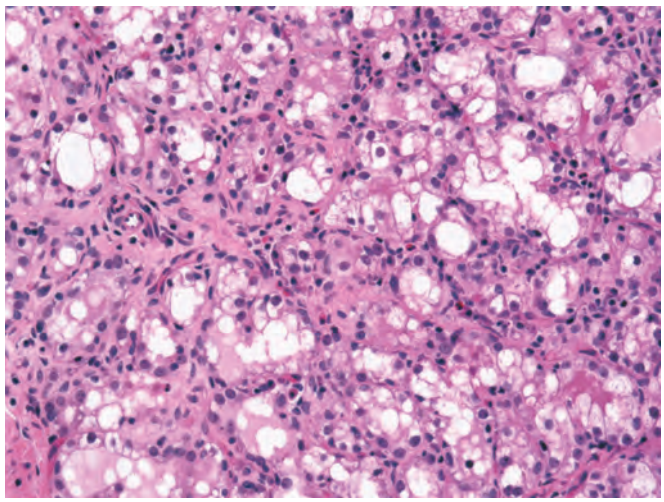

FIGURE 1-7 **Lactating breast tissue.** The glands within the lobules are enlarged and dilated. The stroma within the lobule is diminished. Secretory vacuoles are present within the individual lobular epithelial cells. Hematoxylin and eosin (H&E) stain. (Photomicrograph courtesy of Dr. Syed Hoda.)

ribosomes, and rough endoplasmic reticulum, with a prominent Golgi apparatus, are apparent in the epithelial cells. Complex protein, mild fat, and lactose synthetic pathways are activated, as are water–ion transport mechanisms. These processes are initiated by the activation of hormone-specific membrane receptors. Changes in cyclic adenosine monophosphate stimulate milk synthesis through the induction of messenger and transfer RNA. Prolactin stimulates cyclic adenosine monophosphate–induced protein kinase activity, resulting in the phosphorylation of milk proteins. Polymerase activity and cellular transcription are enhanced (17).

Large fat vacuoles develop and move toward the apex of the cell. At the same time, the nucleus also moves toward the apex. As the water intake of the cell increases, longitudinal cellular striations may be observed. Ultimately, the vacuoles pass from the cell along with part of the cell membrane and cytoplasm; the apical cell membrane reconstitutes as secretion takes place.

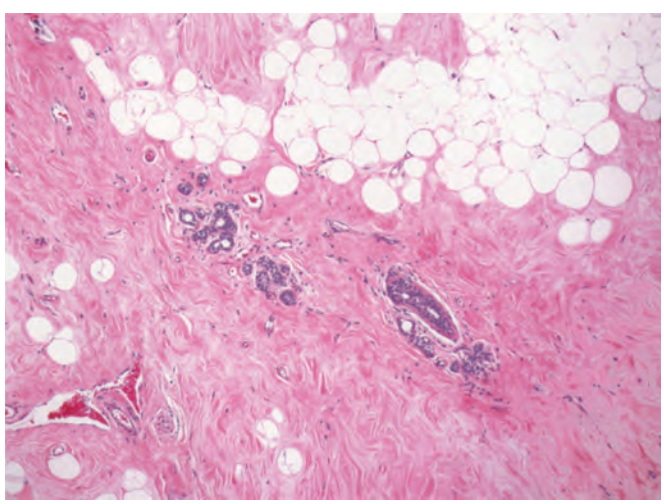

FIGURE 1-8 **Atrophic breast tissue in a postmenopausal woman.** Only a few atrophic ducts and lobules are present amid dense fibrous and fatty tissue. Hematoxylin and eosin (H&E) stain. (Photomicrograph courtesy of Dr. Syed Hoda.)

Enhanced activity occurs during suckling. Fat is secreted chiefly through an apocrine mechanism, lactose is secreted through a merocrine mechanism, and the secretion of proteins occurs as a result of a combination of mechanisms. Ions enter the milk by diffusion and active transport. Relatively little holocrine secretion is thought to take place. The end result of secretion and subsequent intraductal dilution of extracellular fluid is milk, comprising a suspension of proteins—casein, β-lactalbumin, and β-lactoglobulin—and fat in a lactose–mineral solution. The white appearance of milk is due to emulsified lipids and calcium caseinate, whereas the yellow color of butterfat is due to the presence of carotenoids.

Mechanisms of Milk Ejection

The removal of milk by suckling is aided by active ejection. Sensory nerve endings in the nipple–areolar complex are activated by tactile stimuli. Impulses pass by way of sensory nerves through the dorsal roots to the spinal cord. In the spinal cord, impulses are relayed through the dorsal, lateral, and ventral spinothalamic tracts to the mesencephalon and lateral hypothalamus. Inhibition of PIF secretion permits the unimpeded secretion of prolactin from the anterior pituitary. Simultaneously, through a different pathway in the paraventricular nucleus, the synthesis of oxytocin occurs. Oxytocin is released from the posterior pituitary neurovesicles by impulses traveling along the neurosecretory fibers of the hypothalamoneurohypophyseal tract. Oxytocin released into the systemic circulation acts on the myoepithelial cells, which contract and eject milk from the alveoli into the lactiferous ducts and sinuses. This phenomenon is specific to oxytocin, and changes in intramammary ductal pressures of 20 to 25 mm Hg may be observed in relation to peak blood levels. Oxytocin also acts on the uterus and cervix to promote involution. This effect may be stimulated by cervical dilatation and by vaginal stretching through the ascending afferent neural pathways (Ferguson reflex).

Complex neuroendocrine interactions determine normal lactation. An appreciation of these mechanisms is essential to the understanding of abnormalities and to the treatment of problems of lactation (17).

Menopause

Menopause is the result of the atresia of more than 400,000 follicles that are present in the ovaries of a female fetus at 5 months' gestation. Declining ovarian function in late premenopause through the menopause leads to regression of epithelial structures and stroma. Menopausal involution of the breast results in reduction of both the number of ducts and lobules. Stromal changes dominate and fat deposition increases while the regression of connective tissue continues. The duct system remains, but the lobules shrink and collapse (Fig. 1-8). Lymphatic channels are also reduced in number in the postmenopausal breast (36). The last structures to appear with sexual maturity are the first ones to regress (17).

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CHAPTER 2

Stem Cells in Breast Development and Carcinogenesis: Concepts and Clinical Perspectives

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CHAPTER CONTENTS

There has been accumulating evidence for the existence of a subcomponent of cancer cells that have stem cell properties and have been termed "cancer stem cells." Although the concept that cancer originates from the transformation of "germ cells" or "stem cells" was first proposed over 150 years ago, it is only recently that advances in stem cell biology have allowed for a more direct testing of the cancer stem cell hypothesis. Stem cells are defined by their ability to undergo self-renewal, as well as multi-lineage differentiation. This self-renewal can be either asymmetric or symmetric. Self-renewal is distinguished from other proliferative processes in that at least one of the progeny of self-renewal is identical to the initial stem cell. In all other replicative processes, the progeny of division undergo a series of differentiation events (1). In asymmetric stem cell self-renewal, one of the two progeny is identical to the initial stem cell, whereas the other cell is a committed progenitor cell, which undergoes cellular differentiation. Because the product of an asymmetric self-renewal division is one stem cell and one differentiated cell, this process maintains stem cell numbers. In contrast, symmetric self-renewal results in the production of two stem cells; by its very nature this results in stem cell expansion. Although stem cells themselves are slowly dividing, progenitor cells derived from them are highly proliferative (2). This expanding progenitor cell also has the ability to differentiate into the lineages comprising the adult tissue. Embryonic stem cells are pluripotent, able to differentiate into all derivatives of the three primary germ layers (ectoderm, endoderm, and mesoderm), whereas adult stem cells are multipotent, able to form all of the cell types that are found in the mature tissue of an organ. In the mammary gland, these differentiating cells generate three lineages: ductal epithelial cells, which line ducts; alveolar epithelial cells, which are the milk-producing cells; and myoepithelial cells, which are contractile cells lining ducts and alveoli.

Based on this definition, cancer stem cells retain key stem cell properties. These properties include self-renewal, which initiates and drives tumorigenesis, and differentiation, albeit aberrant, which contributes to cellular heterogeneity (3)

In breast cancer, the discovery of tumor cells that display stem cell properties provides a possible explanation as to why cancer may be so difficult to eradicate, as well as suggesting strategies for the targeting of this cell population. This chapter will examine the implications of the cancer stem cell hypothesis and enable an understanding of carcinogenesis, as well as its implications for developing new strategies for prevention and therapy of breast cancer.

IDENTIFICATION OF NORMAL BREAST STEM CELLS

The existence of adult mammary stem cells was established nearly 50 years ago when DeOme et al. (4) observed that tissue fragments of epithelium isolated from several different regions of the mammary gland were able to reconstitute the entire mammary ductal tree upon transplantation. Later, serial transplantation experiments by Charles Daniel and colleagues (5) demonstrated that stem cells exist throughout the life span of the mouse. Further studies by Smith and Medina (6) suggested that mammary stem cells were present in all portions of the ductal mammary tree at all developmental stages. In 2006, two complementary studies demonstrated that a single cell from either the $CD24^{lo}$ (heat-stable antigen)/ $CD29^{hi}$ (α1-integrin) (7) or $CD24^{lo}/CD49f^{hi}$ (α6-integrin) (8) epithelial population isolated from an adult virgin mouse could generate a functional mammary gland when transplanted into the cleared fat pad of recipient mice.

Further analysis of the $CD24^{lo}CD29^{hi}$ cells revealed that this was a basal population of cells that was ERα-negative (9). Limiting dilution transplantation experiments by Smalley and co-workers (10) illustrated that $CD24^{lo}$ ERα-negative basal cells displayed the highest stem cell activity (as defined by mammary repopulating units), whereas ERα-positive luminal cells exhibited very little stem cell activity. Conversely, Booth and Smith (11) suggested that long-lived, slow-dividing, label-retaining ERα-positive cells comprise a progenitor cell population that can directly respond to hormones. The relationship of these cells characterized *in situ* to the $CD24^{lo}$ cells identified by fluorescence activated cell sorting remains to be established. A well-established *in vitro* system for assays of stem cell behavior—the mammospheres culture system—is a nonadherent assay in which mammary stem cells are cultured as floating cell colonies, without inducing cell differentiation. It was shown that human breast epithelial cells formed mammospheres after 7 to 10 days of culture, which maintained a primitive phenotype and therefore did not express markers associated with terminal differentiation (12,13). In culture conditions which favored cell differentiation, cells isolated from dissociated mammospheres were shown to have the capacity for multi-lineage differentiation in two dimensional culture (as assessed by expression of cell-type specific markers) and in three-dimensional culture gave rise to lobular-alveolar structures (12).

Ginestier et al. (14) have described the expression of aldehyde dehydrogenase 1 (ALDH1) as a stem cell marker that can be utilized to isolate human mammary stem cells. ALDH1 is a detoxifying enzyme responsible for the oxidation of intracellular aldehydes. This enzyme may play a role in early differentiation of stem cells through its role in oxidizing retinol to retinoic acid (15). It is expressed in hematopoietic and neuronal stem and progenitor cells and can be detected utilizing an enzymatic assay (ALDEFLUOR; Aldagen, Durham, North Carolina) (16). Human mammary epithelial cells with a high enzymatic activity for ALDH (ALDEFLUOR positive), isolated from reduction mammoplasties, were able to reconstitute human mammary gland structures when implanted in the humanized fat pad of NOD/SCID mice. Using ALDH1 antibody to immunostain paraffin-embedded sections of human normal breast epithelium researchers identified a relatively rare population of ALDH1-positive cells located in the terminal ductal lobular units (TDLUs). ALDH1-positive cells appeared to form a bridge in the lumen that was located at the bifurcation point of side branches in the TDLUs (14). This is consistent with recently published data demonstrating that human stem/progenitor cells are localized in the ductal part of the TDLU structures (17).

The identification of mammary stem cell markers and the development of *in vitro* and murine models utilizing these cells should facilitate the study of adult breast stem cells to elucidate their role in mammary development. Furthermore, defining the pathways that regulate mammary stem cell self-renewal and differentiation should shed light on events involved in breast carcinogenesis.

BREAST CARCINOGENESIS

Traditionally, cancer has been considered as a multistep process defined by the sequential mutation of key genes driving the uncontrolled clonal expansion of a cell. However, important recent progress in basic research has challenged these concepts at different levels. First, the role of the tumor microenvironment is now well recognized, including the interaction with the extracellular matrix (ECM) and the immune system (18,19). Indeed, epithelial cells are dependent on interactions with specific components of the ECM for survival, proliferation, and differentiation. In addition, the initial steps in tumor establishment are associated with a deficiency in the mechanisms of immunosurveillance. Second, the role of epigenetic deregulation, as opposed to genetic aberrations, in most human tumors is becoming increasingly evident. Epigenetic mechanisms appear to play a fundamental role in cancer establishment and progression, and their deregulation has been reported at multiple levels, including DNA methylation, histone modifications, and microRNA expression (20–24). Third, a "cancer stem cell" model of tumorigenesis has gained experimental support. This model suggests that tumors are sustained in their pathological growth by a small subpopulation of tumor cells with "stem-like" properties, in a way analogous to normal organogenesis. *Cancer stem cell* (CSC) is an operational term to functionally define this distinct subpopulation of tumor cells with deregulated potential for self-renewal, excessive proliferation, and aberrant differentiation into heterogeneous progeny, generating intratumor heterogeneity (25,26) Indeed, classical models of carcinogenesis can be described as "stochastic" or "random," in which any cell in an organ, such as the breast, can be transformed by the right combination of mutations (27). As a result, all or most of the cells in a fully developed cancer are equally malignant (Fig. 2-1). It follows that strategies designed to treat and ultimately cure these cancers require the killing of all these malignant cells. Conversely, the cancer stem cell hypothesis is a fundamentally different model composed of two separate, but interrelated components. The first is that tumors originate in tissue stem and/or progenitor cells through the deregulation of the normally tightly regulated process of self-renewal (28). As a consequence, it is believed that tumors contain a cellular component that retains key stem cell properties including self-renewal, which initiates and drives carcinogenesis and differentiation, albeit aberrant, that contributes to tumor cellular heterogeneity (Fig. 2-1B) (29). However, it is important to emphasize that the CSC and stochastic model of carcinogenesis are not mutually exclusive and probably both mechanisms contribute to tumor heterogeneity. As a result tumors may be constituted by multiple CSC clones which evolve during tumor development and treatment.

ISOLATION AND CHARACTERIZATION OF BREAST CANCER STEM CELLS

Even though important progress has been made, the isolation and characterization of cancer stem cells remains a challenge. In order to validate the method selected as an appropriate technique to isolate cancer stem cells, it is crucial to use assays that can assess the stem cell properties of self-renewal and differentiation. Presently, the gold standard for identifying breast cancer stem cell activity is the xenograft model based on the orthotopic injection of human breast cancer cells into the humanized clear mammary fat pad of immunodeficient mice. The cancer stem cell population is characterized by enhanced tumorigenicity and is able to regenerate the tumor upon serial passage, whereas the tumor cell population depleted of cancer stem cells cannot sustain tumor growth upon serial transformation (Fig. 2-2). In addition to self-renewal, cancer stem cells retain the ability to differentiate, albeit abnormally, generating non–self-renewing cell populations that constitute the bulk of a tumor. Development

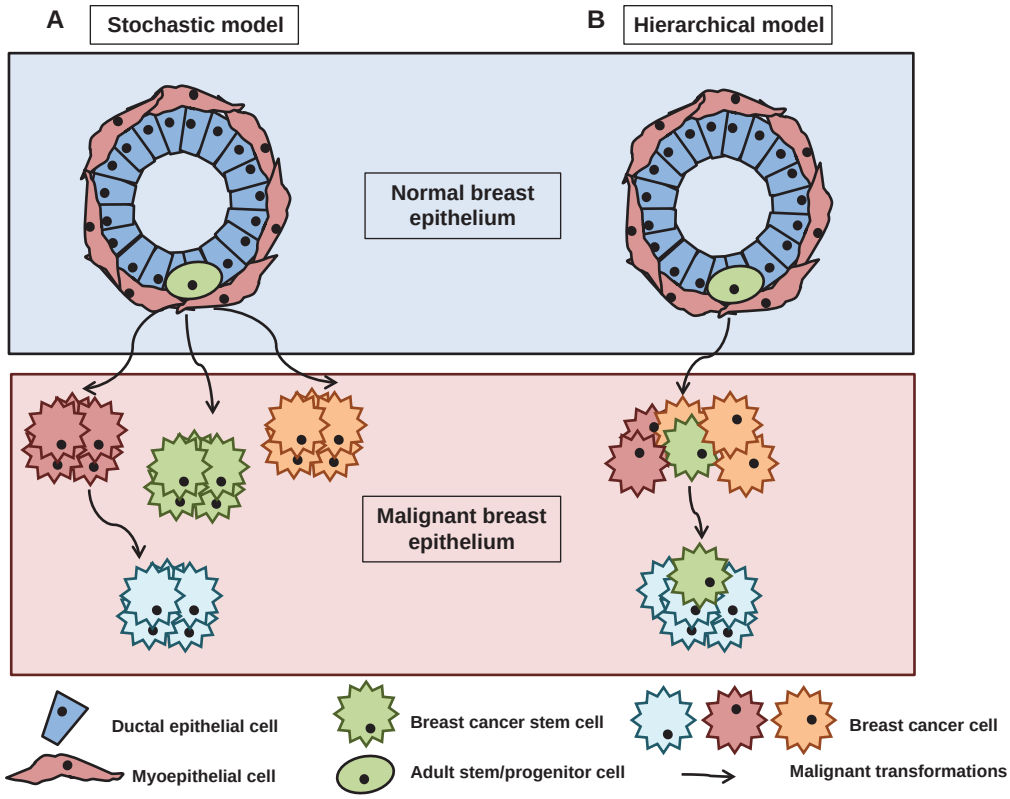

FIGURE 2-1 Two Models of Breast Carcinogenesis. **A:** According to the stochastic model any mammary epithelial cell can be transformed by the right combination of mutations and resultant cancer cells of different phenotypes have extensive proliferation potential. **B:** According to the stem cell hierarchical model, cancers originate from the malignant transformation of a normal breast stem/progenitor cell. Most cancer cells have only limited proliferative potential, but cancer stem cells that have self-renewal capacity drive tumorigenesis.

of *in vitro* assays such as the mammosphere assay has been also used for enrichment of cancer stem cell population. This method is a nonadherent colony forming assay developed by Dontu et al. (30) where only cells with self-renewal capacity are able to survive and grow in anchorage-independent conditions while differentiated cells will undergo anoikis.

In summary, several different techniques have been utilized to enrich for and identify breast cancer stem cells. The *in vitro* cancer stem cell assays provide an important tool for mechanistic studies as well as for screening of specific drugs targeting this population. However, at this time, self-renewal can only be confirmed by serial passage in xenograft models. A potential limitation of these systems relates to the microenvironmental difference found in humans compared to NOD/SCID mice (31). Another important characteristic of both *in vivo* and *in vitro* assays to be taken into account is that these techniques may only detect proliferating stem cells but not dormant cancer stem cells.

BCSC MARKERS

The first evidence for the existence of cancer stem cells in human solid tumors came from the study of Al-Hajj et al. (32) where they utilized techniques based on seminal studies identifying leukemic stem cells by Bonnet and Dick (33). Utilizing cell surface markers and flow cytometry, these authors isolated a tumorigenic population of cells in human breast cancer that displayed cancer stem cell properties. This population was defined by the expression of cell surface markers ($CD44^+/CD24^{-/low}/lin^-$). When injected in the mammary fat pad of NOD/SCID mice as few as 200 of these cells were able to form tumors, whereas 20,000 cells that did not display this phenotype failed to generate tumors. Tumors that formed in mice recapitulated the phenotypic heterogeneity of the initial tumor. The ability to serially transplant the tumors from an enriched stem cell population provides strong support for the existence of stem cells in breast cancers. CD44 appears to be also expressed in cancer stem cells in other tumor types including colon, pancreas, prostate, and head and neck (34–37).

Recently it has been suggested that expression of the cell surface markers EpCAM and CD49f can be used to define functional populations of normal mouse and human mammary cells. Based on *in vitro* and mouse fat pad re-implantation studies it has been suggested that $EpCAM^-$ $CD49f^+$ cells represent mammary stem cells, $EpCAM^+CD49^+$ (double-positive cells): luminal progenitors; $EpCAM^+CD49f^-$: differentiated luminal cells; and $EpCAM^-CD49f^-$: stromal cells. However, double positive ($EpCAM^+CD49f^+$) so-called luminal progenitor cells, have been found to give rise to basal as well as luminal cells when cultured *in vitro*. These results suggest that in addition to luminal progenitors, the $EpCAM^+CD49f^+$ population may also contain a sub-population with stem cell characteristics. A recent study in triple negative breast cancer demonstrated the existence of two different subpopulations based on CD49f expression: $CD49f^-$ quiescent cells and $CD49f^+$ cells. $CD49f^-$ quiescent cells present high tumor-initiating potential as compared to $CD49f^+$ cells. Gene expression analysis reveals that $CD49f^-$ quiescent cells overexpress epithelial-to-mesenchymal transition-driving genes, reminiscent of tumor-initiating cells and claudin-low breast cancer (38). Emerging studies suggest that while $CD49f^+/EpCAM^-$ and $CD44^+/CD24^-$ cells may represent the EMT-like CSC phenotype, $ALDH^+$ cells may represent the MET-like CSC phenotype. These two CSC states may be interconvertible. EMT-like CSCs

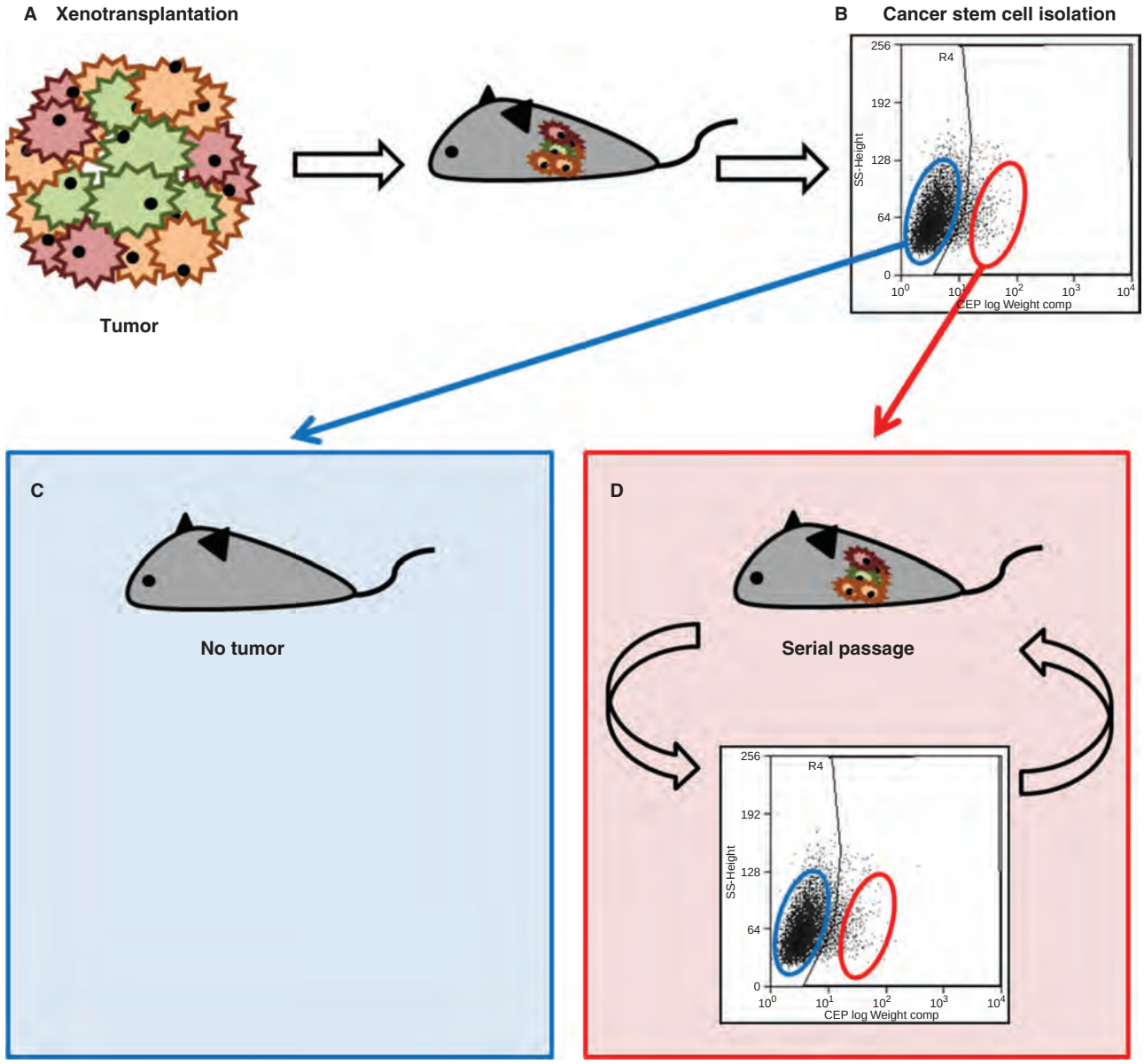

FIGURE 2-2 **Isolation and characterization of breast cancer stem cells. A:** The xenograft model involves introduction of tumor cells into the cleared fat pad of not otherwise specified/severe combined immunodeficiency (NOD/SCID) mice that have been humanized by the introduction of human mammary fibroblasts. **B:** When the xenograft is established, breast cancer stem cells can be separated from the rest of the tumor cells utilizing different techniques such as the ALDEFLUOR (Aldagen, Durham, North Carolina) assay. **C:** When transplanted, the cancer stem cell population initiates and maintains tumor growth upon serial passage, whereas the tumor cell population depleted of the cancer stem cell population fails to generate tumors **D**.

have a mesenchymal morphology, are largely quiescent, invasive, and characterized by expression of the CSC markers $CD24^{-}CD44^{+}$ and are $EpCAM^{-}CD49f^{+}$. In contrast, the MET (mesenchymal epithelial transition) state of CSCs is characterized by active self-renewal and expression of the CSC markers ALDH and $EpCAM^{+}CD49f^{+}$. A subpopulation of cells expressing both $CD24^{-}CD44^{+}$ and ALDH may represent cells in transition between these states. This transition is regulated by signals originating in the microenvironment that could be a potential therapeutic target.

ALDEHYDE DEHYDROGENASE 1

ALDH enzymatic activity has been recently used to isolate normal human breast stem and progenitors cells (14). The authors demonstrated that ALDEFLUOR-positive cells isolated from human breast cancer display properties of cancer stem cells shown by the ability of these cells, but not ALDEFLUOR-negative cells, to generate tumors in NOD/SCID mice. Serial passages of the ALDEFLUOR-positive cells generate tumors that recapitulated the phenotypic heterogeneity

of the initial tumor. Interestingly, the ALDEFLUOR-positive cell population detected in breast tumors has a small overlap with the previously described cancer stem cell, $CD44^+/CD24^-/lin^-$ phenotype (32). In the tumors investigated, the overlap represented approximately 1% or less of the total cancer cell population. The ALDEFLUOR-positive $CD44^+/CD24^-/lin^-$ cells appeared to be highly enriched in tumorigenic capability, being able to generate tumors from as few as 20 cells. ALDH1 immunostaining of paraffin-embedded specimens was utilized to identify breast cancer stem cells *in situ*. Analysis of ALDH1 expression in 577 human breast carcinomas showed that this stem or progenitor cell marker is a powerful predictor of poor clinical outcome and correlates with tumor histological grade, ER and PR negativity, proliferation index as assessed by Ki-67 expression, and *ERBB2* overexpression.

LINEAGE TRACING

Recent studies utilizing mouse models of glioblastoma, skin and intestinal tumors provide important validation of the cancer stem cell model (39–41). These studies provide the first evidence that CSC arise de novo during tumor development in intact organs. Lineage tracing methods take advantage of fluorescent marking of stem cells and their progeny allowing for the visualization and monitoring of cancer stem cells. Chen et al. and Driessens et al., together with Schepers et al., traced individual cells in intact tumors and demonstrated that cancer cells are organized hierarchically. Using lineage tracing Driessens et al. observed that the cells present an important variability in proliferation potential with only 20% able to generate daughter cells capable of tumor regeneration. Moreover, the studies of Chen et al. suggested that targeting both CSC and their progeny improved therapeutic outcome *in vivo*. These studies raise the issue of a possible evolutionary competition between non-stem cells and stem cells within the tumor, with the non-stem cells presence representing a brake for the tumor development. In accordance with this idea Driessens et al. observed enrichment of the CSC population and a concomitant decrease in the non-stem cell population during cancer progression. Together these results suggest that prevention of the increase in the stem-like compartment would retard tumor progression.

THERAPEUTIC IMPLICATIONS OF BREAST CANCER STEM CELLS

Although advances have been made in the treatment of localized breast cancer, there has been less progress in the treatment of advanced metastatic disease. Some of this lack of progress may be due to the failure of current therapies to target cancer stem cells (Fig. 2-3). The cancer stem cell hypothesis has important implications for the development of cancer therapeutics. Recent evidence indicates that breast CSC (42) as well as CSC from other tumor types, are relatively resistant to both radiation and chemotherapy (43). There are several postulated mechanisms for this resistance. Stem cells proliferate slowly; they are largely in the G0 phase of the cell cycle for extended periods of time, making them resistant to cell-cycle–dependent chemotherapeutic agents. In addition, CSC expressed increased adenosine triphosphate–binding cassette proteins known to efflux chemotherapeutic drugs. Indeed, ABCG2, or breast cancer–resistance protein, was initially identified in breast cancers. This molecule is overexpressed in stem cells and has been utilized to purify breast and other stem cells by exclusion of Hoechst dye, generating the so-called side population detected by flow cytometry (44). In addition, enzymes such as ALDH that are highly expressed in stem cells are able to metabolize chemotherapeutic agents such as cyclophosphamide (45).

CSC may also express increased levels of antiapoptotic molecules such as survivin and BCL2-family proteins (46). Current clinical trial designs have largely been based on

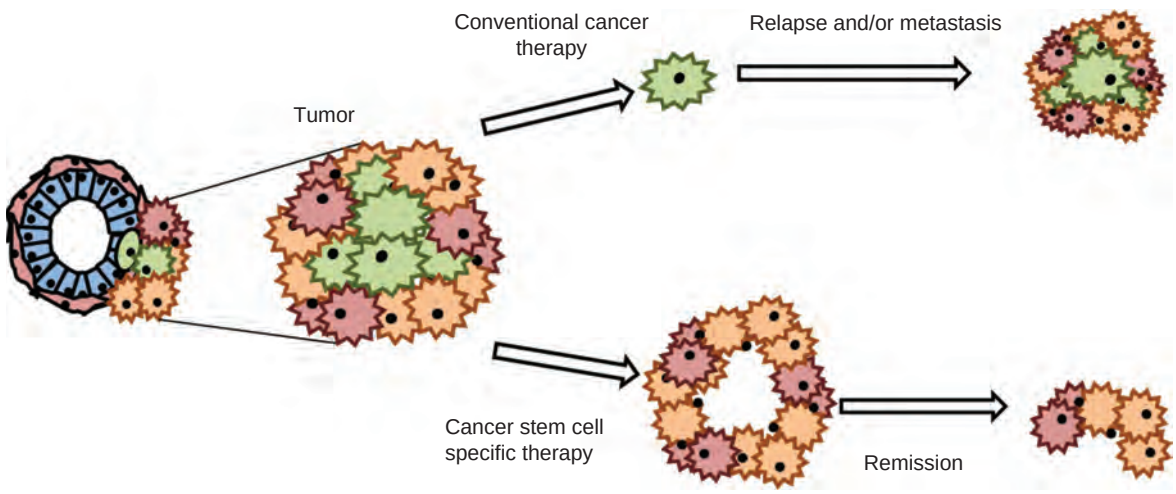

FIGURE 2-3 **Therapeutic implications of breast cancer stem cells.** Current therapies may shrink tumors by killing cells forming the tumor bulk. Because cancer stem cells are less sensitive to these therapies, they remain viable after therapy and re-establish the tumor. In contrast, therapies that target the cancer stem cell population limit tumor growth. Thus, even if cancer stem cell–directed therapies do not shrink tumors initially, they may eventually lead to cures. Furthermore, there is increasing evidence that cancer stem cells may play an important role in mediating tumor metastasis. The development of therapies targeting the cancer stem cell population may provide new opportunities to target metastatic disease.

strategies aimed at producing tumor regression. Indeed, the Response Evaluation Criteria in Solid Tumors (RECIST) criteria measuring tumor response have been utilized to assess the efficacy of new therapeutic agents (47).

However, in breast cancer, as is the case with other malignancies, tumor regression does not correlate well with patient survival (48). In the neoadjuvant setting, only a complete pathologic response correlates with recurrence and survival, whereas partial response does not (49). Together with studies demonstrating resistance of breast CSC to chemotherapy and radiation therapy, these studies suggest that the limitations of present therapies may relate to their inability to target the cancer stem cell component. Recent neoadjuvant studies demonstrating an increase in the proportion of $CD44^+/CD24^-$ breast CSC after chemotherapy suggest that this is the case (50,51). Furthermore, Korkaya et al. (52) have recently found that *ERBB2* overexpression in normal human mammary epithelial cells as well as mammary carcinomas increases the proportion of stem cells as indicated by ALDH1 expression. The clinical relevance of this was demonstrated in a recent neoadjuvant breast cancer trial. Tumor regression induced by neoadjuvant chemotherapy was associated with an increase in $CD44^+/CD24^-$ cancer stem cells in residual tumors. In contrast, breast cancers with *ERBB2* amplification had an increased proportion of $CD44^+/CD24^-$ cells before treatment that was reduced by administration of the *ERBB2* inhibitor lapatinib (53). Moreover Magnifico and colleagues used several HER2-overexpressing breast cancer cell lines to show an important role for HER2 in maintaining the cancer stem cell population. They show that within each cell line, cells displaying stem cell properties such as sphere formation or increased aldehyde dehydrogenase expression also have increased HER2 expression compared with the bulk cell population. Furthermore, they show that the HER2 inhibitor trastuzumab or the combined HER2 and epidermal growth factor inhibitor lapatinib are able to specifically target this HER2-overexpressing cancer stem cell population (54). Using breast cancer cell lines, mouse xenograft models, and matched human primary and metastatic tissues, Ithimakin et al. (55) show that HER2 is selectively expressed in, and regulates self-renewal of, the cancer stem cell population in estrogen receptor-positive (ER^+), $HER2^-$ luminal breast cancers. Although trastuzumab had no effects on the growth of established luminal breast cancer mouse xenografts, administration after tumor inoculation blocked subsequent tumor growth. HER2 expression is increased in luminal tumors grown in mouse bone xenografts, as well as in bone metastases from patients with breast cancer as compared with matched primary tumors. Furthermore, this increase in HER2 protein expression was not due to gene amplification but rather was mediated by receptor activator of NF-κB (RANK)-ligand in the bone microenvironment. These studies suggest that the clinical efficacy of adjuvant trastuzumab may relate to the ability of this agent to target the CSC population in a process that does not require HER2 gene amplification.

The clinical efficiency of *ERBB2* inhibitors provides evidence for the effectiveness of agents capable of targeting breast cancer stem cells. In addition, elucidation of other pathways that regulate breast cancer stem cells, such as Notch and Hedgehog may provide new targets for therapeutic development.

NOTCH PATHWAY

In mammals, there are four Notch receptors (Notch1 to Notch4), which interact with surface bound or secreted ligands (Delta-like 1, Delta-like 3, Delta-like 4, Jagged 1 and Jagged 2). Upon ligand binding, Notch receptors are activated by serial cleavage events involving members of the ADAM protease family followed by intramembranous cleavage regulated by γ-secretase (presenilin). Following proteolytic cleavage, the intracellular domain of Notch translocates to the nucleus to act on downstream targets such as the Hes and Hey transcription factors. Evidence for the role of Notch signaling in mammary development has been provided by transgenic models. The Notch pathway has been shown to play an important role in mammary carcinogenesis. Stimulation of Notch signaling resulted in a 10-fold increase in the number of secondary mammospheres obtained after dissociation of the primary spheres and Notch activation acts as a regulator of asymmetric cell fate decisions by promoting mammary self-renewal (56). Since γ-secretase is necessary for Notch processing γ-secretase inhibitors are able to inhibit Notch signaling. These results suggest that Notch is required for CSC expansion. Another study demonstrated different targeted subpopulations for Notch1 and Notch4 (57). Notch4 inhibition in $EpCAM^+/CD44^+/CD24^{lo}$ subpopulation decreased sphere formation efficiency *in vitro* and abrogated tumor formation *in vivo*, while down regulation of Notch1 resulted in decreased tumor growth and rate. These data suggest a role of Notch4 in CSC maintenance and initiation, and a role of Notch1 in tumor proliferation. A relationship between Notch and HER2 signaling has been suggested by the demonstration that the HER2 promoter contains Notch-binding sequences. In addition, tumor cells derived from HER2 transgenic mice cultured *in vitro* in the presence of a γ-secretase inhibitor form spheres at lower efficiency compared to untreated cells (58). These studies show important interactions between the Notch and HER2 pathways, both of which are involved in the regulation of cancer stem cells. As in the previously discussed studies, it was shown that lapatinib was able to reduce the cancer stem cell population following neoadjuvant chemotherapy. In metastatic disease, the clinical end points of tumor regression or time to tumor progression may reflect changes in bulk cell populations. The efficacy of trastuzumab or lapatinib in this setting may reflect the overexpression of HER2 in both cancer stem cells and bulk cell populations. In contrast, in the adjuvant setting, tumor recurrence may be driven by the cancer stem cell compartment. This compartment in turn may be driven by pathways such as Notch that do not depend on HER2 amplification. This could explain the benefit of HER2 inhibition in the adjuvant setting in patients whose tumors do not display HER2 amplification suggested by retrospective analysis of trastuzumab adjuvant clinical trials. It would be interesting to determine whether these tumors display Notch activation, which has been reported to occur in as many as 40% of human breast cancers (59). In these patients, inhibition of Notch signaling in addition to HER2 blockade represents a rational therapeutic strategy. These concepts may be tested in future trials as γ-secretase inhibitors that inhibit Notch signaling are currently in clinical development (60).

HEDGEHOG PATHWAY

The Hedgehog pathway is critical for many developmental processes. In the absence of Hedgehog, a cell-surface transmembrane protein Patched (PTCH) acts to prevent high expression and activity of a seven membrane spanning receptor Smoothened (SMO). When extracellular Hedgehog is present, it binds to, and inhibits, PTCH, allowing SMO to accumulate and inhibit the proteolytic cleavage of the Ci protein with subsequent activation of nuclear transcription factors including Gli1 and Gli2. In the mammary gland, the

TABLE 2-1

Clinical Trials Targeting Cancer Stem Cells

Tumor Type	*Target*	*Drug*	*Investigator and Institution*
Acute myeloid leukemia	NF-κB	Parthenolide	C. Jordan, University of Rochester
Breast	Notch	γ-secretase inhibitor (GSI)	A. Schott, University of Michigan, J. Chang, Baylor University
Glioblastoma	Chk1/Chk2	Debromohymenialdisine	J. Rich, Duke University
Multiple myeloma	CD20-I^{125}	Bexxar	A. Jakuboviak, University of Michigan
Multiple myeloma	CD20	Rituximab	W. Matsui, Johns Hopkins University
Advanced solid tumors	Notch2/3	OMP-59R5	D. Smith, University of Michigan
Advanced solid tumors	DLL4/Notch		D. Smith, University of Michigan
Metastatic breast cancer	Notch	MK0752	A. Schott, University of Michigan
Head and neck cancer	Hedgehog	IPI-926	A. Jimeno, University of Colorado
Ovarian cancer	NFkB	Metformin	R. Buckanovich, University of Michigan
Breast cancer	CXCR1	Reparixin	A. Schott, University of Michigan

Hedgehog pathway is required for normal development. Alterations in Hedgehog signaling result in defects in both embryonic and postnatal mammary gland development. Utilizing *in vitro* culture systems and NOD/SCID mice, Liu et al. (61) demonstrated that hedgehog signaling mediated by the polycomb gene *BMI1* regulates the self-renewal of both normal and malignant human mammary stem cells. This process is blocked by specific inhibitors such as cyclopamine (11-deoxojervine). This compound has been shown to inhibit tumor growth in several mouse models. In order to reduce cyclopamine toxicity several cyclopamine derivatives such as IPI-96 have been developed, which are currently in Phase I clinical trials.

OTHER PATHWAYS

Other pathways that regulate the self-renewal and fate of cancer stem cells are being elucidated. In addition to pathways such as Wnt, Notch, and Hedgehog, known to regulate self-renewal of normal stem cells, tumor suppressor genes such as PTEN (phosphatase and tensin homolog on chromosome 10) and p53 have also been implicated in the regulation of normal and malignant breast stem cell self-renewal. It is believed that these pathways are deregulated in cancer stem cells, leading to uncontrolled self-renewal of these cells, which may generate tumors that are resistant to conventional therapies. Reduced PTEN expression is found in approximately 40% of $HER2^-$ amplified breast cancers, an alteration associated with trastuzumab resistance (62). PTEN downregulation increases the breast CSC population via Akt activation of the Wnt signaling pathway (63). The Akt inhibitor perifosine was able to partially block this pathway, reducing the CSC population. In a recent study Korkaya et al demonstrate that PTEN deletion in HER2-overexpressing breast cancer cells activates an IL6 mediated inflammatory feedback loop (64). This results in an expanded CSC population displaying an EMT phenotype, a process mediated by both autocrine and paracrine mechanisms, which in turn confer trastuzumab resistance. In addition, the authors demonstrate that interfering with this feedback loop utilizing an IL6 receptor (IL6R) antibody reduces the CSC population and inhibits tumor growth and metastasis.

Studies by Singh and colleagues (65) further our understanding of these pathways by showing interactions between the IL-8/CXCR1/2 axis and HER2 signaling in the regulation of BCSCs. These studies confirm previous work showing independent roles for these pathways in regulating the self-renewal of BCSCs. CXCR1 is a receptor for the cytokine interleukin-8 (IL-8), and it has been shown that recombinant IL-8 increased BCSC self-renewal as determined by the ability of these cells to form tumor spheres as well as by increased ALDH expression (66). Singh and colleagues show the clinical importance of IL-8 by directly measuring IL-8 levels in plural effusions and ascites from 10 patients with metastatic breast cancer. Of interest, they show a clear association between metastatic fluid IL-8 levels and ability of cells isolated from these effusions to generate primary and secondary tumor spheres. Reparixin, a small-molecule inhibitor of CXCR1/2, inhibits BCSC in mouse xenografts (66). On the basis of this, a phase I clinical trial combining reparixin with chemotherapy in women with advanced breast cancers has been initiated. Moreover, the studies of Singh and colleagues suggest that $HER2^-$ blocking agents may synergize with CXCR1/2 inhibitors in targeting the BCSC population. The simultaneous targeting of interacting extrinsic and intrinsic CSC regulatory pathways may result in more efficient elimination of BCSC populations improving patient outcome.

In summary, the cancer stem cell model suggests that it may be necessary to target and eliminate cancer stem cells in order to eradicate cancers. Drugs that interfere with stem cell self-renewal or survival may prove effective in targeting these cell populations. Because normal and tumoral stem cells share many common regulatory pathways, it will be critical to identify agents that have a therapeutic index between normal and cancer stem cells. A number of agents targeting breast cancer stem cell self-renewal pathways are now entering early phase clinical trials (Table 2-1). These trials will provide a direct test of the cancer stem cell hypothesis.

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SECTION II

Diagnosis and Management of Benign Breast Disease

CHAPTER 3

Physical Examination of the Breast

Monica Morrow

CHAPTER CONTENT

Obtaining a careful history is the initial step in a breast examination. Regardless of the presenting complaint, baseline information regarding menstrual status and breast cancer risk factors should be obtained. The basic elements of a breast history are listed in Table 3-1. In premenopausal women, knowing the date of the last menstrual period and the regularity of the cycle is useful in evaluating breast nodularity, pain, and cysts. Postmenopausal women should be questioned about use of hormone replacement therapy, given that many benign breast problems are uncommon after menopause in the absence of exogenous hormones. Specific information about the patient's presenting complaint is then elicited. A breast lump is most often the clinical breast problem that causes women to seek treatment, and remains the most common presentation of breast carcinoma. Haagensen (1) observed that 65% of 2,198 breast cancer cases identified before the use of screening mammography presented as breast masses. Breast pain, a change in the size and shape of the breast, nipple discharge, and changes in the appearance of the skin are infrequent symptoms of carcinoma. The evaluation and management of these conditions are described in Chapters 5, 6, and 7. In general, the duration of symptoms, their persistence over time, and their fluctuation with the menstrual cycle should be assessed.

TECHNIQUE OF BREAST EXAMINATION

A woman must be disrobed from the waist up for a complete breast examination. Although attention to modesty is appropriate, and a gown or drape should be provided, inspection is an important part of the examination, and subtle abnormalities are best appreciated by comparing the appearance of both breasts. Breast examination should be done with the patient in both the sitting and supine positions, and care should be taken at all times to be gentle. The steps of a breast examination are illustrated in Figure 3-1.

The breasts should initially be inspected while the patient is in the sitting position with the arms relaxed (Fig. 3-1A). A comparison of breast size and shape should be made. If a size discrepancy is noted, its chronicity should be determined. Many women's breasts are not identical in size, and the finding of small size discrepancies is rarely a sign of malignancy. Differences in breast size that are of recent onset or progressive in nature, however, may be owing to both benign and malignant tumors, and require further evaluation (Fig. 3-2). Alterations in breast shape, in the absence of previous surgery, are of more concern. Superficially located tumors can cause bulges in the breast contour or retraction of the overlying skin. The skin retraction seen with superficial tumors may be caused by direct extension of tumor or fibrosis. Tumors deep within the substance of the breast that involve the fibrous septa (Cooper's ligaments) can also cause retraction. Retraction is not itself a prognostic factor except when caused by the direct extension of tumor into the skin and, for this reason, it is not a part of the clinical staging of breast cancer (2). Although retraction is often a sign of malignancy, benign lesions of the breast, such as granular cell tumors (3) and fat necrosis (4), also cause retraction. Other benign causes of retraction include surgical biopsy and thrombophlebitis of the thoracoepigastric vein (Mondor's disease) (5) (Fig. 3-3).

The skin of the breasts and the nipples should also be carefully inspected. Edema of the skin of the breast (*peau d'orange*), when present, is usually extensive and readily apparent. Localized edema is frequently most prominent in the lower half of the breast and periareolar region, and is most noticeable when the patient's arms are raised. Although breast edema usually occurs as a result of obstruction of the dermal lymphatics with tumor cells, it can also be caused by extensive axillary lymph node involvement related to metastatic tumor, primary diseases of the axillary nodes, or axillary dissection. Some degree of breast edema is very common after irradiation of the breast and should not be considered abnormal in this circumstance. Erythema is another sign of a pathologic process that is evident on inspection (Fig. 3-4). It may be caused by cellulitis or abscess in the breast, but a diagnosis of inflammatory carcinoma should always be considered. The erythema of inflammatory carcinoma usually involves the entire breast; it is distinguished from the inflammation caused by infection by the absence of breast tenderness and fever. A small percentage of large-breasted women have mild, dependent erythema of the most pendulous portion of the breast, a condition that resolves when they lie down, and that is of no concern.

Examination of the nipples should include inspection for symmetry, retraction, and changes in the character of the skin. The new onset of nipple retraction should be regarded with a high index of suspicion, except when it occurs immediately after cessation of breast-feeding. Ulceration and eczematous changes of the nipple may be the first signs of Paget's disease.

TABLE 3-1

Components of the Medical History of a Breast Problem

All Women
- Age at menarche
- Number of pregnancies
- Number of live births
- Age at first birth
- Family history of breast cancer, including affected relative, age of onset, and presence of bilateral disease
- History of breast biopsies (and histologic diagnosis, if available)

Premenopausal Women
- Date of last menstrual period
- Length and regularity of cycles
- Use of oral contraceptives

Postmenopausal Women
- Date of menopause
- Use of hormone replacement therapy

The initial nipple abnormality may be limited in extent, but, if untreated, it progresses to involve the entire nipple.

After inspection with the arms relaxed, the patient should be asked to raise her arms to allow a more complete inspection of the lower half of the breasts (Fig. 3-5). Inspection is completed with the patient contracting the pectoral muscles by pressing her hands against her hips. This maneuver often highlights subtle areas of retraction that are not readily apparent with the arms relaxed.

The next step in the examination is palpation of the regional nodes. Examination of the axillary and supraclavicular nodes is done optimally with the patient upright. The right axilla is examined with the physician's left hand while the patient's flexed right arm is supported (Fig. 3-1B). This position allows relaxation of the pectoral muscle and access to the axillary space, and is reversed to examine the left axilla. If lymph nodes are palpable, their size and character (soft, firm, tender) should be noted, as well as whether they are single, multiple, or matted together. An assessment of whether the nodes are mobile or fixed should also be made. Based on this information, the physician can assess whether the nodes are clinically suspect. Many women have palpable axillary nodes secondary to hangnails, minor abrasions of the arm, or folliculitis of the axilla, and nodes that are small (<1 cm), soft, and mobile (especially if bilateral) should

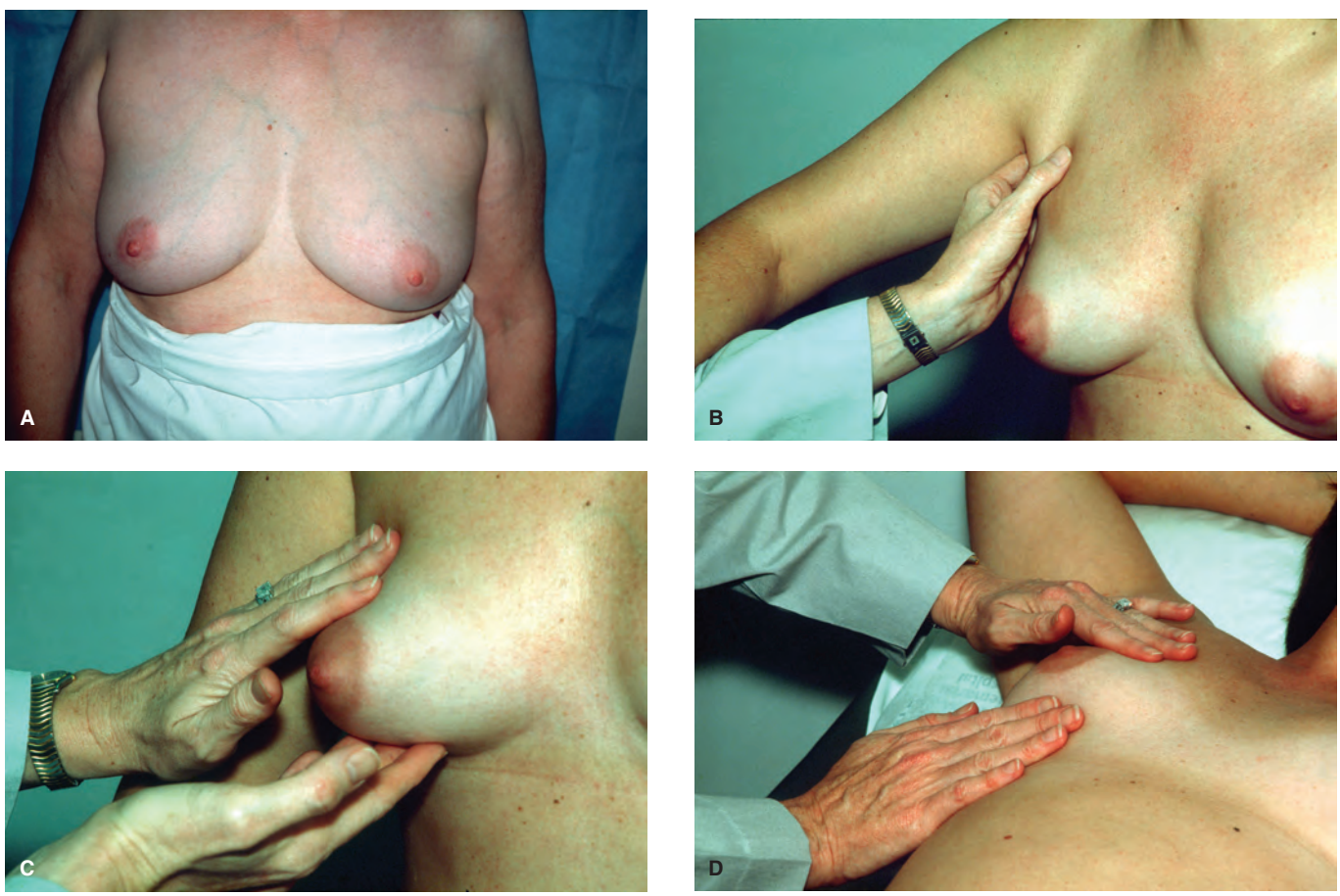

FIGURE 3-1 **Inspection of the patient in the upright position with arms relaxed (A).** Palpation of the axillary nodes **(B)**. The patient's ipsilateral arm is supported to relax the pectoral muscle. Palpation of the breast in the upright position **(C)**. Palpation of the breast in the supine position **(D)**. The breast is stabilized with one hand.

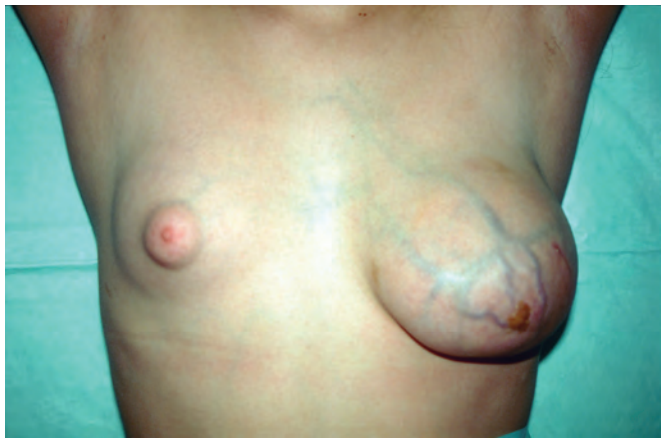

FIGURE 3-2 Marked breast asymmetry owing to a benign breast tumor.

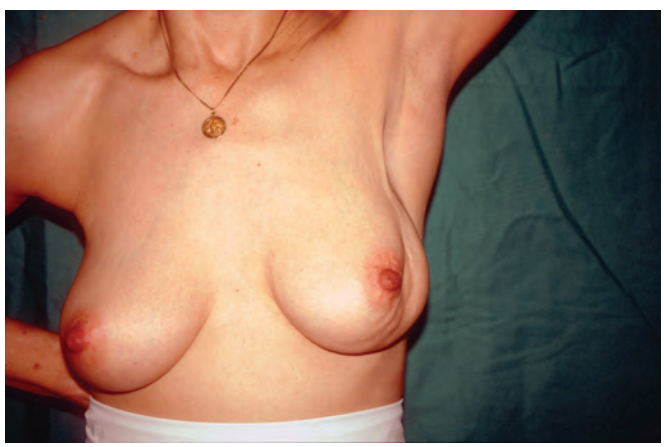

FIGURE 3-3 **Breast retraction caused by thrombophlebitis of the thoracoepigastric vein (Mondor's disease).** Seen is the characteristic pattern of lateral retraction superior to the nipple and crossing to the midline below the nipple.

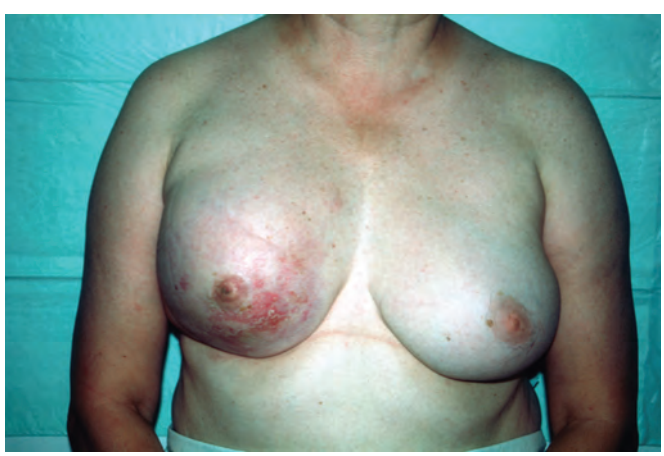

FIGURE 3-4 Signs of locally advanced breast cancer that are apparent on inspection: breast asymmetry, erythema, and eczema owing to dermal involvement with tumor.

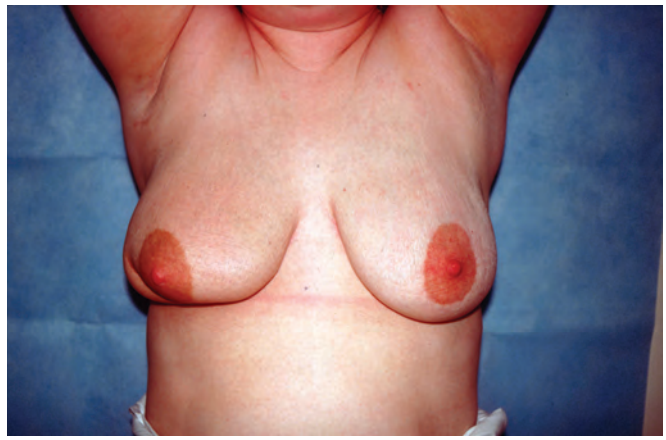

FIGURE 3-5 Retraction in the inferior right breast that is apparent only when the patient's arms are raised.

not be regarded with a high level of suspicion. In contrast, palpable supraclavicular adenopathy is uncommon and is an indication for further evaluation.

After the nodal evaluation is completed, palpation of the breasts should be done with the patient erect. Examination of the breast tissue in this position allows detection of lesions that might be obscured with the patient supine, such as those in the tail of the breast. The breast should be gently supported with one hand while examination is done with the flat portions of the fingers (Fig. 3-1C). Pinching breast tissue between two fingers always results in the perception of a mass and is a common error of inexperienced examiners and women attempting self-examination.

The breast examination is completed with the patient in the supine position and the ipsilateral arm raised above the head (Fig. 3-1D). In patients with extremely large breasts, it may be necessary to place a folded towel or a small pillow beneath the ipsilateral shoulder to elevate the breast, but this is not routinely necessary. The breast tissue is then systematically examined. Whether the examination is done using a radial search pattern or concentric circular pattern is unimportant, provided that the entire breast is examined. The examination should extend superiorly to the clavicle, inferiorly to the lower rib cage, medially to the sternal border, and laterally to the midaxillary line. Examination is done with one hand while the other hand stabilizes the breast. The degree of pressure needed to examine the breast tissue varies, but should not cause the patient discomfort.

One of the most difficult aspects of breast examination results from the nodular, irregular texture of normal breasts in premenopausal women. Normal breasts tend to be most nodular in the upper outer quadrants where the glandular tissue is concentrated, in the inframammary ridge area, and in the subareolar region. The characteristics that distinguish a dominant breast mass include the absence of other abnormalities of a similar character, density that differs from the surrounding breast tissue, and three dimensions. Generalized lumpiness is not a pathologic finding. Comparing the breasts is often helpful in determining whether a questionable area requires further evaluation. If the patient notices a mass that is not evident to the examiner, she should be asked to indicate the area of concern. The location of the perceived abnormality and the character of the breast tissue in the region should be described in the

medical record. If uncertainty remains regarding the significance of an area of nodular breast tissue in a premenopausal woman, a repeat examination at a different time during the menstrual cycle may clarify the issue. If a dominant mass is identified, it should be measured, and its location, mobility, and character should be described in the medical record. The identification of a dominant mass is an indication for further evaluation. The steps in the evaluation of a palpable mass are described in Chapter 5.

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CHAPTER 4

Management of the Palpable Breast Mass

Richard J. Bleicher

CHAPTER CONTENTS

The breast mass is the most common symptom of women presenting to breast centers, accounting for more than half of the complaints. Although most are benign, the presence of a mass can cause considerable anxiety because of the concern for cancer. The most important task of the physician evaluating a breast mass is to exclude the presence of malignancy, and provide an accurate diagnosis.

The presence of a mass should never be dismissed because of young age, male gender, or a lack of risk factors such as a family history of cancer. Diagnostic delays of breast cancer are a common cause for litigation, and such claims are most frequently seen for non-Hispanic white women in their 40s who are premenopausal, married, have a history of fibrocystic change, and who are enrolled in an HMO. Although delays in the diagnosis of a breast cancer may need to be 8 months or longer to be detrimental, no factor should override an expeditious and thorough evaluation, which must provide an explanation that is concordant with the patient's history, physical examination, imaging, and pathologic findings.

HISTORY

A thorough history is the first step in the proper evaluation of any breast mass. Historical elements must, at bare minimum, include a proper breast history which includes current and prior symptoms, risk factors for cancer, and the patient's gynecologic and menstrual history. The etiology of previous masses should be detailed, and specifics about any current and prior breast problems must include the character, frequency, severity, and duration of the issue.

Breast evaluation nearly always includes diagnostic imaging. The complete history must therefore include details about mammograms, ultrasounds, and magnetic resonance imaging (MRI), including the dates, findings, and follow-up for abnormalities on these studies. Although annual mammographic screening is currently recommended for average-risk women aged 40 years and older, many patients are either not aware of this recommendation or choose not to follow it. MRI is also recommended as a screening modality only in women whose lifetime risk is ≥20% to 25% (1), but MRIs are still being used outside this setting.

Other symptoms such as palpable lymph nodes, breast pain, skin changes, nipple inversion, and the character of any discharge (including color, bilaterality, number of ducts involved, and spontaneity) should also be assessed, as these complete the history and may narrow the differential diagnosis. While a complete review of systems is often performed solely to satisfy reimbursement criteria, discussion of other organ systems may contribute substantially to understanding the current illness and to determine a patient's candidacy for certain treatments, especially if a mass is found to be malignant (Table 4-1).

Past medical history may also shed light on current findings, either clarifying an ongoing process, or suggesting something that can recur over a woman's lifetime. Mass-forming lesions are listed in Table 4-2. Certain

TABLE 4-1

Examples of Potential Contributions by the Review of Systems

System	*Contribution*
General	Fever suggests an inflammatory process.
Neurologic	Deficits suggest metastatic disease.
Pulmonary	Cough or compromise clarify operative candidacy.
Cardiac	Compromise may contraindicate operation or anthracycline chemotherapy.
	Inability to lie flat contraindicates whole-breast radiotherapy.
Integument	Nipple changes suggest Paget's disease.
	Breast erythema and edema suggest mastitis, or breast cancer that is locally advanced or inflammatory.
	Symptoms of active collagen vascular disease contraindicate radiotherapy.
Musculoskeletal	Back or bone pain suggest metastatic disease.
	Inability to abduct the arm over the head may contraindicate whole-breast radiotherapy.
Gynecologic	Active menses contraindicate aromatase inhibitor administration.
Hematologic	Frequent ecchymosis and bleeding suggest a need for preoperative evaluation.
	Deep venous thrombosis may contraindicate tamoxifen therapy.

benign entities may present as a recurring mass, such as pseudoangiomatous stromal hyperplasia, fibroadenomas, duct ectasia, mastitis, or abscess formation.

A discussion of past surgical history, including breast surgeries and needle biopsies, often reminds patients to mention prior benign conditions such as fibrocystic change, simple cysts, fibroadenomata, and fat necrosis. Knowledge of a patient's prior breast pathology is important for overall assessment and to help determine their risk of cancer. Often, patients are unfamiliar with specifics of their pathology and simply told that their prior biopsies are "benign," but this lay description may encompass atypical hyperplasia (a lesion requiring further evaluation if recently diagnosed), lobular carcinoma *in situ* (LCIS, a high-risk marker), or other entities that confer elevated risk. Pathology reports and/or slides may be of assistance to complete the evaluation if details are uncertain.

In men, the history should include additional questions about hepatic dysfunction, sexual dysfunction, and current medications to rule out potential causes of gynecomastia which can present as a central breast mass. Clearance of testosterone can be impaired by hepatic dysfunction, resulting in increased peripheral conversion of testosterone to estradiol and estrone, resulting in stimulation and hypertrophy of the breast tissue. Sexual dysfunction may indicate abnormal testosterone levels. Several medications such as H_2 blockers and phenytoin, and drugs such as marijuana have also been associated with gynecomastia. Acute hypertrophy may also be painful, and associated symptoms should therefore be elicited.

TABLE 4-2

Breast Lesions That May Present as a Palpable Abnormality

Abscesses	Idiopathic granulomatous mastitis
Adenopathy	Invasive carcinoma
Amyloidosis	Lactating adenomas
Duct ectasia	Lipomas
Ductal carcinoma *in situ*	Lymphadenopathy
Epidermal inclusion cysts	Mucoceles
Fat necrosis	Pseudoangiomatous stromal hyperplasia
Fibroadenomata	Sarcomas, including phyllodes tumors
Fibrocystic change	Sarcoidosis
Focal fibrosis	Seromas
Galactoceles	Simple and complex cysts
Gynecomastia	
Hamartomas	
Hematomas	

PHYSICAL EXAMINATION

A presenting symptom that is designated as a new breast "mass" can span everything from a barely perceptible thickened region of the breast to a large fungating cancer or severe adenopathy. Physical examination is important prior to any diagnostic imaging so that the study can be chosen and targeted appropriately, and so that the radiologist can best assist in evaluating what has been seen on examination. Normal breast tissue can demonstrate nodularity which is difficult to distinguish from an abnormal process, causing difficulty for patients as well as physicians. One study of 542 patients under 30 years of age referred for a breast mass found that among the 80% of masses detected by self-breast examination, only 53% were true masses, underscoring the difficulties seen in younger women (2). A second study by Morrow and colleagues evaluating 605 patients under 40 years of age also found that only 27% had an identifiable etiology other than fibrocystic change (3). Among masses felt to be true abnormalities on examination by the surgeon, 28% were false positives.

In some cases, the physician will not detect any abnormality on the clinical breast examination even after focusing on the area of concern. In this situation, the patient should be reassured about the absence of worrisome findings and the physician should recheck to ensure that a screening mammogram has been performed within the past year for the average-risk patient who is 40 years of age and older.
In other women, a subtle abnormality that remains ill-defined is detected. Such a lesion, sometimes referred to as a breast "thickening," is one whose extent cannot be clearly defined in three dimensions. These poorly defined areas of prominence may represent a true parenchymal abnormality, or in many cases may reflect the prominence of an underlying rib that elevates the normally nodular breast tissue superficial to it. If there is uncertainty about whether a finding represents a true mass, the clinician should compare it to the mirror-image location in the opposite breast, and if applicable, palpate that region of breast tissue again once it has been moved off the underlying bony prominence. If any level of concern remains, further imaging evaluation is required, and for those physicians whose experience evaluating breast

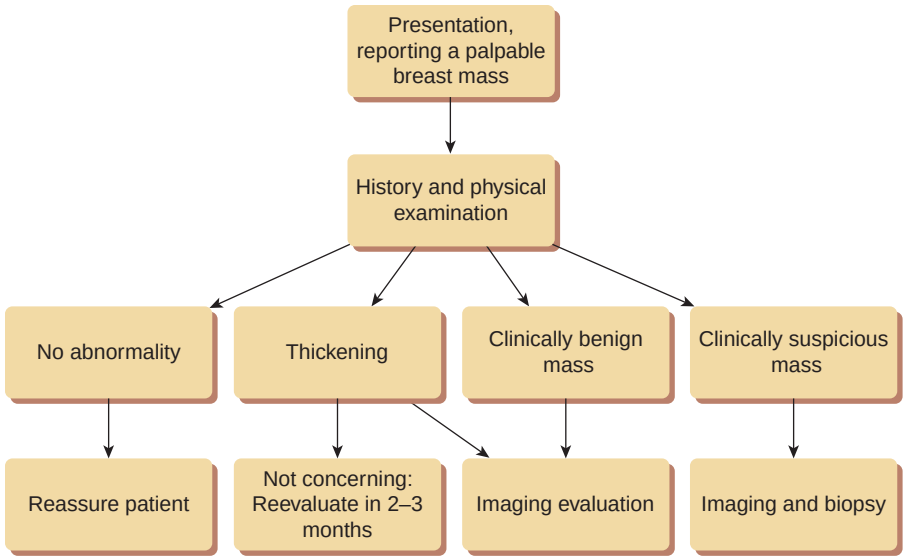

FIGURE 4-1 General schema for initial evaluation of a mass on examination based on its palpable characteristics. On presentation with the complaint of a mass, four findings can occur: (i) No abnormality noted, (ii) a thickening that may be either uncertain or equivocal, (iii) a clinically benign mass, or (iv) a clinically suspicious mass. These characteristics determine the next appropriate step in evaluation. When the characteristics of a thickening are equivocal or uncertain, imaging is indicated.

masses is limited, a follow-up examination in 2 to 3 months after the initial visit is appropriate.

When the examination is complete, the patient can be characterized as having four possible findings: (i) no abnormality present, (ii) a thickening without the characteristics of a dominant mass, (iii) a dominant mass with benign characteristics on palpation, or (iv) a dominant mass with malignant characteristics (Fig. 4-1).

Documentation

The documentation of any findings present on physical examination should be performed consistently and include a description of the superficial appearance of the breasts, including the skin, nipples, and areolae, as well as whether a mass or retractions can be detected by observation alone, or with movement. Exanthems, nipple inversion, and the character of any discharge should be noted.

When documenting the characteristics of a mass, detail is of the utmost importance as it assists in the formulation of a differential diagnosis. Many women have diffusely nodular breasts and therefore the size of the mass and its location should be detailed. At minimum, the mass should be described by indicating the breast in question and the quadrant of the mass, although it is helpful to specify more detail whenever possible by utilizing tangents emanating from the nipple as numbers on the clock when facing the patient. The mass is also described by its distance from the nipple along that tangent, such as "a 2-cm left breast mass at the 4:00 position, 6 cm from the nipple." Other characteristics that should be specified include whether its borders are smooth or irregular, details about its consistency (such as being soft, firm, or scirrhous), and whether it is discrete or an indistinct thickening. Characteristics associated with malignancy should also be noted. These include fixation to the chest wall or skin, skin satellite nodules, or edema of the skin (including *peau d'orange*) and ulceration. These characteristics are indicative of cancer and assist in its evaluation and staging.

The Axilla

The location of some masses may be difficult to distinguish between being present in the tail of the breast or the low axilla. Although normal lymph nodes are usually not palpable, small nonsuspicious lymph nodes may be detectable especially in thin individuals, often described as "shotty" nodes (the term originating from and referring to shot or pellets of lead and not "shoddy," as in poor quality). Lymph nodes may vary in size from several millimeters to several centimeters when abnormally enlarged, and tend to be discrete oblong nodules that have greater freedom of movement than breast parenchymal masses unless the nodes are fixed to one another or to the chest wall. These should also be described in detail, paying particular attention to the number of palpable nodes, fixation, laterality, and size.

The Male Breast

In men, there is usually less breast tissue, except in those with gynecomastia. Most of the breast tissue is located behind and concentric to the nipple–areola complex, and gynecomastia is typically described as disc-like or plate-like. Eccentricity in relation to the nipple and areola should be noted as such lesions are more likely to be malignant. Despite the smaller amount of breast tissue, the examination and documentation for the male breast remains similar to the female examination.

RADIOLOGIC EXAMINATION

Mammography

Mammogram remains the standard of care for the evaluation of breast abnormalities, and is necessary even when a mass very clearly seems malignant. When a palpable abnormality is found, a diagnostic mammogram is performed that consists of at least one view in addition to those taken in a screening study. A skin marker is placed over the palpable area of interest, and additional views are taken if deemed appropriate by the radiologist. Mammographic imaging may be sufficient if a suspicious mass is found, corresponding to the area in question. If nothing is seen on mammogram or if the mass appears to be benign, characterization by ultrasound is indicated, as mammograms typically miss approximately 10% to 25% of cancers detectable by physical examination regardless of tumor size (4), and they cannot differentiate solid from cystic abnormalities.

When possible, mammograms should be obtained prior to a biopsy of any mass because of the consequent mammographic changes that may occur. The two exceptions to this are in evaluating the pregnant and very young patient

(covered below). Hann et al. reviewed mammographic results immediately after stereotactic biopsy, and demonstrated that among 113 cases, 76% demonstrated changes due to the core biopsy, with 58 (51%) having a core biopsy–induced hematoma (5). There were 31 (27%) lesions where the visualized lesion size changed, and three cases (3%) where hematoma obscured the ability to see calcifications at the site.

Prior mammograms from outside facilities should be obtained for comparison prior to any intervention. Review of all imaging by all treating physicians is critical for correlation to the palpable abnormality. If a breast cancer is diagnosed histologically without the use of bilateral imaging, the clinician should ensure that a bilateral mammogram has been obtained within the past 6 months to rule out evident multicentric or contralateral disease requiring simultaneous intervention, even if no other palpable findings are present on examination.

The inability to see a palpable mass on mammogram should prompt an ultrasound, but the inability to see the lesion on either set of imaging does not mean that the lesion should be disregarded. If the lesion is discrete, biopsy should be performed. MRI is sometimes performed as an additional step to evaluate a mass that is mammographically occult, although MRI adds little because it is a poor substitute for the required pathologic diagnosis due to its lack of specificity. A palpable mass not seen on mammogram or ultrasound should undergo needle biopsy as the next step.

Mammography in Men

Although mammography in men may confirm that a mass is of low clinical suspicion or assist in cases where body habitus makes a patient's physical examination more difficult, it generally adds little to the workup of the palpable breast mass. The physical examination in males is particularly important, largely because of the smaller amount of breast tissue that allows a prominence of male breast cancers on examination and the low prevalence of benign breast masses other than gynecomastia. In a Mayo Clinic study evaluating mammograms performed on men, 196 were performed for breast masses and other symptomatic complaints. Among these, 1 benign-appearing mammogram among 203 missed a cancer (0.5%), but all three cancers in this series presented with a discrete palpable mass, 2 associated with overlying retractions and 1 with interval enlargement and lymphadenopathy (6). In a series of 104 male patients with cancer, Borgen et al. also reported that most patients presented with more than one symptom, including masses in 77, nipple retraction in 18, bloody discharge in 16, skin ulceration in 10, and others with Paget's disease, clinical inflammatory carcinoma, and fixed tumors (7). These series suggest that male cancers usually present with at least one suspicious physical examination finding, and while bilateral mammography may be considered in men once a cancer is suspected or diagnosed to rule out bilaterality, its role and benefit in the routine evaluation of the male breast mass has yet to be defined.

Ultrasound

Ultrasound enables directed characterization of an abnormality, but is not a screening study. Ultrasound is most commonly used to determine whether a breast mass is cystic or solid, and to characterize its appearance. Solid masses may appear benign or malignant, and cystic masses are characterized as simple or complex.

Cyst Evaluation

Cysts are most frequently seen between the ages of 40 and 49 years (8) but account for only 10% of masses in women younger than 40, and 25% of masses in women overall (3). More than half of all women who have cysts develop more one than during their lifetime, which may present synchronously or metachronously. Ultrasound can characterize them as simple, containing a smooth, thin wall that is well circumscribed with few internal echoes, or complex, which is defined as any cyst that doesn't meet these criteria, specifically having a significant solid component, internal echoes or a fluid-debris level, scalloped or irregular borders, and the presence of septations. Ultrasound is 98% to 100% accurate for characterization of benign cysts when strict criteria are utilized (9). Complex cysts have an overall rate of malignancy as low as 0.3%, but complex cystic lesions containing a significant solid component may be malignant in up to 23% of cases and so complex cysts are generally aspirated.

Cysts that appear simple on ultrasound have a negligible risk of cancer, and do not require aspiration unless the patient is symptomatic. In such cases, aspiration is performed to relieve the distension and discomfort and not for fluid evaluation. Complex cysts require aspiration to rule out bloody fluid which is suggestive of malignancy. Benign cyst fluid is typically green, yellow, or brown, and should not be sent for cytology because dead epithelial cells present in that fluid may appear atypical despite the low likelihood of malignancy. One study evaluating 6,747 cysts in 4,105 women with nonbloody aspiration found no cancers (8).

Ultrasound is often the only imaging study required for a clinically benign breast mass found in women younger than 35 years, because of the substantially lower risk of malignancy, and because breast density often precludes mammographic visualization in this age group. Despite this difficulty in younger women, bilateral mammograms remain standard and should still be obtained when breast cancer is diagnosed because of its potential to assess the presence of multicentric or bilateral disease. Digital mammography has demonstrated some benefit over analogue studies in younger women and those with dense breasts (10), but in those who are the most difficult to assess, MRI may be of assistance because it is not affected by breast density.

In the young woman, masses that are benign to palpation may undergo an attempt at aspiration prior to ultrasonographic imaging. Those with nonbloody benign cyst aspirate in whom the aspiration resolves the palpable abnormality may undergo observation. When planning to perform an aspiration, one must be cognizant that a traumatic aspiration can cause a bloody aspirate or potentially a hematoma, leading to further unnecessary workup and making ultrasound assessment more difficult. It is therefore important to attempt blind aspiration only in cases where the lesion is easily accessible by minimal manipulation and few needle passes.

For those in whom the cyst recurs, repeat aspiration is acceptable, although with multiple recurrences, a mammogram (because of the small increase in risk of malignancy) and ultrasound (to further evaluate the cyst) should be considered, and excision is an option primarily reserved for a suspicious lesion or when repeat aspirations are no longer desired by the patient.

Solid Mass Evaluation

The physical examination is important in combination with imaging to assess solid lesions. One of the more common solid abnormalities seen in young women are fibroadenomas (11), but these have also been found in women in their 40s and 50s (12). These masses are typically round or multilobulated, firm or "rubbery," nontender, and freely mobile within the breast parenchyma. The physical examination for diagnosis of the fibroadenoma is helpful, but not definitive, as demonstrated by one study evaluating women

under 35 years of age in whom a clinical diagnosis of a fibroadenoma was made. Although imaging and histologic evaluation in this subset was not specified, in the 77 women where the mass persisted, only 56 (72%) were confirmed histologically to be fibroadenomas by FNA (13).

Combining imaging and physical examination for evaluation of the palpable mass improves cancer detection over imaging alone. van Dam and colleagues found that in their series of 201 patients, ultrasound and mammogram each had respective sensitivities for cancer detection of 78% and 94% and specificities of 94% and 55% (14). When combining ultrasound, mammogram, and physical examination together, sensitivity increased to 97% for cancer detection, but with a decrease in specificity to only 49%. In the Sydney Breast Imaging Accuracy Study in which 240 women with, and 240 age-matched women without cancer were evaluated, ultrasound had a 76% sensitivity for cancer and an 88% specificity. Most notable was the significant sensitivity advantage that ultrasound had over mammography in women aged 45 and younger (85% vs. 72%), suggesting that ultrasound is a critical addition to mammography in the evaluation of breast lesions in young women (15).

Unfortunately, the common and benign fibroadenoma can be difficult to distinguish by imaging from the uncommon and malignant phyllodes tumors. Bode et al. reviewed ultrasonography and core biopsy with subsequent excision performed on 57 fibroadenomas and 12 phyllodes tumors, finding that 42% of the phyllodes tumors were initially felt to be benign on ultrasound, while 46% of the fibroadenomas were indeterminate or suspicious (16). This underscores the need for the triple test (see below), which is standard even when imaging suggests a benign solid mass (Fig. 4-2).

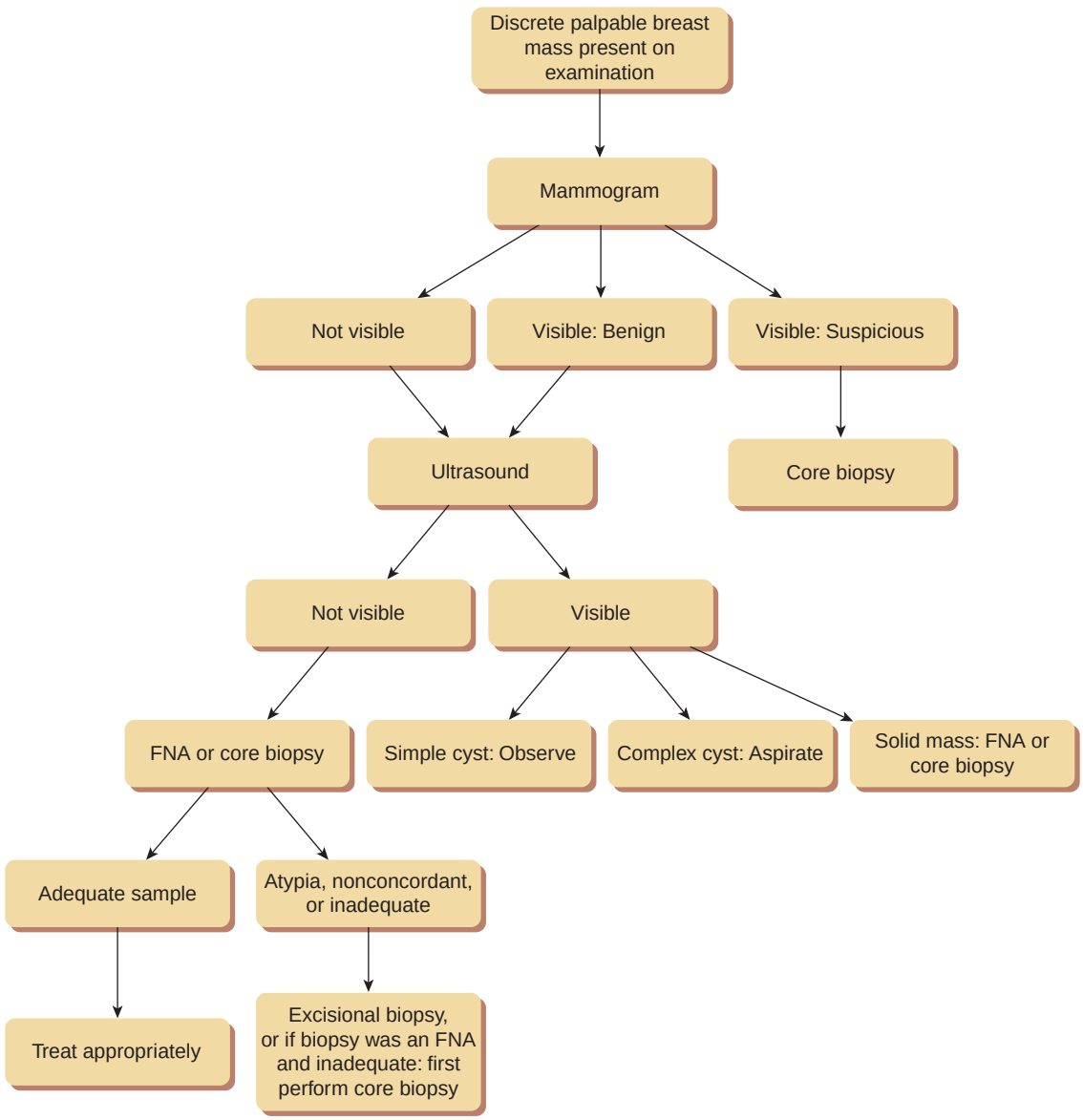

FIGURE 4-2 **Specific schema for evaluation of a discrete mass on examination.** Evaluation workflow, including imaging and tissue diagnosis, based on the presence of a discrete mass on examination. If a mass is found to be clinically suspicious on examination, imaging should still be performed, but in such as case a tissue diagnosis is indicated, regardless of the imaging findings.

Magnetic Resonance Imaging

There are few indications for MRI in the workup of breast masses. MRI is best suited for settings where standard imaging techniques are insufficient, or where a patient's elevated breast cancer risk outweighs the false-positives, costs, and disadvantages of the modality. The absence of a lesion noted on MRI does not negate the presence of a concerning mass on physical examination. MRI has an 85% negative predictive value for cancer in palpable masses containing calcifications, which drops to less than 80% when no calcifications are present. MRI is highly sensitive, but also nonspecific. One study of 1,909 women with a significant familial risk of cancer demonstrated a threefold increase in the number of unnecessary biopsies because of the MRIs performed (17).

PATHOLOGIC EXAMINATION

Triple-Test Evaluation

Masses that are found to be solid on imaging require triple-test evaluation which refers to physical examination, radiologic examination, and needle biopsy performed by core or fine-needle aspiration (FNA). The triple test requires concordance between the three aspects of evaluation and is not confirmatory if a mammogram does not visualize the lesion or if an FNA contains insufficient cells for diagnosis. The latter case mandates core needle biopsy for completion of the triple-test evaluation without surgery.

The triple test is performed even in cases where masses are considered benign on imaging because some malignant lesions can have a benign appearance. In one series of 191 patients, Steinberg et al. found the sensitivity and specificity of triple test to be 95.5% and 100%, respectively (18). In a smaller series of 46 lesions in 43 patients, concordance between the three modalities provided a positive predictive value and specificity of 100%, while nonconcordance dropped the positive predictive value to 64% (19). The triple test also saved an average of $1,412 per case in comparison with open biopsy, demonstrating that it provides accurate diagnostic results and is cost-effective, despite the use of both imaging and pathologic evaluation. In one of the largest series evaluating the combination, benign triple tests in 2,184 patients demonstrated only 7 (0.32%) with carcinoma on follow-up (20).

Postbiopsy Follow-Up

Although the accuracy of the triple test is high, benign concordant results do not obviate further surveillance of a palpable mass. Serial examinations and imaging at 6-month intervals for 1 to 2 years are often recommended to ensure stability, and growth should prompt surgical excision, especially in older women where benign masses are less frequently seen. Even fibroadenomas undergoing needle biopsy should be followed as those that are monoclonal have been reported on very rare occasions to transform into or recur as phyllodes tumors. There is no consensus regarding a threshold for excision when growth of a lesion occurs, although one series noted that 20% growth on ultrasound over 6 months was the 95th percentile in women under 50 and the 90th percentile in those 50 and older (21). They found that all masses excised with slower growth were benign, and recommended that a 6-month growth rate of 20% become the threshold above which excision should be performed. This threshold has not been universally adopted, however, and smaller growth rates may prompt excision as there are no data relating outcome to growth rates of masses initially diagnosed as benign.

The triple test has been found to be the most accurate combination of modalities, but anxiety over a palpable mass remains an indication for surgical excision once the relevant literature and data have been disclosed to the patient. Prior to performing a core biopsy to complete the triple test there should be a discussion with the patient. The triple test implies observation if the biopsy is concordant and benign, and the consent process should clarify that the patient is comfortable with leaving the mass *in situ*.

Fine-Needle Aspiration

FNA involves the use of a handheld syringe and needle to percutaneously aspirate a tumor mass in order to obtain cytology for evaluation. This was first described in detail by Martin and Ellis in 1930, and is most commonly employed for palpable breast lesions that do not require imaging in order to target the lesion. FNA has been established as a variably accurate method of diagnosis and clinicians should consequently perform validation of their own results. In a large meta-analysis of 29 studies comprising 31,340 aspirations, the sensitivity of FNA varied from 65% to 98% and specificity ranged between 34% and 100% (22).

FNA has the advantages of being easily performed with readily available equipment, requiring only a syringe and an appropriately sized needle. Its biggest limitations are that insufficient material may make proper diagnosis difficult, and FNA usually cannot rule out the presence of an invasive component for the uncommon mass that is pure DCIS (ductal carcinoma *in situ;* see below). It also does not capture histologic architecture making subtyping difficult and it is inaccurate for some masses such as hamartomas.

Core Needle Biopsy

Core needle biopsy is associated with slightly greater discomfort and higher cost, but provides more tissue than FNA and provides histologic architecture to better classify pathologic subtype. It is less morbid than excisional biopsy, and even in early series comparing core needle to excisional biopsy, the results were identical in 90% of lesions. In the case of malignancy, the presence of invasion can be more easily assessed with core biopsy than FNA. Westenend and colleagues (23) performed both FNA and core needle biopsy in 286 breast lesions, of which 232 were palpable masses. FNA and core biopsy demonstrated no statistical differences in either sensitivity (92% and 88%, respectively), overall positive predictive value (100% and 99%, respectively), or the number of inadequate specimens (7% for both). The diagnostic differences were present in their specificity, which was higher at 90% for core biopsy (as vs. 82% for FNA), and for the positive predictive value of suspicious lesions (100% vs. 78%), and atypia (80% vs. 18%). In a multi-institutional study by Parker et al., among 1,363 lesions undergoing core and excisional biopsy under image guidance, only 15 (1.1%) false-negative core biopsies occurred, of which 12 were performed using stereotaxis, and 3 using ultrasound guidance (24). Although this study was performed for lesions detected by imaging, it underscores the value of utilizing imaging with core biopsy for those areas of thickening that are equivocal on examination. Core biopsy remains the current standard of care for evaluation of masses of the breast.

Incisional Biopsy

Incisional biopsy is very rarely performed. This method of tissue sampling refers to the intentional surgical excision of only a portion of a mass. Palpable lesions requiring biopsy are typically removed by excising the entire lesion (see below). When a mass cannot be excised *in toto*

(such as a large fungating cancer), a core biopsy or FNA is nearly always the preferred method of diagnosis, thereby avoiding the associated morbidities, including operative and anesthesia risks. Markers such as estrogen and progesterone receptors as well as HER2/neu overexpression can be obtained from core biopsy, also eliminating any need for incisional or excisional biopsy.

Excisional Biopsy

The surgical excision of a lesion in the breast with the intent to remove it entirely is referred to as an excisional biopsy. In 2013, excisional biopsy is no longer the standard of care for the initial diagnosis of palpable breast masses, except where needle biopsy is not feasible for technical reasons, is nonconcordant with imaging or exam, is nondiagnostic, or demonstrates a high-risk lesion such as atypia.

Unfortunately, excisional biopsies are all too often performed without specimen orientation for the pathologist. For those excisional biopsies that demonstrate a malignancy, lack of orientation may necessitate complete reexcision of the entire cavity for even a single positive margin. This results in needless resection of tissue, especially as orientation of excisional biopsy specimens is simple to perform. It is also inadvisable to perform intraoperative frozen section of an excisional biopsy because of the concerns about the accuracy of the analysis (25). Intraoperative assessment of an excised mass has few advantages other than to satisfy immediate physician and patient curiosity, and no change in definitive surgery (such as conversion from breast conservation to mastectomy) should ever be performed based on an initial result and without an in-depth discussion about treatment options. The specific schema for imaging and treatment of a discrete mass is shown in Figure 4-2.

SPECIFIC CLINICAL SETTINGS

The Young Patient

Assessment of the young female patient with a breast mass poses a challenge because of the difficulties in imaging dense breast tissue, because of the greater nodularity seen in those 30 and under whose breasts contain a lower proportion of fat, and because cosmetic and sexuality concerns about treatment tend to be greater in women of younger age. Malignancy is rare in women under 30, but complete evaluation of all masses is still required, including a tissue diagnosis for those masses found to be solid. In a large series of 542 women under 30 who presented with the complaint of a breast mass (2), only 2% of cases were demonstrated to be malignant on biopsy, and among the benign lesions, the most common diagnosis was fibroadenoma, accounting for 72% of cases, with fibrocystic change next in frequency at 8%.

The evaluation and treatment of young women should proceed similarly to older women, although with their increased breast density ultrasound is the primary modality used to characterize a mass. If ultrasound demonstrates that the lesion is solid, core biopsy or FNA is indicated, and if malignancy is found, bilateral mammographic evaluation should then be performed. Likewise, if a lesion that is discrete is not seen on ultrasound, mammographic evaluation may characterize the lesion, but needle biopsy (or excision if not possible) should be performed as with any other age group. In the younger woman in whom a nonsuspicious lesion is less well defined, reexamination within 2 to 3 months at a different point during the menstrual cycle may demonstrate resolution of the lesion, implying fibrocystic change. If any question remains, needle biopsy should be performed, but if the results are felt to be non concordant, excision may be considered.

Care must be taken when excising lesions in younger adolescents. In addition to considering the cosmetic outcome of the scar that will be lifelong for the patient, the central subareolar breast bud can be mistaken for a new breast mass. This subareolar tissue should be spared because this is the origin of the ducts and deposition of fat that becomes the mature breast in the adult. Surgical damage of the breast bud has been reported to cause breast hypoplasia and significant disfigurement.

Young male patients referred for breast masses will predominantly be adolescents found to have gynecomastia. Welch et al. reviewed all male breast patients at a large tertiary pediatric hospital that were referred for ultrasound. The patients were between 1 month and 18 years, and 72% of the 25 patients, between 7 and 18 years of age, were found to have gynecomastia, 13 of which were unilateral and three bilateral but asymmetric (26). In most cases, adolescent male gynecomastia can be observed as it will resolve in adulthood.

The Pregnant Patient

The pregnant patient poses a dilemma when presenting with a breast mass. During pregnancy, the proliferative effect of circulating hormones causes the breasts to become increasingly nodular and engorged, making the physical examination extremely difficult. A nodule found prior to pregnancy or early in its course should be evaluated promptly and not observed. This is because the increasing proliferation of glandular elements and consequent nodularity during pregnancy and lactation can obscure an initial finding. Ultrasound is the imaging modality of choice, as this will determine whether a mass represents a simple cyst, a galactocele, an abscess, or a benign lymph node. The sensitivity of mammography and ultrasound for pregnancy associated breast cancer are 78% and 100%, respectively.

Even with shielding, mammography is incorrectly thought by many to be contraindicated during pregnancy, even by physicians, despite its delivery of only 0.5 mGy to the fetus in comparison to the 1.0 mGy of normal background radiation that the fetus receives over the 9 months of pregnancy. Although MRI is safe, the gadolinium used as the contrast agent is contraindicated, leaving MRI without contrast as an option that is less optimal than ultrasound.

If the mass is solid, needle biopsy should be attempted prior to mammogram since mammography will not provide a definitive diagnosis of a solid mass. Core biopsy in the pregnant patient prior to mammography will also reduce unnecessary fetal irradiation, even though the consequent risk is low. If malignancy is diagnosed, bilateral mammography with fetal shielding is then appropriate.

Core biopsy is the best option for tissue sampling in the pregnant patient. Fine-needle aspiration is more difficult to perform and is associated with a higher risk of false-positives during pregnancy due to the proliferative changes that occur within the breast. Although core biopsy during pregnancy has the added risk of milk fistula, this should not deter or raise the threshold for its use in the evaluation of a palpable mass. In theory, core biopsy should have a lower risk of milk fistula than excisional biopsy, but this has not been proven. Excisional biopsy is not appropriate during pregnancy when core biopsy is an option because of its unnecessary morbidity and cost.

Ductal Carcinoma *In Situ*

As with any malignancy, ductal carcinoma *in situ* (DCIS) can be found in association with a mass, although it most commonly now presents as calcifications on mammogram without abnormal examination findings. Comedo DCIS is generally high grade and more likely to contain invasion which is why it is the only subtype likely to present with a mass, and why it accounted for the majority of DCIS cases detected before mammography was routinely used.

Core needle biopsy is the current standard of care for the diagnosis of breast masses; however, 10% to 20% of lesions diagnosed as DCIS by core needle biopsy are found to be understaged on final excision, demonstrating invasion. Meijnen et al. evaluated 172 DCIS lesions diagnosed by core biopsy, and found that a mass on examination or a mass on imaging were the two most significant independent risk factors for the presence of invasion (27). It remains unclear whether DCIS that presents as a mass in men also has a higher risk of invasion because the series have been too small and too few to make generalizations.

The Patient with a Personal History of Cancer

The patient who has a history of breast cancer has undergone either breast-conserving therapy or mastectomy. In those women who have had BCT, surgical scarring and radiation-induced changes may make evaluation more difficult. Mammography after BCT is less sensitive overall and specifically in the quadrant of the prior surgery, which may explain why 45% of recurrences after BCT can be detected only by palpation. In the patient who has had a mastectomy without reconstruction, abnormal nodularity on examination is most commonly found in the scar or skin and should immediately undergo biopsy, as imaging is likely to add little to the evaluation. In those having had a mastectomy and reconstruction, ultrasound or MRI may assist in characterizing recurrences. Imaging may be of benefit in this setting so that adequate surgical planning can help minimize any risk to the reconstruction.

OTHER MASS-FORMING LESIONS

Hematoma

Hematomas of the breast are most commonly reported as a result of iatrogenic intervention, either in evaluation of a breast lesion or subsequent to its treatment, although spontaneous hematomas have been reported. They have also been rarely reported to identically mimic carcinoma on presentation. Physicians most likely encounter breast hematomas on examination after core biopsy, where it may be difficult to determine whether a lesion is truly palpable or whether a thickening in that location is due to a small amount of bleeding. Core needle biopsy can result in hematoma, and although significant bleeding is uncommon, a malignancy may be obscured in extreme examples (5). Postbiopsy hematoma rates range widely from less than 1% (24) to 51% (5). When any question about a lesion's palpability exists, needle localization should be planned in case the thickened area is solely due to hematoma and resolves by the date of surgery, leaving a nonconcordant mass.

The appropriate management of a hematoma varies with its presentation. A palpable mass may be present with or without ecchymosis, which can sometimes extend laterally to the chest wall, below the inframammary fold and over to the opposite breast. In most cases, observation with use of supportive garments and non-NSAID analgesics is sufficient, although hematomas in the postoperative period require a low threshold for reexploration. Expanding hematomas should be explored and evacuated with the intent to achieve hemostasis.

Seroma

Seromas are localized regions of serous fluid that usually occur after iatrogenic intervention. In some cases, ultrasound may be required to differentiate a seroma from a solid nodule, depending on the degree of distension of the surrounding tissue. The breast contains an extensive lymphatic network, and any operative site may develop a seroma. While these are advantageous at local breast excision sites by maintaining breast contour, large seromas may create a palpable mass. When present after mastectomy, they may impede flap healing by interfering with skin adherence to the chest wall. Finally, a postreconstruction seroma can create a palpable mass that is most easily evaluated with ultrasound.

There are few data on what predisposes women undergoing BCT to develop significant breast seromas. Most investigations have focused on those that develop after axillary dissection, but factors that are known to contribute to seroma formation generally include the use of cautery, the extent of the dissection and amount of disease present, primary tumor size, patient weight, the use of chemotherapy, and the type of surgery performed. Seromas are usually of little consequence and confer few symptoms, but when they become bothersome to the patient they may be ameliorated with a small number of repeated aspirations.

Fat Necrosis

Fat necrosis is a phenomenon that is occasionally seen in the breast due to its high fat content, and is significantly correlated with trauma or surgical intervention. Fat necrosis results from lipase-induced aseptic saponification of adipose tissue that can create mass lesions that are tough to distinguish from carcinoma. Oil or lipid cysts are one manifestation of fat necrosis that can be seen on imaging and are composed of a confined pool of neutral lipid surrounded by a membrane. This pathognomonic finding is not present in all cases, but when evident demonstrates a characteristic lucent center with a water-density rim that may calcify with time. Such a lesion does not require further evaluation, especially with a history of trauma. Unfortunately, many cases of fat necrosis do not present in this fashion and may contain calcifications or fibrosis, which can appear as a spiculated mass and have a scirrhous feel on examination. Such a presentation makes the diagnosis uncertain and necessitates core or excisional biopsy for diagnosis. On diagnosis, no treatment is required.

Hamartomas

Hamartomas, previously known as fibroadenolipomas or lipofibroadenomas because of their components, are benign lesions that are often palpable as a mass and can grow to extremely large sizes, pushing the breast tissue outward as they grow rather than replacing it. Although they have been reported in men, they are most commonly seen in women, and traditionally appear mammographically as a fibrofatty mass, but may have a variable mammographic appearance. Ultrasound appearance is usually solid, but cystic regions may be present in 24% of cases. While most hamartomas have a benign radiographic appearance, biopsy is recommended as with other solid masses to confirm the diagnosis.

Neither FNA nor core biopsy can accurately make the diagnosis of a hamartoma without correlation to imaging findings because of the variety of elements required to make a diagnosis. FNA results, at best, in a diagnosis of a nonspecified benign lesion (28) because the cytologic features overlap with other benign disease. Core biopsy also often yields an insufficient variety of tissue types for a diagnosis, and surgical excision may be required when imaging correlation is not performed in order to reach a definitive diagnosis. Hamartomas have on occasion been seen in association with atypia, as well as *in situ* and invasive malignancies, but correlation to these more concerning pathologic entities has not been found consistently enough to universally recommend surgical excision.

If the diagnosis of hamartoma is entertained on evaluation of a breast mass, mammograms should be obtained and core biopsy attempted, while providing the pathologist with the imaging and clinical findings. Surgical excision may be required for definitive diagnosis, and clear margins should be sought because of the possibility of recurrence. As with any large solid mass, discomfort or anxiety regarding the lesion is an indication for excision, as is enlargement on subsequent follow-up.

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CHAPTER 5

Management of Disorders of the Ductal System and Infections

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CHAPTER CONTENTS

Disorders of the ductal system can present as nipple discharge, nipple inversion, a breast mass, or periareolar infection.

NIPPLE DISCHARGE

Nipple discharge accounts for approximately 5% of referrals to breast clinics. It is a frightening symptom because of the fear of breast cancer. Approximately 95% of women presenting to the hospital with nipple discharge have a benign cause for the discharge. Discharge associated with a significant underlying pathologic process is spontaneous and more likely to be unilateral, arise from a single duct, be persistent (defined as more than twice per week), be troublesome, and be bloodstained or contain blood on testing. One study of 416 women with discharge identified bloody nipple discharge (odds ratio 3.7) and spontaneous discharge (odds ratio 3.2) as significant factors associated with a causative lesion (1).

For this reason, the physician must establish whether the discharge is spontaneous or induced, whether it arises from a single or from multiple ducts, and whether it is from one or both breasts. The characteristics of the discharge also need to be defined: whether it is serous, serosanguineous, bloody, clear, milky, green, or blue-black. The frequency of discharge and the amount of fluid also need to be assessed; this assessment is important for milky discharge, as galactorrhea should be diagnosed only if the milky discharge is spontaneous, copious in amount, and arises from multiple ducts of both breasts.

Investigations

Assessment should include the performance of a complete physical examination (Chapter 4) to identify the presence or absence of a breast mass. During the examination, firm pressure should be applied around the areola as pressure over a dilated duct will often produce the discharge; this is helpful in defining where an incision should be made for any subsequent surgery. The nipple is squeezed with firm digital pressure and, if fluid is expressed, the site and character of the discharge are recorded. Testing the discharge for hemoglobin determines whether blood is present. Bloody discharge increases the risks of cancer being the cause for the discharge with an odds ratio (OR) 2.27, 95% confidence intervals (CI) 1.32–3.89, $p < .001$. In a recent meta-analysis, up to 20% of patients who had a bloodstained discharge or who had a discharge containing moderate or large amounts of blood had an underlying malignancy (2). The absence of blood in nipple discharge is not an absolute indication that the discharge is not related to an underlying malignancy; in one series of 108 patients the sensitivity of hemoccult testing was only 50% (3). If the discharge is serous or colored but spontaneous and persistent, then malignancy still needs to be excluded. Age is said to be an important predictor of malignancy; in one series, 3% of patients younger than 40 years of age, 10% of patients between ages 40 and 60 years, and 32% of patients older than 60 years who presented with nipple discharge as their only symptom were found to have cancer. Cytology of nipple discharge is of little value in determining whether duct excision should be performed. In a recent study of 618 patients who had nipple discharge cytology, the sensitivity and specificity of cytology were 16.7% and 66.1%, respectively. In comparison, the sensitivity for macroscopically bloodstained discharge was 60.6% with a specificity at 53.6% (4). Although some studies have reported better results with cytology, the variability of reported results is such that it cannot be relied on in the routine assessment of nipple discharge.

Two related techniques have emerged: ductal lavage, in which fluid-yielding nipple ducts are cannulated at their

orifices and lavaged with saline while the breast is intermittently massaged (Chapter 20); and ductoscopy, in which discharging or fluid-yielding duct orifices are dilated and intubated with a microendoscope, and the lumen directly visualized. Both techniques have significant potential in terms of allowing repeated sampling of ductal epithelium over time and diagnosing the cause of nipple discharge (5). To learn ductoscopy takes longer than 6 months to overcome technical problems. Fiberoptic ductoscopy applied to 415 patients with nipple discharge was successful in identifying a lesion in 166 patients (40%) (6). Of these 166, 11 were subsequently shown to have ductal carcinoma *in situ* (DCIS); ductoscopy was suspicious in 8, a sensitivity of 73%, with a specificity of 99% and a positive predictive value of 80% (6). DCIS in this series tended to affect more peripheral ducts compared with papillomas. Numerous other small series have evaluated ductoscopy in nipple discharge (7,8). The sensitivity for malignancy in these other series varies from 81% to 100% (8). Ductoscopy appears of particular value for directing duct excision (7) and for detecting deeper lesions that can be missed by blind central duct excision (8). Surgical resection of lesions visualized on ductoscopy is facilitated by transillumination of the skin overlying the lesion. Lesions visualized by ductoscopy can be sampled; in one report, 38 of 46 women with biopsy-proved papillomas were observed for 2 years with no case of missed cancer becoming evident (8). Newer biopsy devices using vacuum assistance are now available for diagnostic assessment and can be ductoscope or sonograph guided.

Ductal lavage increases cell yield approximately 100 times compared with analysis of discharge alone, averaging 5,000 cells per washed duct in one series (6). The sensitivity for cytology obtained by ductal lavage in this series was 64%, with a 100% positive predictive value. Other studies have reported lower sensitivities in the range of 50%, but a high specificity and a high overall accuracy rate (5). Both ductoscopy and ductal lavage remain investigative techniques, and the evidence that they are valuable in the detection of significant breast disease is limited.

Imaging of the ductal tree by ductography or galactography can identify intraductal lesions. Although this investigation has only a 60% sensitivity for malignancy, a filling defect or duct cutoff has a high positive predictive value for the presence of either a papilloma or a carcinoma (9). In one report, ductography-directed excisions were significantly more likely than central duct excisions to identify a specific underlying lesion (10). Ductography in one large study was, however, a poor predictor of underlying pathology and could not exclude malignancy (11). The value of ductography is that like ductoscopy, it can allow identification of the site of any lesion in younger women, allowing localization and excision of the causative lesion while retaining the ability to lactate.

Mammography has a high overall sensitivity for breast cancer, but not all malignant lesions that cause nipple discharge are visible mammographically and most patients with nipple discharge have negative mammograms (Chapter 12). In one series, the sensitivity of mammography for malignancy in patients with nipple discharge was only 57% with a positive predictive value of 16.7% and a negative predictive value of 91.4% (3). Nonetheless, mammography should be performed in women of appropriate age, because if a lesion is visualized it may help establish the cause of the discharge. Ultrasound has a low sensitivity for malignancy in patients with nipple discharge but is a valuable method for localizing intraductal abnormalities, especially papillomatous lesions, in patients with no other clinical or radiologic findings (12). Any lesion visualized can be biopsied by core biopsy or excised using a vacuum-assisted large core biopsy device. (10,13) Patients with a visible lesion on ultrasonography appear significantly more likely to have malignancy than those women with a negative scan (10).

Controversy surrounds the need to excise lesions seen on breast imaging and diagnosed as papillomas on core biopsy. Although it has been traditional to recommend excision of core biopsy–proven papillary lesions, imaging follow-up rather than excision may be safe providing there is imaging–histopathologic correlation and that all atypical and discordant lesions are excised (14). The use of vacuum-assisted biopsy (VAB) to remove papillomas can avoid the need for surgical excision. In large papillomas, magnetic resonance imaging (MRI) may aid assessment of the presence of malignancy, which is more likely if an enhancing rim is seen. The use of MRI to evaluate the ductal tree is gaining interest but should not be part of the standard investigation of nipple discharge. In one series, MRI was performed in 52 patients with nipple discharge and had a positive predictive value of 56% with a negative predictive value of 87% (11) (Chapter 14).

If clinical examination demonstrates a mass lesion or mammography or ultrasonography identifies an abnormality suspicious of malignancy, then core biopsy of the lesion should be performed and the lesion managed appropriately (Section VII: Management of Primary Invasive Breast Cancer). If no abnormality is found on clinical or mammographic examination, patients are treated according to whether the discharge is from a single duct or multiple ducts (Fig. 5-1). Surgery is indicated in cases of spontaneous discharge from a single duct that is confirmed on clinical examination and has one or more of the following characteristics:

- Is bloodstained or contains moderate or large amounts of blood on testing
- Is persistent and stains clothes (occurs on at least two occasions per week)
- Is associated with a mass
- Is a new development in a woman older than 50 years of age, but is not thick or cheesy

Discharge from multiple ducts normally requires surgery only when it causes distressing symptoms, such as persistent staining of clothes. Some breast units adopt an age-related policy: Patients younger than age 30 years who have serous, serosanguineous, or watery discharge are observed, with microdochectomy reserved for cases in which discharge persists at review; patients older than 45 years of age are treated by a formal excision of the major duct system on the affected side; patients between 30 and 45 years of age are deemed suitable for either approach. The current evidence is that total duct excision is more effective than microdochectomy at establishing a specific diagnosis and has a lower chance of missing any underlying malignancy in women more than 40 years of age (15). Today, many units incorporate ductography and ductoscopy into their management protocols, particularly in younger women (Fig. 5-1). The problem is how to treat a patient with nipple discharge in whom imaging, including ductography or ductoscopy and ductal lavage, fails to identify any serious lesion. Some argue that as discharge from malignant disease is more likely to be bloodstained, there is no place for conservative management of bloodstained discharge and that all patients with bloodstained discharge should undergo duct excision unless investigation has identified a specific benign cause (16). Others argue that in selected patients, who have no clinical

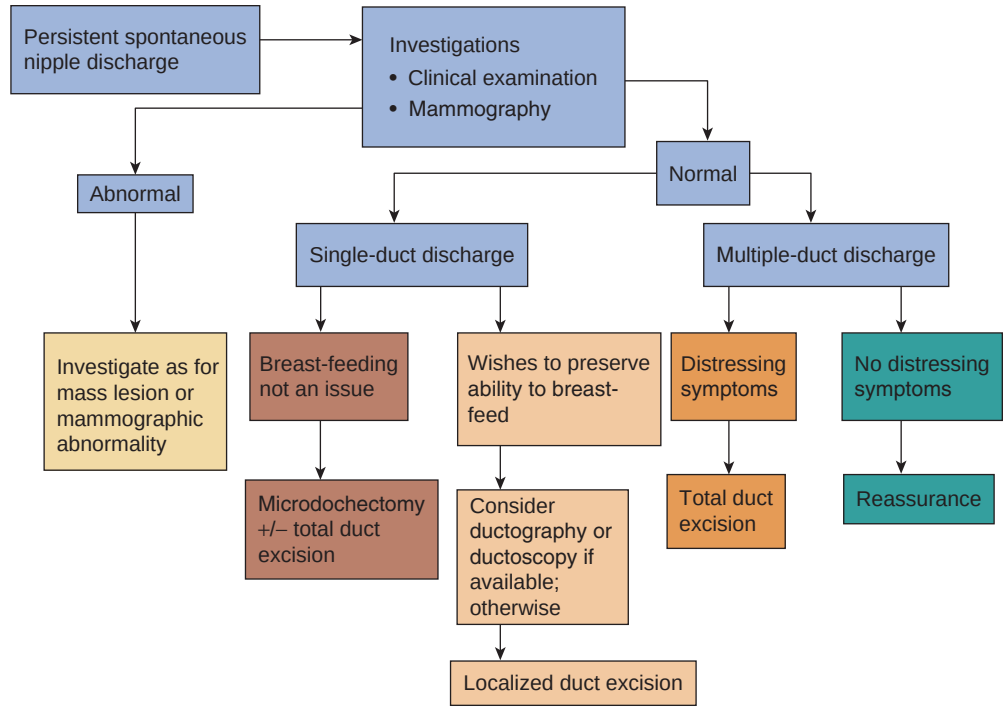

FIGURE 5-1 Investigation of nipple discharge.

or imaging abnormality, short-term observation with repeat evaluation is reasonable (17). A period of observation, particularly in younger women (≤35 years of age), is appropriate if the history of discharge is short but if spontaneous discharge persists (≥2 per week) at review 4 to 6 weeks later and the discharge can be expressed from a single duct on examination, then surgical excision is indicated to establish the cause of the discharge.

Differential Diagnosis of Nipple Discharge

Physiologic Causes

In two-thirds of nonlactating women, a small quantity of fluid can be expressed from the ducts of the nipple if the nipple is cleaned, the breast massaged, and pressure applied. This fluid is physiologic secretion and varies in color from white to yellow to green to brown to blue-black; it is thought to represent apocrine secretion, as the breast is a modified apocrine gland. This physiologic secretion usually emanates from multiple ducts, and the discharge from each duct can vary in color. It is commonly found after pregnancy and is often noticed after a warm bath or after nipple manipulation. The discharge is not usually spontaneous or bloodstained and no specific treatment is required.

Intraductal Papilloma

A true intraductal papilloma develops in one of the major subareolar ducts and is the most common lesion causing a serous or bloody nipple discharge. In approximately half of women with papillomas, the discharge is bloody; in the other half, it is serous (9). Papillomas should be differentiated from papillary hyperplasia, which affects the terminal duct lobular unit and can also cause nipple discharge. Central papillomas consist of epithelium covering arborescent fronds of fibrovascular stroma attached to the wall of the duct by a stalk (Fig. 5-2). The covering epithelium has a two-cell population, with a cuboidal or columnar cell lining covering an underlying layer of myoepithelial cells. A mass may be felt on examination in as many as one-third of cases. Occasionally, the papilloma is so close to the nipple that it can be seen in the orifice of the duct at the nipple. The treatment of choice is microdochectomy. A solitary papilloma is not thought to be a premalignant lesion and is considered by some to be an aberration rather than a true disease process. Papillary lesions can be difficult to characterize on core biopsies.

Multiple Intraductal Papillomas

In approximately 10% of patients with intraductal papillomas, multiple lesions are found; usually, two or three occur, often in the same duct. The term *multiple intraductal papilloma syndrome* is reserved for the rare and distinctive group of patients in whom one duct system contains five or more large and often palpable papillomas with a peripheral distribution. Nipple discharge is less common than in

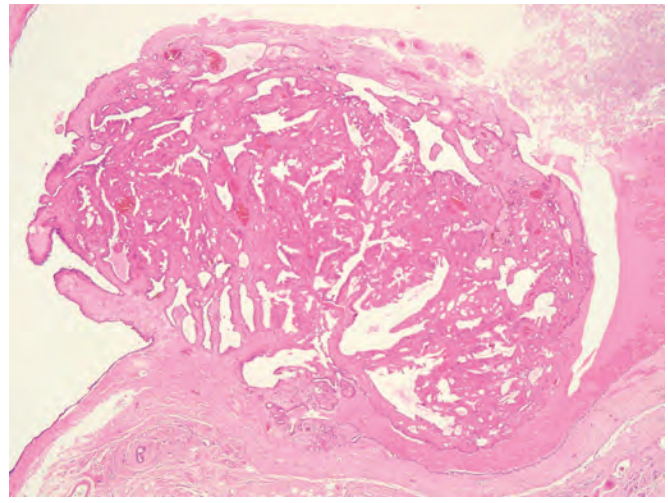

FIGURE 5-2 Histology of duct papilloma.

patients with a solitary intraductal papilloma. In one study, multiple papillomas were reported to be associated with an increased risk of breast cancer, but any increased risk is almost certainly associated with areas of atypical epithelial hyperplasia rather than with the papillomas themselves (18). Repeated excision of papillomas in patients with multiple intraductal papillomas can result in significant breast asymmetry. One option in such patients is to excise such lesions using ultrasound guidance by percutaneous vacuum-assisted biopsy (Fig. 5-3). This provides sufficient material for the pathologist to assess whether lesions are benign and whether atypia is present. Some patients have multiple recurrent peripheral papillomas involving a whole ductal system and in such patients surgery to excise the affected ductal tree should be considered. A segmental excision is often possible with subsequent breast reshaping.

Juvenile Papillomatosis

A rare condition, juvenile papillomatosis, affects women between the ages of 10 and 44 years (19). The common presentation is nipple discharge +/– a discrete mass lesion. In one series of 13 patients, 11 had peripheral and 2 central lesions (19). Three of the 13 presented with nipple discharge; 2 had a palpable peripheral mass lesion, and the remainder had nipple discharge alone. Treatment is by complete excision. Patients with this condition may be at some increased risk of subsequent breast cancer, and close clinical and radiological surveillance of any woman with this condition is indicated.

Carcinoma

An invasive or noninvasive cancer can cause nipple discharge. Only rarely does an invasive cancer cause nipple discharge in the absence of a clinical mass. In most series, DCIS is responsible for up to 10% to 20% of unilateral spontaneous nipple discharges (2). Nipple discharge alone or in association with a mass or Paget's disease is the presenting feature in approximately one-third of symptomatic *in situ* cancers. With the advent of mammography, increasing numbers of noninvasive cancers are being detected and, overall, nipple discharge is the presenting symptom in 7% to 8% of cases of DCIS (Chapter 25). Scant data exist on the frequency with which *in situ* cancers that cause nipple discharge are visible on mammography, but it is recognized that a significant percentage of malignant lesions causing nipple discharge are not visible on mammography. A diagnosis of invasive or noninvasive cancer is often established only by microdochectomy, but this operation is rarely, if ever, therapeutic. Despite a high rate of reported occult nipple–areolar complex involvement (20), a number of studies have demonstrated that breast-conserving surgery with nipple preservation is possible in patients presenting with DCIS or invasive carcinoma who have nipple discharge (21–23). Bauer et al. in 1998 reported that 11 of 43 patients with breast cancer with nipple discharge were successfully treated by breast-conserving surgery. In the study by Cabioglu et al. (20), nipple preserving surgery was successfully performed in one-half of all patients presenting with breast cancer and nipple discharge. There were no local recurrences in those patients who had radiotherapy postoperatively. Concerns about the safety of nipple-preserving breast-conserving surgery in patients with nipple discharge were raised by the retrospective review of Obedian and Haffty (21). Local disease recurrence was noted in 6 of 17 patients with nipple discharge. Patients in this series who underwent central excisions incorporating the nipple had a lower recurrence rate than those patients who had conservation of the nipple–areolar complex. However, this difference did not reach significance. The problem with such retrospective series is that margins were not adequately documented in most patients. It cannot, therefore, be determined whether the high local recurrence rates reported by Obedian were attributable to residual tumor underneath the nipple. Although Cabioglu et al. (21) argue that long-term results obtained from larger series will be required before definitive conclusions can be drawn, they conclude that nipple-preserving breast-conserving surgery can be performed safely providing that negative margins are achieved and appropriate radiotherapy and systemic therapies are administered.

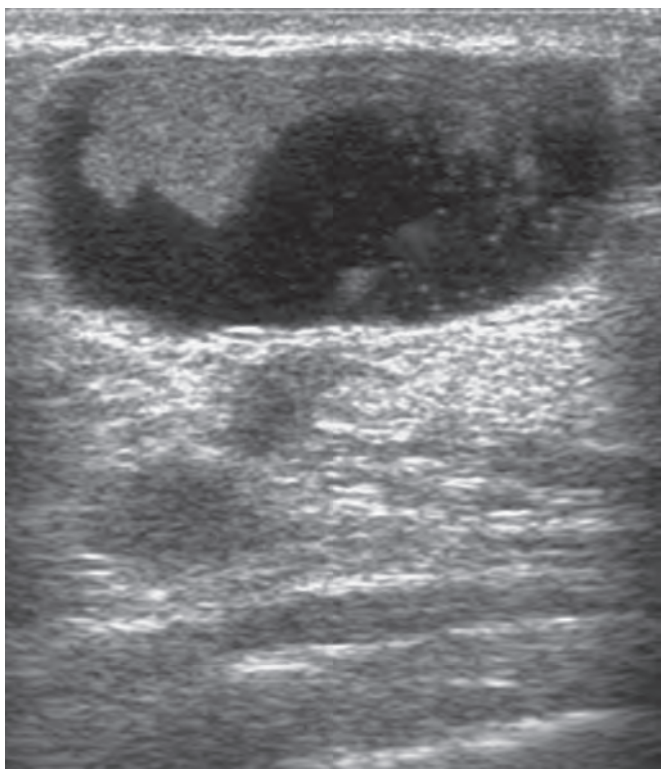

FIGURE 5-3 Ultrasound of an intraduct papilloma characteristic of those seen in multiple papilloma syndrome—such lesions can be excised by mammotomy.

Bloody Nipple Discharge in Pregnancy

Nipple discharge with blood present, either visibly or cytologically, during pregnancy or lactation is common. In 20% of women who experience nipple discharge during pregnancy, blood is evident clinically. The likely cause is hypervascularity of developing breast tissue; it is benign, usually settles quickly, and requires no specific treatment. Only if it persists is investigation required.

Galactorrhea

Galactorrhea is characterized by copious bilateral milky discharge not associated with pregnancy or breast-feeding. Thick, creamy white discharge is not galactorrhea. A careful drug history should be taken because a number of drugs, particularly psychotropic agents, cause hyperprolactinemia. Blood should be taken in patients with galactorrhea to measure prolactin, and if prolactin levels are significantly elevated (≥1,000 mU/L) in the absence of any drug cause, then a search for a pituitary tumor should be instituted. A diagnosis of hyperprolactinemia is suggested

by a history of galactorrhea, amenorrhea, and relative infertility. Galactorrhea disappears after appropriate drug therapy or surgical removal of any pituitary adenoma. Appropriate drug therapy includes administration of cabergoline. Bromocriptine is an alternative, but it is no longer used because it produces significant side effects in up to one-third of patients including, very rarely, strokes (24). For patients with troublesome galactorrhea who are intolerant of medication, bilateral total duct ligation is effective.

Periductal Mastitis and Duct Ectasia

A variety of terms have been applied to the conditions now known as periductal mastitis and duct ectasia. Haagensen first introduced the term *duct ectasia* and considered the condition to be an age-related phenomenon; he believed that breast ducts dilated with age and that stagnant secretions in these dilated ducts leaked into surrounding tissues to cause periductal mastitis. This description of events ignores the findings that periductal inflammation predominates in young women, whereas duct dilatation increases in frequency with advancing age; the sequence of events described by Haagensen is therefore incorrect. If periductal mastitis and duct ectasia are related, then patients with duct ectasia would be expected to have a history of episodes of periductal mastitis. In a study of 186 patients with the clinical syndrome of duct ectasia, only 1 (0.5%) had a history of previous periductal mastitis; in contrast, 97 (70%) of 139 patients with the clinical syndrome of periductal mastitis reported a previous clinical episode of periductal mastitis (25).

Clinical Syndromes

Periductal mastitis is characterized clinically by episodes of periareolar inflammation with or without an associated mass, a periareolar abscess, or a mammary duct fistula. Nipple retraction can be seen early at the site of the affected duct and is often subtle. Nipple discharge can also occur and is often purulent.

The clinical features of duct ectasia include nipple retraction at the site of the shortened duct or ducts and creamy or cheesy, viscous, toothpaste-like nipple discharge. Patients with green discharge from multiple ducts are often diagnosed as having duct ectasia, but most of these have leaking physiologic breast secretion. In one large series, periductal mastitis principally affected women between the ages of 18 and 48 years, whereas most patients who presented with duct ectasia were aged between 42 and 85 years.

Etiology

Aging is an important factor in the cause of duct ectasia. The frequency of the condition increases with age and in one postmortem study, 48% of women aged 60 years or older had pathologic evidence of duct ectasia. Although early studies suggested that the lesions of both periductal mastitis and duct ectasia are sterile, when appropriate transport media are used, bacteria can be isolated from 83% of periareolar inflammatory masses and 100% of nonlactational abscesses and mammary duct fistulae. The organisms isolated are frequently anaerobic. In contrast, in a study of duct ectasia lesions bacteria were identified in only 1 of 11 patients, indicating that these lesions are usually sterile.

An association between smoking and periductal mastitis was first reported in 1988 (26). A subsequent study showed that heavy smokers are more likely to have recurrent infections including abscesses and mammary duct fistulae than light smokers or nonsmokers. Studies with carefully matched cases and controls have shown a significant excess of smokers among patients with clinically diagnosed periductal mastitis, but not in women with clinically diagnosed duct ectasia. How cigarette smoking causes periductal mastitis is unclear. Substances in cigarette smoke may either directly or indirectly damage the wall of subareolar ducts. Accumulation of toxic metabolites—such as lipid peroxidase, epoxides, nicotine, and cotinine—in the breast ducts has been demonstrated to occur in smokers within 15 minutes. Smoking has also been shown to inhibit growth of gram-positive bacteria *in vivo* and *in vitro*, leading to an overgrowth of gram-negative bacteria. This may affect the normal bacterial flora and allow overgrowth of pathogenic aerobic and anaerobic gram-negative bacteria, and would explain the presence of these organisms in the lesions of periductal mastitis. Microvascular changes have also been recorded in smokers and may result in local ischemia (27). The combination of damage caused by toxins, microvascular damage by lipid peroxidases, and altered bacterial flora appears to explain why smokers develop periductal mastitis.

Etiologic data thus suggest that periductal mastitis and duct ectasia are separate conditions with different causes. Duct ectasia appears to be an involutionary phenomenon, whereas periductal mastitis is a disease in which smoking and bacteria are important causal factors.

Other Causes of "Nipple" Discharge

Other diseases of the nipple–areolar complex can present with "nipple" discharge, including nipple adenoma, eczema, Paget's disease, ulcerating carcinoma, and long-standing nipple inversion with maceration. Nipple adenoma is rare, but easy to diagnose (Fig. 5-4). It usually presents with a bloodstained discharge or change in contour or color of the nipple. Occasionally, an ulcer develops. Clinically, there is a nondiscrete mass in the substance of the superficial layer of the nipple. Definitive treatment is complete excision. Eczema or dermatitis can sometimes involve the nipple and is usually caused by irritation from chemicals on clothes or in cosmetics. Eczema can be differentiated from Paget's disease in that eczema affects primarily the areola and only rarely spreads onto the nipple. In contrast, Paget's disease affects the nipple first and only secondarily affects the areola. Treatment for eczema is removal of any aggravating factor, such as perfumed soap or detergents, by the use of hypoallergenic washing materials for clothes and skin, and prescription of topical corticosteroids. Short courses of potent corticosteroids are often more effective at resolving nipple eczema than longer courses of dilute preparations.

Long-standing nipple inversion with maceration is rare but is seen in some elderly people. The injured skin produces a discharge, which can be purulent. Treatment is by careful cleaning of the affected area. Repeated nipple trauma caused by friction from rubbing of clothes on the nipple during jogging and cycling is sometimes sufficiently severe to cause nipple excoriation and bleeding.

NIPPLE INVERSION OR RETRACTION

The terms *inversion* and *retraction* are often used interchangeably, although some call the condition *inversion* only when the whole nipple is pulled in (Fig. 5-5), and use the term *retraction* when part of the nipple is drawn in at the site of a single duct to produce a slit-like appearance (Fig. 5-6). These changes can be congenital or acquired. The acquired causes, in order of frequency, are duct ectasia, periductal mastitis, carcinoma, and tuberculosis.

All patients with acquired nipple inversion or retraction should have a full clinical examination and, if the patient is

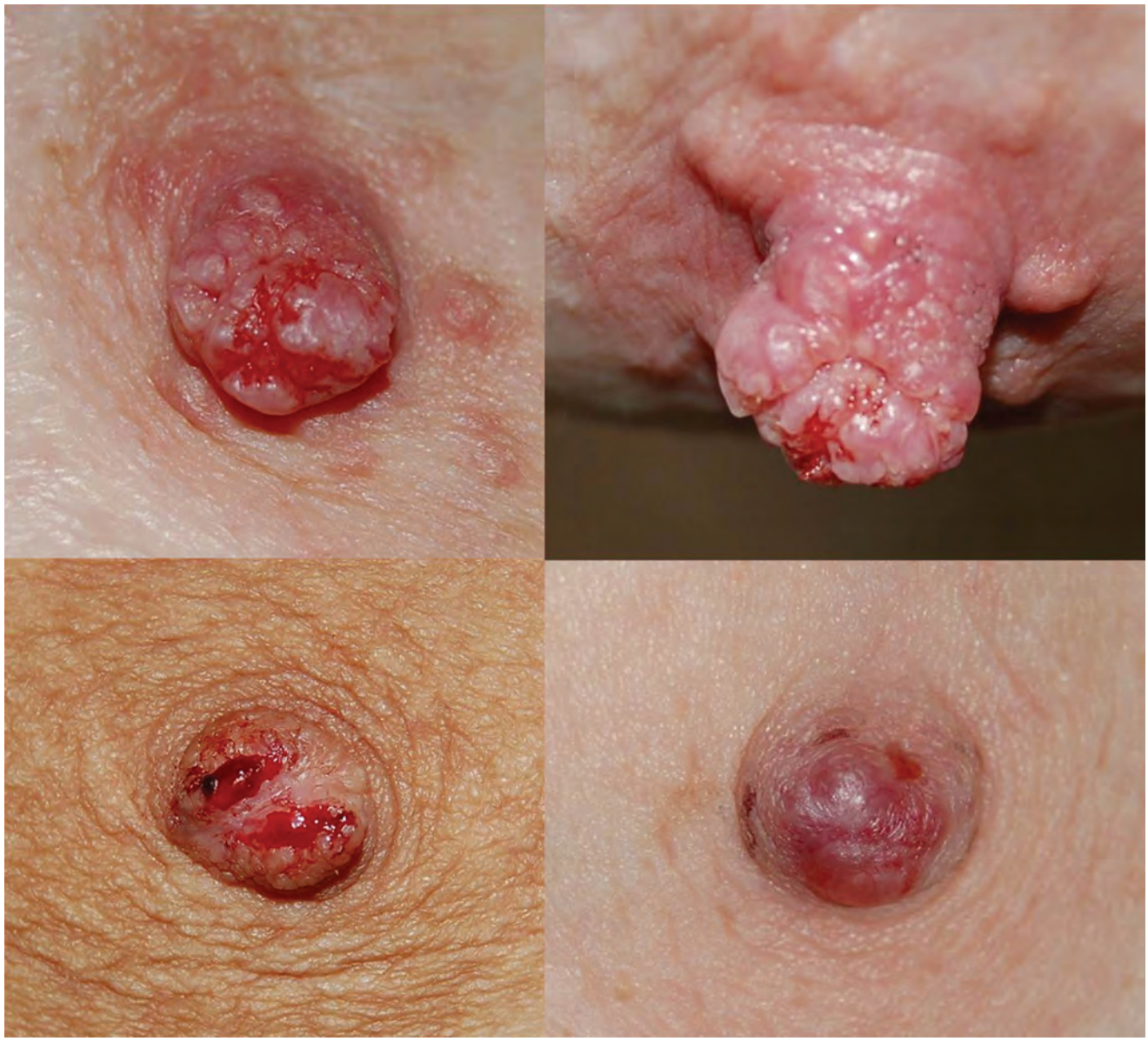

FIGURE 5-4 Nipple adenomas.

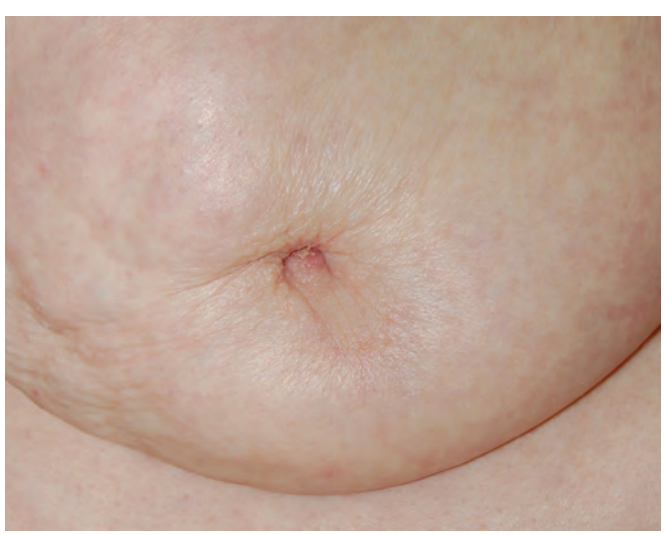

FIGURE 5-5 Nipple inversion from breast cancer.

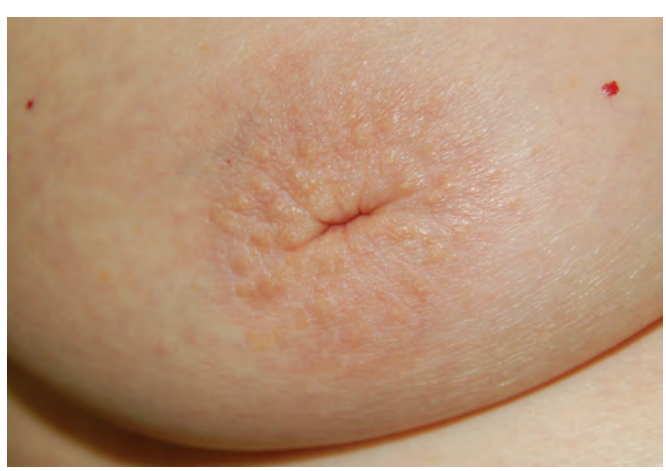

FIGURE 5-6 Slit-like nipple retraction from duct ectasia.

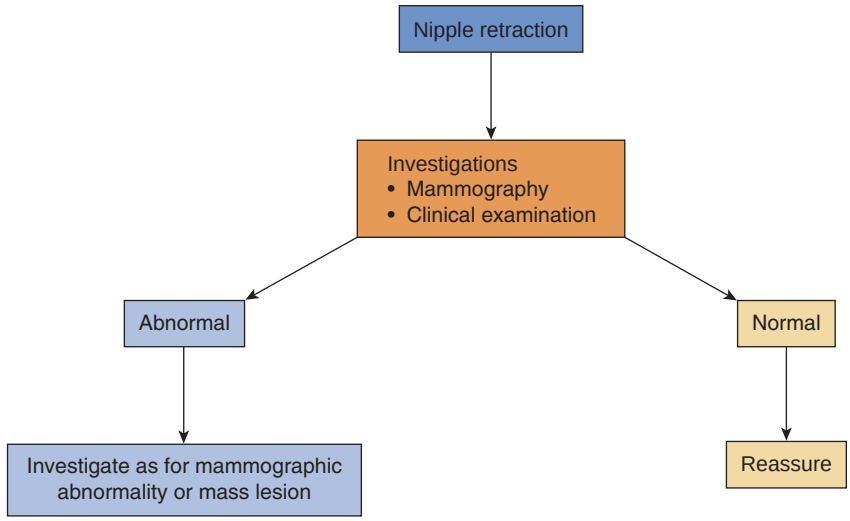

FIGURE 5-7 Management of nipple retraction.

older than 35 years, a mammogram. Management depends on the presence or absence of a clinical or mammographic abnormality (Fig. 5-7). Central, symmetric, transverse slit-like retraction is characteristic of benign disease; nipple inversion occurring in association with either breast cancer or inflammatory breast disease is more likely to involve the whole of the nipple and, in a breast cancer, to be associated with distortion of the areola, which may be evident only when the breast is examined in different positions (Figs. 5-5 and 5-6). Benign nipple retraction requires no specific treatment, but can be corrected surgically if the patient requests it and the surgeon considers the operation appropriate. Division or excision of the underlying breast ducts (total duct division or excision) may be required to evert the nipple; patients should be warned that they will not be able to breast-feed after this procedure and may lose some nipple sensation.

OPERATIONS FOR NIPPLE DISCHARGE OR RETRACTION

Microdochectomy

Microdochectomy is indicated for spontaneous, persistent single-duct discharge and can be performed either through a radial incision across the areola or through a circumareolar incision centered over the discharging duct. A circumareolar incision leaves a better cosmetic scar. The discharging duct is cannulated either with a probe or a blunt-ended needle through which methylene blue can be injected. These various procedures allow the involved duct to be identified under the surface of the nipple. The discharging duct is dissected distally into the breast; a portion of duct over a distance of approximately 5 cm is removed because almost all significant disease affects the proximal 5 cm (9,28). If the remaining duct within the breast appears abnormal and dilated, then the distal duct can be excised or opened and any pathologic lesion in the remaining duct can be visualized and removed. This is an important maneuver because ductoscopy indicates that many significant lesions affect ducts some distance from the nipple. When performing a duct excision directed by ductoscopy, having visualized the abnormality in the duct, transmitted light immediately proximal or at the site of the lesion is used to direct the surgical excision. Once excision has been performed, the nipple should be squeezed gently to ensure that the discharging duct has been removed. Drains are not necessary after this procedure, any significant defect can be closed with mobilization of adjacent breast tissue, and the skin is closed in layers with absorbable sutures. Papillomas visible on ultrasonography can be removed by needle localization or percutaneous vacuum-assisted biopsy.

Total Duct Excision or Division

Total duct excision can be a diagnostic procedure in older patients with nipple discharge and is indicated for multiple troublesome duct discharge or nipple eversion, and as treatment for periductal mastitis and its associated complications. For nipple eversion duct division may be all that is required. Because the lesions of periductal mastitis usually contain organisms (Table 5-1), patients having operations for this condition should receive appropriate perioperative antibiotic treatment. Options for antibiotic therapy include amoxicillin–clavulanate or a combination of erythromycin and metronidazole hydrochloride. Some surgeons prefer total duct excision in older women with single-duct discharge who no longer wish to breast-feed. The reasoning is that is it more likely than single-duct excision to obtain a specific diagnosis (15,16) and if there is a condition, such as duct ectasia, that affects all the ducts underneath the nipple, then any further discharge from the other affected ducts will be prevented. A circumareolar incision based at the six o'clock position is used unless a previous scar exists, in which case the same scar is reused. Dissection is performed under the areola down either side of the major ducts. Curved tissue forceps are passed around the ducts, and these are delivered into the wound. The ducts are secured and then divided from the undersurface of the nipple and, if a total duct excision is being performed, a 2- to 5-cm portion of ducts is excised depending on whether the operation is diagnostic or therapeutic.

For patients having cosmetic nipple eversion, the procedure can be performed through a small incision either at the areolar margin or at the base of the nipple and the ducts are divided sufficiently to ensure that the nipple everts. If the operation is being performed for periductal mastitis, the back of the nipple must be cleared of all ducts up to the nipple skin because recurrence can occur when residual diseased ductal tissue is left. In periductal mastitis only 2 to 3 cm of all the ducts need to be removed as the disease affects only the subareolar ducts. If the nipple was inverted before the operation, it is everted either by dividing the fibrous tissue which is keeping the nipple inverted or manually by firm

TABLE 5-1

Organisms Responsible for Different Types of Breast Infection and Appropriate Antibiotics

Type of Infection	*Organism*	*No Penicillin Allergy*	*Penicillin Allergy*
Neonatal	*Staphylococcus aureus* (rarely *Escherichia coli*)	Flucloxacillin (500 mg four times daily)	Erythromycin (500 mg twice daily)
Lactational	*S. aureus* (rarely *S. epidermidis* and streptococci)	Flucloxacillin (500 mg four times daily)	Erythromycin (500 mg twice daily)
Skin associated	*S. aureus* (500 mg four times daily)	Flucloxacillin (500 mg twice daily)	Erythromycin
Nonlactating	*S. aureus*, enterococci, anaerobic streptococci, *Bacteroides* spp.	Co-amoxiclav (375 mg three times daily)	Combination of erythromycin (500 mg twice daily) with metronidazole (200 mg three times daily)

digital pressure to stretch the tissue stopping the nipple from everting; only rarely are sutures required under the nipple to maintain nipple eversion. No drains are placed, and the wound is closed in layers with absorbable sutures. Patients should be warned before surgery that this operation results in significantly reduced nipple sensitivity in up to 40% of women.

BREAST INFECTION

Breast infection presenting to surgeons is much less common clinically now than it was previously because of early use of antibiotics in the community. It is occasionally seen in neonates, but most commonly affects women between the ages of 18 and 50 years. In the adult, breast infection can be considered lactational or nonlactational. Infection can also affect the skin overlying the breast, and occurs either as a primary event or secondary to a lesion in the skin, such as an epidermoid cyst, or a more generalized condition, such as hidradenitis suppurativa. The organisms responsible for different types of breast infection and the most appropriate antibiotics with activity against these organisms are summarized in Table 5-1 (29). The guiding principle in treating breast infection is to give antibiotics as early as possible to stop abscess formation; if the infection or inflammation fails to resolve after one course of antibiotics, then abscess formation or an underlying cancer should be suspected (30).

Mastitis Neonatorum

Continued enlargement of the breast bud in the first week or two of life occurs in approximately 60% of newborns, and these enlarged buds can become infected, most often by *Staphylococcus aureus*, although the responsible organism is sometimes *Escherichia coli*. In the early stage, antibiotics (flucloxacillin) can control infection; however, if a localized collection is evident on ultrasound, incision and drainage, by aspiration or a small stab incision placed as peripherally as possible so as not to damage the breast bud, is effective at producing resolution.

Lactational Infection

Lactational infection is now less common than it used to be. The infection is usually caused by *S. aureus*, but it can also be caused by *S. epidermidis* and *Streptococcus* species. The first stage is often development of a cracked nipple or a skin abrasion due to nipple trauma from breast-feeding that results in both swelling, which compresses the subareolar breast ducts, and a break in the body's defense mechanisms, which increases the number of bacteria on the skin of the breast. Bacteria then gain access to the breast ducts through the macerated nipple and infect the poorly draining segments. Infection is most common in a first pregnancy during the first 6 weeks of breast-feeding but is also seen during weaning. Symptoms include pain, erythema, swelling, tenderness, or systemic signs of infection. Clinically, the breast is swollen, tender, and erythematous; if an abscess is present, a fluctuant mass with overlying shiny, red skin may be present (Fig. 5-8). Axillary lymphadenopathy is not usually a feature. Patients can be toxic with pyrexia, tachycardia, and leukocytosis. Antibiotics given at an early stage usually control the infection and stop abscess formation. Because more than 80% of staphylococci are resistant to penicillin, flucloxacillin or amoxicillin–clavulanate are given, except in patients with a penicillin sensitivity, for whom erythromycin or clarithromycin is usually effective. Tetracycline, ciprofloxacin, and chloramphenicol should not be used to treat infection in breast-feeding women because they enter breast milk and may harm the child. Patients whose condition does not improve rapidly on appropriate antibiotic therapy require hospital referral and assessment with ultrasonography to determine whether pus is present and to exclude an underlying neoplasm (Fig. 5-9).

Inflammatory cancers can be difficult to differentiate from abscesses. If an abscess is evident on ultrasonography and the overlying skin is not thinned or necrotic, the abscess can be aspirated to dryness following injection of local anesthesia into the skin and the breast tissue and the cavity irrigated with local anesthetic to minimize pain and to dilute thick pus. The abscess should be irrigated until all the pus is evacuated and the fluid aspirated is clear. A combination of repeated aspiration and oral antibiotics is usually effective at resolving local abscess formation and is the current treatment of choice for most breast abscesses (29,30). Aspiration should be repeated every 2 to 3 days until no further pus is obtained. Characteristically, the fluid aspirated changes over a few days from pus to serous fluid and then to milk. If the skin overlying the abscess is thinned and pus is visible superficially on ultrasonography, then after application of local anesthetic cream or infiltration of local anesthetic into the overlying skin, a small incision (mini-incision) is made over the point of maximal fluctuation, and the pus is drained (29). The cavity is then irrigated with local anesthetic solution, which produces some pain relief. Irrigation is continued every few days until the incision site closes. If the skin overlying the abscess is clearly necrotic, the necrotic skin can be excised to allow the pus to drain.

Few lactational abscesses require drainage under general anesthesia. The placement of drains and packing of

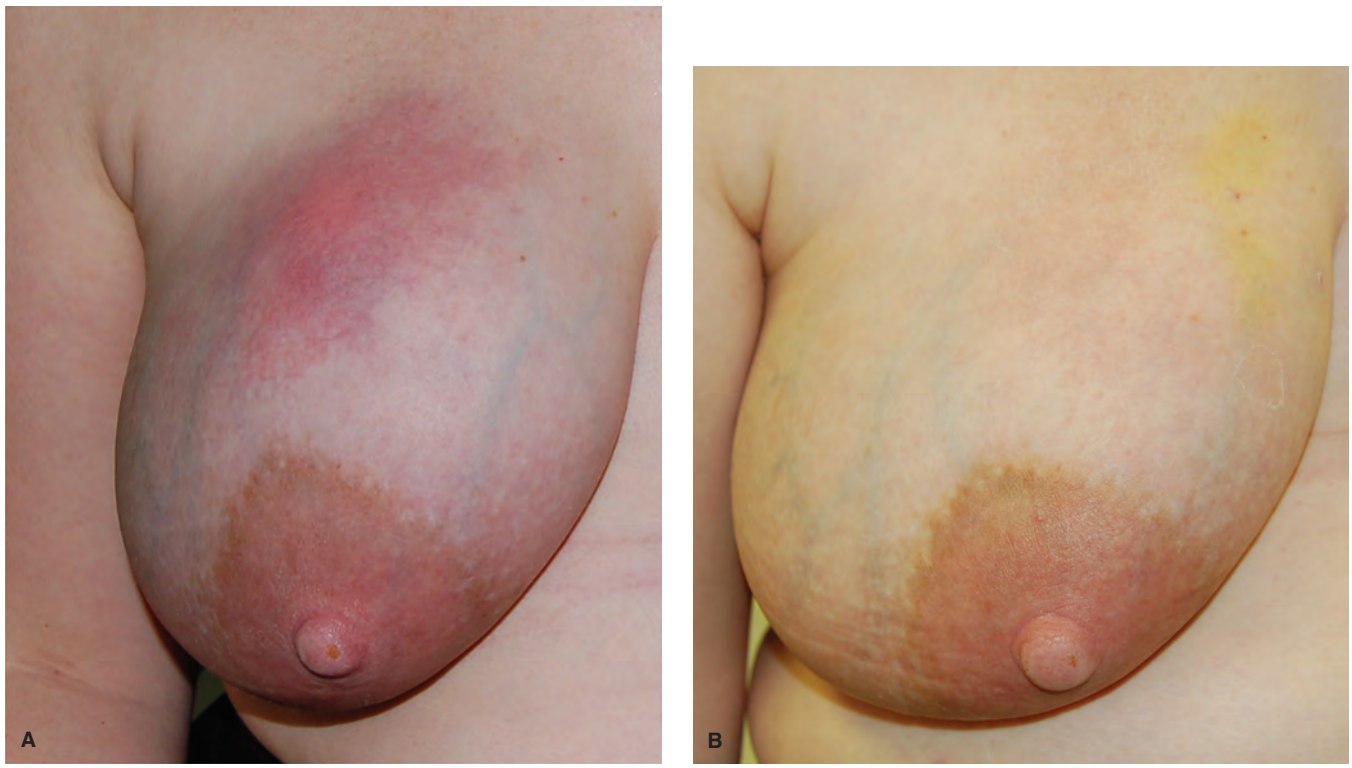

FIGURE 5-8 **(A)** Lactational breast infection: large abscess was present on ultrasound which was treated by aspiration with rapid resolution **(B)**.

the wound are unnecessary. Breast-feeding should be continued if possible because this promotes drainage of the engorged segment and helps resolve infection. The infant is not harmed by bacteria in the milk, nor by flucloxacillin, amoxicillin–clavulanate, or erythromycin. Patients who have incision and drainage of their breast abscesses performed under general anesthesia are more likely to stop breast-feeding compared with those treated by mini-incision or aspiration and antibiotic therapy. Only rarely in women with severe and extensive breast infection is it necessary to suppress lactation with cabergoline. Rarely in patients treated with multiple courses of antibiotics a walled-off abscess develops known as an antibioma. Previously these were excised. This is unnecessary and they are aspirated or drained through a small incision until no more pus is present and they resolve, although it can be many months before the mass resolves and the breast feels normal.

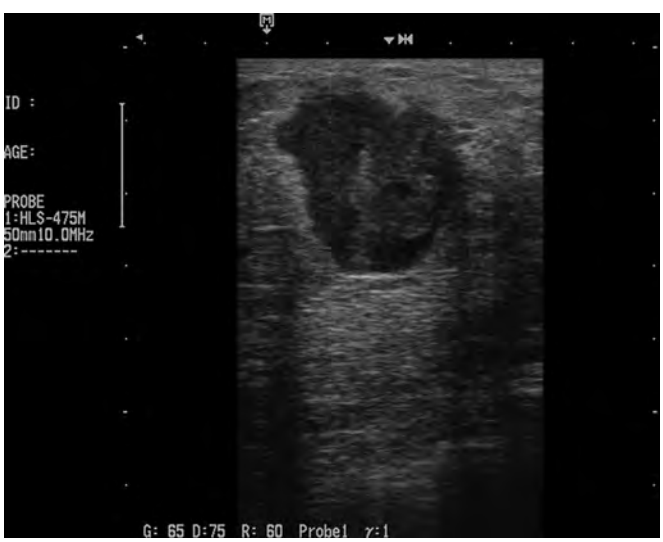

FIGURE 5-9 Ultrasound of an abscess.

Nonlactational Infection

Nonlactational infections can be divided into those occurring centrally in the breast in the periareolar region and those affecting peripheral breast tissue.

Periareolar Infection

Periareolar infection is most commonly seen in young women; the mean age of occurrence is 32 years, and most are cigarette smokers. The underlying pathologic process is periductal mastitis (29,31). It can present as periareolar inflammation, with or without a mass, a periareolar abscess, or a mammary duct fistula. A patient presenting with periareolar inflammation without a mass should be treated with antibiotics that are active against both the aerobic and anaerobic bacteria seen in these lesions (Table 5-1). If the infection does not resolve after one course of antibiotics, ultrasonography should be performed to determine whether a localized abscess is present. A patient who presents with or develops an abscess should be treated by recurrent aspiration and oral antibiotics or incision and drainage under local anesthesia (Fig. 5-10). After resolution of the infective episode, patients older than age 35 years should have mammography performed, because very rarely infection can develop in association with comedo necrosis in an area of ductal carcinoma *in situ*. Up to half of patients with periareolar sepsis experience recurrent episodes of infection; the only effective long-term treatment for these women is

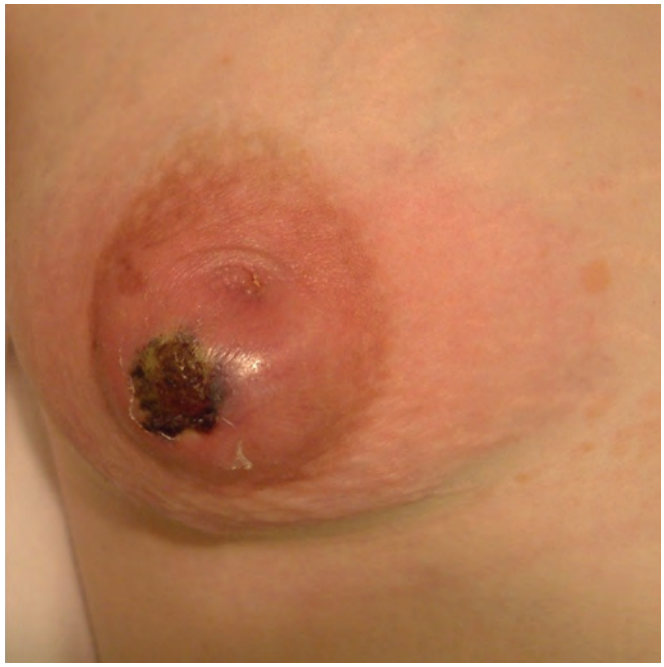

FIGURE 5-10 Periareolar abscess with skin necrosis: the abscess can be drained by excision of the necrotic skin.

removal of all the affected ducts by total duct excision. This operation to remove all the subareolar ducts up to the nipple skin is usually curative. Rarely subareolar abscesses can be caused by actinomyces species; these resolve following incision and drainage (32).

Mammary Duct Fistula

A mammary duct fistula is a communication between the skin, usually in the periareolar region, and a major subareolar breast duct (29) (Fig. 5-11). Fistulae occur most commonly after incision and drainage of nonlactational breast abscesses, although they can occur following spontaneous discharge of a periareolar inflammatory mass or after biopsy of an area of periductal mastitis. Patients usually have preceding episodes of recurrent abscess formation and report purulent discharge through the fistula opening. Occasionally, more than one external opening is present usually at the areolar margin, either from a single affected duct or from multiple diseased ducts.

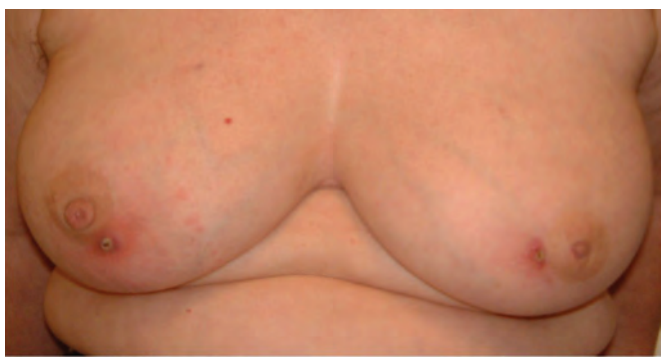

FIGURE 5-11 **Mammary duct fistula.** Bilateral mammary duct fistula. On each side the fistula is discharging in the periareolar region. The affected duct is pulled toward the fistula.

Treatment is surgical, and consists either of opening up the fistula tract and leaving it to granulate (33) or excising the fistula and affected duct or ducts (a total duct excision is also usually required) and closing the wound primarily under appropriate antibiotic cover. The incision to excise the fistula can be radial directly over the fistula tract or circumareolar incorporating the fistula opening. The latter incision produces a superior cosmetic outcome.

Peripheral Nonlactational Breast Abscess

Peripheral nonlactational breast abscesses are less common than periareolar abscesses and have been reported to be associated with a variety of underlying disease states, such as diabetes, rheumatoid arthritis, steroid treatment, and trauma. *S. aureus* is the organism usually responsible, but some abscesses contain anaerobic organisms. Peripheral nonlactational breast abscesses are three times more common in premenopausal women than in menopausal or postmenopausal women and in most no obvious underlying cause is evident; following resolution of infection, mammography is indicated in women older than 35 years to exclude any underlying comedo DCIS. Systemic evidence of malaise and fever is usually absent. Management is the same as for other breast abscesses, with aspiration or incision and drainage (Fig. 5-12).

Skin-Associated Infection

Cellulitis

Cellulitis is an uncommon infection in the breast and can be difficult to distinguish from inflammatory breast cancer or benign erythematous conditions of the breast (Fig. 5-13). Pain is a prominent feature of breast cellulitis associated with erythema, swelling, and warmth. Treatment is with antibiotics (Table 5-1).

Eczema

Patients with eczema involving the skin overlying the breast may develop secondary cellulitis. Appropriate treatments for eczema reduce the likelihood of recurrence.

Epidermoid Cysts

Epidermoid cysts are discrete nodules in the skin that often are referred to as sebaceous cysts, but there is no sebaceous component. These cysts are common within the skin of the breast and can become infected, forming local abscesses that are best treated by mini-incision and drainage rather than aspiration because the material in the abscess is too thick to aspirate.

Hidradenitis Suppurativa

Hidradenitis suppurativa is a condition that affects the apocrine sweat glands and can result in recurrent infection and abscess formation of the skin of the lower half of the breast as well as the axilla (29,32,34–36). It is more common in smokers. Treatment involves keeping the area of skin as clean and dry as possible, draining any abscesses, and stopping smoking. A variety of drug treatments have been tried but are only partially effective. Excision and skin grafting of the affected skin has been tried and has a success rate of up to 50%.

Intertrigo

Intertrigo is inflamed skin in the inframammary folds, often due to moisture and maceration (37) (Fig. 5-14). This can be a recurrent problem in women with large ptotic breasts that make contact with the chest wall. Fungi play

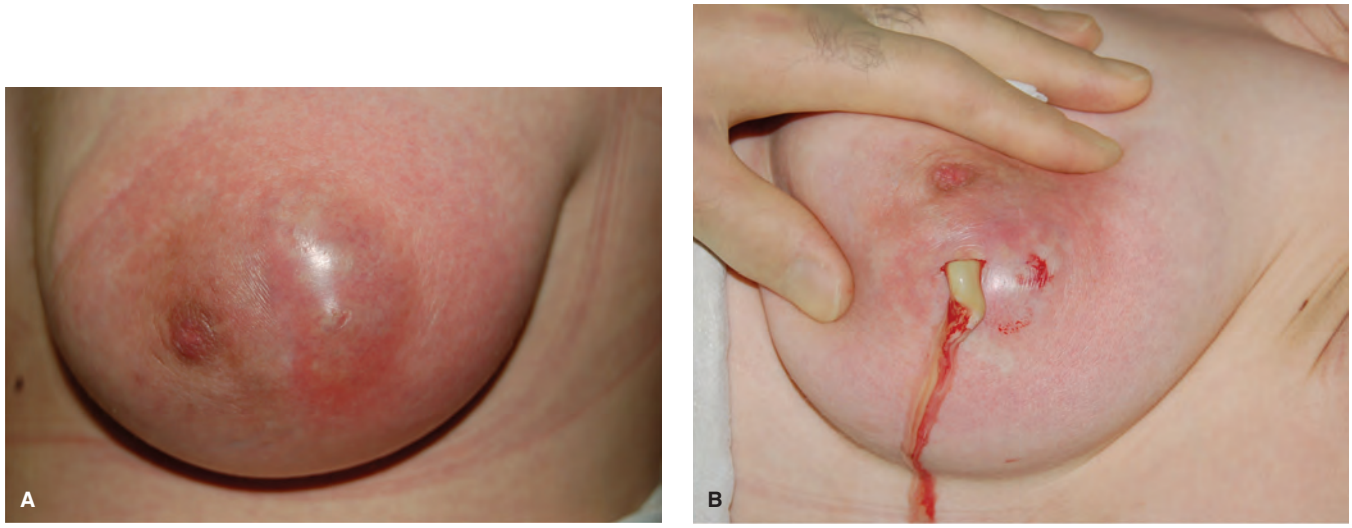

FIGURE 5-12 **(A)** Peripheral abscess: note the shiny thin skin. This abscess was treated by min-incision and drainage with resolution **(B)**.

no aetiological role in this condition. The primary management of intertrigo is to educate the patient about keeping the area as clean and dry as possible. The skin should be washed gently two or more times a day with simple soap, a mild cleansing solution, or hypoallergenic skin wipes, then dabbed dry with a towel or dried with a hair dryer at a low setting (37). Preventive measures include wearing cotton against the skin and keeping the skin dry and clean. Steroids and creams including antifungal agents are not effective; they may aggravate the condition and should be avoided.

Piercing

Nipple rings can result in subareolar breast abscess and recurrent nipple infections, particularly in smokers (38). One study noted that nipple piercing was a significant risk factor for a subareolar breast abscess (OR 10.2 95% CI 1.3–454.4) as is smoking (OR 8.0 95% CI 3.4–19.4) (38).

Pilonidal Sinuses

Pilonidal sinuses affecting the nipple have been reported in hair stylists and sheep shearers because loose hairs penetrate the skin and can result in inflammation and infection (29).

Other Rare Infections

Tuberculosis is rare in Western countries. The breast can be the primary site, but tuberculosis more commonly reaches the breast through lymphatic spread from axillary, mediastinal, or cervical nodes or directly from underlying structures, such as the ribs. Tuberculosis predominantly affects women in the latter part of their childbearing years. An axillary or breast sinus is present in up to 50% of patients. The most common presentation is that of an acute abscess resulting from infection of an area of tuberculosis by pyogenic organisms (29,30). Treatment is with local surgery and antitubercular drug therapy.

Primary actinomycosis (32), syphilis, mycotic, helminthic, and viral infections occasionally affect the breast, but are rare. Actinomycosis organisms can be seen in hidradenitis. *Molluscum contagiosum* can affect the areola and present as wart-like lesions.

Granulomatous Lobular Mastitis

Granulomatous lobular mastitis is characterized by noncaseating granulomata and microabscesses confined to the breast lobule. The condition presents as a firm mass, which is often indistinguishable from breast cancer, or as multiple or recurrent abscesses. Some patients with granulomatous lobular mastitis report that the mass is tender to touch and painful and the overlying skin is sometimes ulcerated (Fig. 5-15). Young women, often within 5 years of pregnancy, are most

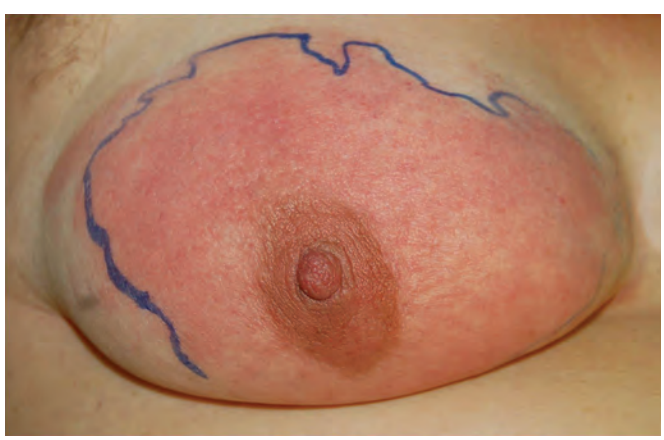

FIGURE 5-13 Cellulitis of the breast.

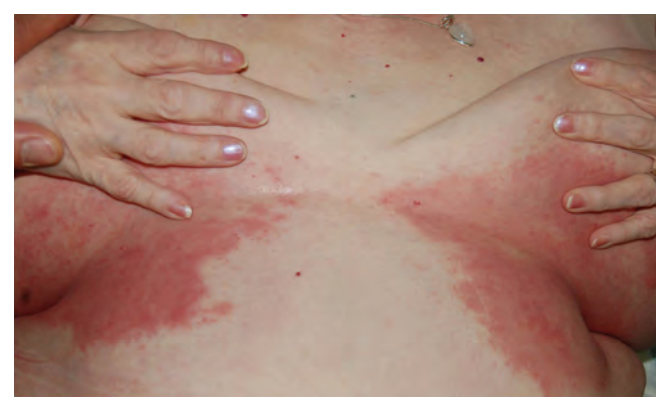

FIGURE 5-14 Intertrigo pre and post.

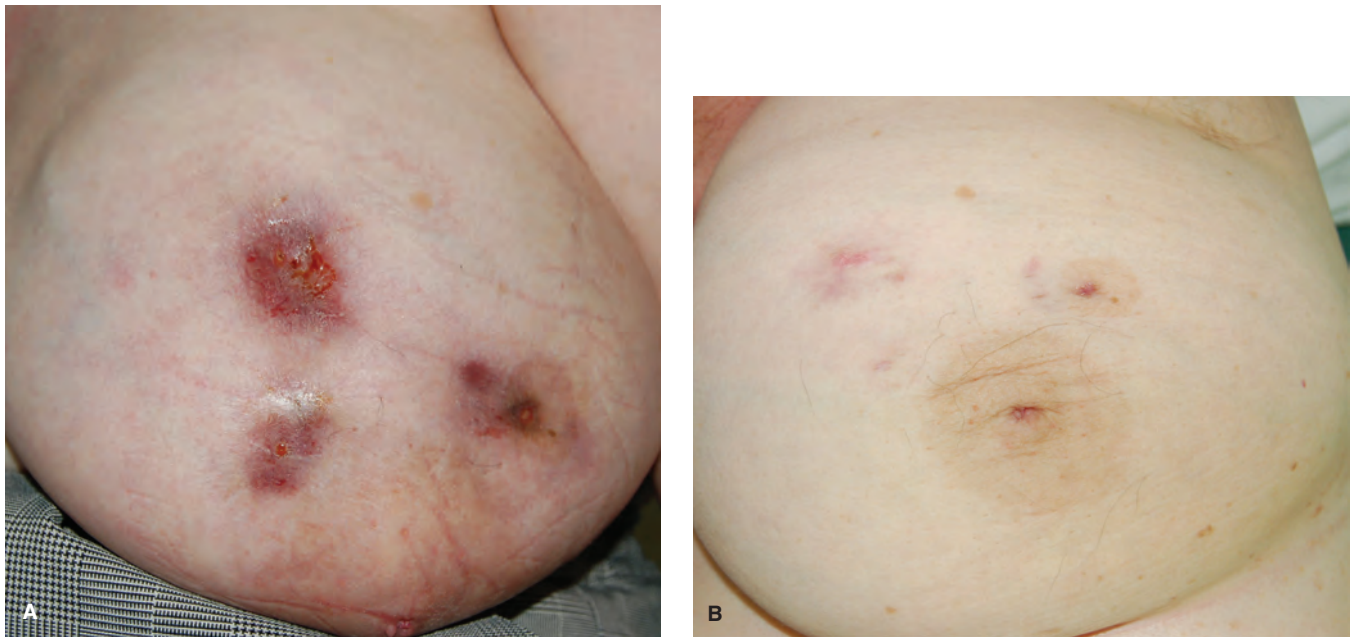

FIGURE 5-15 Granulomatous lobular mastitis at presentation **(A)** and following resolution **(B).**

frequently affected, but not all women with this condition are parous. In contrast to periductal mastitis, it is common in Asian rather than white women and few are smokers. This condition has recently been reported to be associated with hyperprolactinemia (including drug-induced) (39). Prolactin can contribute to a wide variety of physiological and pathological granulomatous cutaneous lesions, and it may do the same in the breast. The frequency of hyperprolactinaemia in women with granulomatosis lobular mastitis is not well documented, so the relevance of this observation is not clear. Rare reported causes of granulomatous mastitis include alpha-1 antitrypsin deficiency and Wegener's granulomatosis. The role of organisms in the etiology of this condition is unclear. One study did isolate corynebacteria from 9 of 12 women with granulomatous lobular mastitis (40). The most common species isolated was the newly described *Corynebacterium kroppenstedtii*, followed by *C. amycolatum* and *C. tuberculostearicum*. These organisms are usually sensitive to penicillin and tetracycline and when antibiotics effective against these organisms have been administered to patients with this condition they do not produce resolution. Any antibiotic treatment should therefore be based on sensitivities as reported by the local bacteriologic service.

A search for the etiology of this condition continues. In patients presenting with a breast mass diagnosed on core biopsy as granulomatous lobular mastitis, excision of the mass should be avoided because it is often followed by persistent wound discharge and failure of the wound to heal. Current treatment involves establishing the diagnosis and observation without any specific treatment because the condition usually resolves slowly over 6 to 12 months. Any abscesses that develop require aspiration or mini-incision and drainage. There is a strong tendency for this condition to recur, but eventually it does resolve spontaneously without treatment (29). Steroids have been tried but without consistent success. More recently, methotrexate as monotherapy given at a dose of 7.5 mg per week, has been claimed to be effective (41). Similar claims were made for steroids. Whether methotrexate alters the course of the condition or merely suppresses the inflammatory component is not clear and given that the condition does resolve spontaneously more studies are required before methotrexate can be considered as an effective therapy for this condition.

Breast Infection after Breast Surgery

Rates of infection after breast surgery vary in relation to the extent of the surgery and risk factors including smoking, obesity, and the presence of diabetes. Rates of infection in excess of 10% are seen after mastectomy (42). Preoperative antibiotics reduce the risk of breast infection by 36% therefore preoperative prophylactic antibiotics in breast surgery patients may be administered routinely. The relative risk of infection if antibiotics are administered in a recent meta-analysis was 0.64, 95% confidence intervals 0.50–0.83, $p < .0005$ (43).

Factitial Disease

Cases of factitious abscess (caused by the patient themselves) are occasionally seen. These patients can have psychiatric problems, but patients appear quite plausible. Factitial disease should be suspected when peripheral abscesses persist or recur despite appropriate treatment. The condition can be difficult to treat because patients are often resistant to help and may be very manipulative.

MANAGEMENT SUMMARY

- Persistent spontaneous nipple discharge accounts for 5% of all symptomatic breast referrals and requires assessment by physical examination and imaging. Surgery is needed for diagnosis in some patients and as many as 20 % will have an underlying malignancy.
- When treating breast infection appropriate antibiotics should be given early to reduce abscess formation. Ultrasound should be performed in patients whose infection does not resolve after a single course of appropriate antibiotics to exclude a breast abscess. Breast abscesses can be treated by repeated aspiration or by incision and drainage.
- Breast cancer should be excluded in patients with an inflammatory lesion that is solid on ultrasound and does not resolve with antibiotics.

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CHAPTER 6

Management of Breast Pain

Robert E. Mansel

CHAPTER CONTENTS

Breast pain is one of the most common problems for which patients consult primary care physicians, gynecologists, and breast specialists. Patients mistakenly think the symptom is associated with early breast cancer, but data do not support any strong relationship with breast pain. The Women's Health Initiative Estrogen plus Progestin intervention trials showed no effect on breast cancer risk in women who took estrogens alone, but a mild effect in those taking equine estrogen plus medroxyprogesterone, particularly if baseline breast tenderness was present (hazard ratio [HR] 2.16), but the effect was much less if no baseline breast tenderness was present (1). Once cancer has been ruled out, reassurance alone will resolve the problem in 86% of those with mild and 52% of those with severe mastalgia (2). A survey of screened women in the UK national program revealed that 69% had experienced severe breast pain, although only 3% had sought treatment. Ader et al. in 2001 attempted to establish the prevalence in the community in the United States. In their study, 874 women between 18 and 44 were recruited for interview by random number dialing in Virginia, and 68% reported some cyclical mastalgia, with 22% describing it as moderate or severe (3). Interestingly, patients on the oral contraceptive pill had less trouble, while there was a positive association with smoking, caffeine intake, and perceived stress. A study from the United States (4) showed the impact of breast pain among a population of 1,171 women attending a general obstetrics and gynaecology clinic. Sixty-nine percent suffered regular discomfort and 36% had consulted about their breast pain. A specialist breast clinic in Ghana reported in 2008 that 72% of women attended because of breast pain. Reading of the literature might suggest that the incidence of breast pain is different in many parts of the world, but these differences are mainly cultural in relation to the willingness of women to consult their physicians about breast pain.

The major clinical issue is to exclude cancer and determine the impact on quality of life in patients complaining of breast pain, as this is the primary reason for medication. Only rarely is intervention required, but, after appropriate patient selection, some may derive great benefit from treatment.

ETIOLOGY

Breast swelling is a frequent event in the late luteal phase of the menstrual cycle. Cyclic mastalgia is a more extreme form of this change, and researchers have sought endocrine abnormalities in those with severe breast pain, particularly measuring estradiol, progesterone, and prolactin, but no major abnormalities have been found (5). One hypothesis suggested that inadequate corpus luteal function is an etiologic factor in women with benign breast disease, but this term has been used to include all nonmalignant breast conditions, blurring the distinction between a variety of benign breast conditions. No evidence of progesterone deficiency has been found during the luteal phase in patients with mastalgia. The confusion in the literature between the symptom of breast pain and the large number of variable pathological descriptions of benign breast conditions has resulted in the belief that the condition is a "disease," rather than physiological responses to menstrual cycles. In the aberrations of normal development and involution (ANDI) classification of benign conditions, mastalgia is regarded as a physiologic disorder arising from hormonal activity with little connection to cancer risk, or true pathologic conditions (6). Another suitable term might be *benign breast change* as this does not suggest cancer or premalignancy.

No consistent abnormality of estradiol has been reported in women with cyclic mastalgia; both normal levels and elevated levels have been reported during the luteal phase. Baseline levels of prolactin are either normal or marginally elevated, but increased prolactin release was found after domperidone stimulation in severe cyclic mastalgia, possibly representing a stress response to prolonged pain.

Ecochard et al. measured a range of personal and endocrine variables in 30 women with mastalgia and 70 control subjects (7). Cases were more likely to report foot swelling or abdominal bloating (43% vs. 19%). Women with mastalgia had higher mean luteal levels of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

No histologic differences have been detected in biopsies from women with and without mastalgia. Immunohistochemical examination of biopsies from 29 women with mastalgia and 29 control subjects revealed no differences in expression of interleukin-6, interleukin-1, and tumor necrosis factor.

CLASSIFICATION

Preece et al. (8) proposed a classification with six subgroups based on a prospective study of 232 patients with breast pain: cyclic mastalgia, duct ectasia, Tietze's syndrome, trauma, sclerosing adenosis, and cancer. This was subsequently simplified into two groups with noncyclic pain: true noncyclic breast pain and those with other causes of chest wall pain (9). Although an accurate diagnosis can be achieved on the basis of history and examination, patients with breast pain can be more simply assigned to one of three groups: cyclic breast pain (around 70%), noncyclic breast pain (20%), or extramammary pain (10%).

Khan and Apkarian (10) studied the differences between cyclic and noncyclic pain using standardized pain questionnaires, including the McGill Pain instrument in 271 women, and found that the level of pain described by the subjects was equivalent to chronic cancer pain, and just less than the pain of rheumatoid arthritis. They noted that women with cyclic pain tended to refer to heaviness and tenderness as found in the Preece study, whereas women with noncyclic pain related the severity to the area of breast involved.

EVALUATION

Important aspects of history-taking include the type of pain, relationship to menses, duration, location, and any other medical problems. The impact of the pain on the everyday activities of the patient, particularly sleep and work, should be established to assess the need for medication.

After inspection, the first aspect of the breast examination should be very gentle palpation of the breasts once the patient has indicated the site(s) of the pain. Having excluded discrete masses, a more probing evaluation should be performed, focusing on the site(s) of pain. After turning the patient half on her side so that the breast tissue falls away from the chest wall, it may be possible to identify that the pain is arising from the underlying rib or costal cartilage. The pain can be reproduced by placing a fingertip on the affected rib and demonstrating to the patient its source.

Nodularity can be associated with mastalgia, but the extent is unrelated to pain severity; in younger women, the finding is so common that it should be considered within the spectrum of normality. If it is apparent that the pain, whether cyclic or noncyclic, is mammary in origin, the decision to treat is based on the subjective assessment of severity, together with the duration of symptoms. This assessment may be facilitated by a daily pain chart that assesses the timing and severity (semiquantitative scale) of the pain. Generally, there should be a history of pain of at least 4 months before hormonal therapy is indicated.

ROLE OF RADIOLOGY

The average age of women entered into trials of treatment for mastalgia is 32 years: In this age group, mammography is not a standard adjunct to clinical evaluation. In the absence of a discrete lump, ultrasonography is also unlikely to give useful information, but any breast lump present requires triple assessment. No specific mammogram findings are associated with breast pain.

Ultrasonography in 212 asymptomatic women and 212 with mastalgia showed the mean maximal duct dilatation was 1.8 mm in normal women compared with 2.34 mm in the 136 with cyclic pain and 3.89 mm in the 76 with noncyclic pain. Dilated ducts were found in all quadrants, but mostly in the retroareolar area, and dilatation did not alter during the menstrual cycle. A highly significant association was found between the extent of ductal dilatation and pain severity.

The meaning of these findings are unclear as no relationship was shown in the cyclic pain patients with the considerable temporal symptoms in this group, but the noncyclic group could be explained by the periductal inflammation often seen in this group.

MONDOR'S DISEASE

Mondor's disease is a rare cause of breast pain, with diagnostic clinical features of local pain associated with a tender, palpable subcutaneous cord or linear skin dimpling. The cause is superficial thrombophlebitis of the lateral thoracic vein or a tributary. The condition resolves spontaneously. Mondor's disease can cause serious alarm because some patients assume that the skin tethering is secondary to an underlying carcinoma, so they are greatly relieved when informed of the benign nature of the condition.

In a series of 63 cases of Mondor's disease, no underlying pathologic process was found in 31 cases. Of the remaining 32, local trauma or surgical intervention was responsible in 15 (47%), an inflammatory process in 6 (19%), and carcinoma in 8 (25%). In view of this, mammography should be performed in women with Mondor's disease who are aged 35 years or older to exclude an impalpable breast cancer.

PSYCHOSOCIAL ASPECTS

Several studies have confirmed that patients with severe mastalgia have psychological morbidity that may be the result rather than the cause of their breast pain. Preece et al. (11) used the Middlesex Hospital Questionnaire to compare patients with mastalgia, psychiatric patients, and minor surgical cases. No significant differences were found between the patients with breast pain and the surgical cases, and both scored significantly lower than psychiatric cases. Only the scores of patients who failed treatment approached those of psychiatric patients. In a small study of 25 women with severe mastalgia, using the Composite International Diagnostic Interview, 45 diagnoses were made in 21 patients (84%): anxiety (n = 17), panic disorder (n = 5), somatization disorder (n = 7), and major depression (n = 16).

A study using the Hospital Anxiety and Depression Scale (HADS) reported high levels of both anxiety and depression in 20 women with severe mastalgia. At Guy's Hospital, HADS was also used to evaluate 54 patients with mastalgia (12). The 33 women with severe pain manifested levels of anxiety and depression comparable with those in women with breast cancer before surgery. Those who responded to treatment had a significant improvement in psychosocial function, but the nonresponders continued to have high levels of distress. Fox et al. (13) conducted a prospective trial in 45 women with mastalgia who kept pain diaries for 12 weeks, with half randomized to listen daily to a relaxation tape during weeks

5 to 8. Abnormal or borderline HADS scores were found at entry in 54%, and a complete or substantial reduction in pain score was measured in 25% of the control subjects and 61% of those randomized to relaxation therapy ($p < .005$).

MASTALGIA AND BREAST CANCER RISK

Because of the lack of precision in classification of benign breast conditions in older studies, it was difficult to determine whether breast pain led to an increased risk of subsequent breast cancer. Foote and Stewart wrote in 1945, "Any point of view that one chooses to take concerning the relation of so-called cystic mastitis to mammary cancer can be abundantly supported from the literature."

Webber and Boyd carried out a critical analysis of the 36 published papers that were available in English before 1984. They set 16 standards, including a description of the study population, a definition of benign disease, follow-up, and a description of the risk analysis. Of the 22 studies reporting an increase in risk, all met more of the standards than the 11 suggesting no increase in risk and the 3 drawing no conclusions.

Since then, a few studies have specifically examined the relation between cyclic mastalgia and breast cancer risk. A French case-control study among premenopausal women—210 younger than 45 years of age with breast cancer, and 210 neighborhood control subjects—matched on year of birth, education level, and age at first full-term pregnancy gave an unadjusted relative risk (RR) for cancer in cyclic mastalgia of 2.66, and after adjustment for family history, prior benign breast disease, and age at menarche, the RR was still significantly elevated at 2.12.

Goodwin et al. (14) recruited 192 women with premenopausal node-negative breast cancer and 192 age-matched premenopausal control subjects. Significant risk variables for breast cancer in the model were marital status, family history, number of years of smoking, prior breast biopsy (before cancer diagnosis), and mean cyclic change in breast tenderness. The odds ratio of cancer for cyclic mastalgia was 1.35, rising to 3.32 in those with severe pain.

Another indication of a possible link between mastalgia and cancer is the relationship between Wolfe grade of mammograms and breast pain. Deschamps et al. (15) determined the Wolfe grades of 1,394 women in the Canadian National Breast Screening Study. All completed a questionnaire, with mastalgia reported by 46%. The extent of dysplasia on mammograms was categorized as Dy2 (25% to 49%), Dy3 (50% to 74%), and Dy4 (≥75%). The odds ratio for a Dy3/4 rating was 1.0 for those who never had breast swelling and mastalgia, whereas it was 2.7 in those reporting both symptoms.

These epidemiologic studies have the problems of recall biases and unknown extent of histologic atypia in the patients who have not had biopsies. In most studies assessing risk using established algorithms, the presence of breast pain is not used as an independent variable in the calculations, unlike prior breast biopsy. That women attend a physician for breast pain, itself results in a higher rate of breast biopsy as noted in the study by Ader et al. (3).

TREATMENT TRIALS

Multiple treatments have been used in women with "benign breast disease," some of whom had nothing more than nodularity without tenderness. Patients with diffusely nodular breasts that are painless require nothing other than exclusion of significant pathology and can be discharged if no other indications for follow-up exist.

Treatment trials for breast pain should have well-documented breast pain classified into cyclic or not, measured with a visual analog scale (VAS) or other rating scales, and ideally using each patient as her own control. Pain should have been present for a minimum of 6 months. Assessment of nodularity should be assessed separately from pain, and has been validated in a study of two experienced blinded physicians assessing 784 women using a VAS giving a highly significant interobserver correlation with a kappa value of 0.865 (16). The overall quality of most published studies has been poor with low numbers of patients recruited, and varying methodologies used. Trials should be of double-blinded, placebo-controlled, randomized design and include a minimum of 20 patients in each arm. Some trials have met these criteria and defined effective drugs or interventions; results are summarized in Table 6-1.

The initial approach by most physicians is to advise reduction in alleged dietary factors associated with breast pain, such as caffeine or saturated fat intake, but the evidence for these interventions is poor. Diuretics are widely used by family physicians to reduce supposed water retention in the luteal phase of the cycle, but are ineffective.

Several agents have been found in controlled trials to be no better than placebo: vitamin E, lynestrenol, mefenamic acid, and caffeine reduction. This is perhaps not surprising because placebo-controlled trials report placebo response rates from 10% to 50%.

As an alternative, more complex approach, reduction in dietary fat can significantly reduce cyclic breast pain. Boyd et al. (17) entered 21 women with a minimum of 5 years of breast pain into a trial in which 11 were shown how to reduce their dietary fat content to 15% of total calories and 10 received general dietary advice. Those in the fat-reduction group had a significant reduction in breast pain. Although a nondrug intervention appeals to many patients, long-term dietary change is a difficult intervention to maintain in premenopausal women with busy lives.

A similar dietary approach of adding the long-chain unsaturated fatty acid gamma-linolenic acid, present in evening primrose oil and starflower oil, provides a nonendocrine approach, but with an efficacy that is questionable. One study entered 103 women with mastalgia into a double-blinded, crossover study comparing evening primrose oil with placebo for 3 months, after which both groups received evening primrose oil capsules for a further 3 months. Cyclic pain was significantly diminished in those given evening primrose oil, but had no effect on noncyclic mastalgia.

However, a systematic literature search by Budeiri to determine the efficacy of evening primrose oil for premenstrual syndrome found no evidence of benefit (18). A more recent Dutch trial also failed to show an advantage for evening primrose oil (19).

In an attempt to resolve this question, one of the largest studies ever performed in both community and hospital patients involving a total of 555 patients was carried out, but with a different placebo arm to the previous trials. This trial failed to show any advantage of the active arms containing gamma-linoleic acid, principally owing to the very large response of 40% reduction in symptoms in the placebo group (20). Despite this, many physicians advise their patients to try this product, which is widely available in nonprescription format, as an initial treatment of breast pain because the incidence of side effects was very low in all the trials. In practical terms it is likely that the patients feel better due to the large placebo effect.

In cyclic mastalgia, most treatments have focused on reduction in estrogen or prolactin drive to the breast cells in the belief that hormonal overstimulation is the predominant

TABLE 6-1

Placebo-Controlled, Randomized Trials of Treatment for Mastalgia with Visual Analog Scoring of Response

Agent	*>20 Subjects/Arm*	*More Than 1 Trial*	*Side Effects*[a]	*Efficacy*	*References*
Endocrine					
Goserelin	Yes	Yes	Yes	Yes	27
Danazol	Yes	Yes	Yes	Yes	21
Bromocriptine	Yes	Yes	Yes	Yes	22
Tamoxifen	Yes	Yes	No	Yes	24
Medroxyprogesterone acetate	No	No	No	No	34
Lynestrenol	No	No	No	No	34
Gestrinone	Yes	No	No	Yes	23,34
Lisuride	Yes	No	No	Yes	
Isoflavone	No	No	No	Yes	28
Nonendocrine					
Fat reduction	No	No	No	Yes	17
Evening primrose oil	Yes	Yes	No	?	18–20
Mefenamic acid	No	No	No	No	
Caffeine reduction	Yes	No	No	No	
Vitamin E	Yes	No	No	No	
Iodine	Yes	No	No	Yes	30,31
Vitex agnus-castus	Yes	No	No	Yes	

[a]Side effects of sufficient severity that treatment was discontinued.

factor in severe breast pain, although as noted above little evidence exists for this hypothesis.

Danazol, an impeded androgen, may relieve pain in up to 93% of patients, but with side effects that include nausea, depression, menstrual irregularity, and headaches in up to two-thirds of patients, sometimes leading to discontinuation of treatment. To reduce side effects, O'Brien and Abukhali (21) conducted a double-blinded, placebo-controlled trial of luteal-phase danazol in 100 women with premenstrual syndrome, including cyclic mastalgia. Danazol or placebo was given during the luteal phase for three cycles, with a significant pain reduction in those treated and similar side effects in both groups.

As an alternative to drugs, some physicians recommend a more supportive brassiere to relieve mastalgia. In a nonrandomized study of 200 Saudi women with mastalgia, 100 were given danazol 200 mg/day and 100 instructed to wear a sports brassiere. Pain was relieved in 85% of those who wore sports brassieres and in 58% of those given danazol, but of the latter group 42% had side effects and 15% stopped treatment. The results of this trial are difficult to interpret due to its nonblinded, nonrandomized structure.

Bromocriptine, a prolactin inhibitor, was also effective in breast pain in several small preliminary studies. In a multicenter European study of 272 women comparing bromocriptine, 2.5 mg twice daily, with placebo, significant symptom relief occurred in the treated group but 29% dropped out because of side effects, mostly nausea and dizziness (22). A double-blinded comparison study in 47 women with severe breast pain treated with bromocriptine and danazol had significantly better pain relief than the placebo group, but the best response was recorded in the danazol group.

A study using the dopamine agonist lisuride maleate for 2 months in a double-blinded, placebo-controlled trial treated 60 women in a 1:1 ratio. Severity of mastalgia was monitored by VAS, but there was neither run-in period nor any pain severity threshold for trial entry. In patients with less pain, the response rate was 8 of 11 (73%) in the treated and 2 of 15 (13%) in the placebo arm. Among those with more severe pain, the respective response rates were 19 of 19 (100%) and 5 of 15 (33%). The main side effect was nausea, experienced by 17% of the treated and 10% of the control subjects. However, the use of dopamine agents has been limited owing to problematic side effects, and they are currently not being used in breast pain.

The efficacy of progesterone vaginal cream has been investigated in two small randomized trials. In a small study, McFadyen reported a minor, nonsignificant benefit for those women given placebo cream. In a larger trial with 80 participants, a greater than 50% reduction in pain was recorded in 22% of the placebo group and in 65% of those given progesterone-containing cream.

A study of 26 women compared medroxyprogesterone acetate tablets, 20 mg/day in the luteal phase of the cycle, with placebo and found no difference in response rate or side effects. In a multicenter, double-blinded, randomized trial, Peters (23) administered the synthetic 19-norsteroid gestrinone to 73 women and placebo to 72 control subjects. A significantly greater reduction in pain was seen in the gestrinone group, with side effects reported by 44% of the treated cases and 14% of the control subjects.

Tamoxifen, a partial estrogen antagonist and agonist, is effective in treating breast pain. In the first double-blinded, crossover, randomized trial, conducted at Guy's Hospital, pain relief occurred in 71% of those given tamoxifen and 38% of control subjects (24). After 3 months, nonresponders switched to the alternative treatment arm, and pain control was achieved in 75% of the tamoxifen group and 33% of the placebo group. The most common side effect of tamoxifen was hot flashes, occurring in 27%.

A similar placebo response was seen in a more recent trial comparing tamoxifen with danazol, but in the group that received tamoxifen 10 mg, a higher response rate was seen and breast pain was controlled in 89%. In two trials that compared

tamoxifen 10 mg with 20 mg, similar response rates were seen but side effects with the lower dose were substantially reduced (21% vs. 64%). When tamoxifen was compared with danazol, similar response rates were seen, but significantly more side effects occurred in those given danazol (90% vs. 50%). When tamoxifen 10 mg was compared with bromocriptine 7.5 mg daily, pain relief was achieved in 18 of 20 (90%) of the tamoxifen group and in 17 of 20 (85%) of those given bromocriptine. Tamoxifen is now being used extensively in the management of breast pain, as an off-label drug because it is not currently licensed for use in benign breast conditions. The safety of this drug in patients without breast cancer is, however, well documented in the prevention trials involving large numbers of normal high-risk women (25). Furthermore, this review of the prevention trials confirms the reduction in benign breast conditions on the drug, which is consistent with the reduction in symptoms seen in the breast pain trials. Patients who are prescribed tamoxifen should be given a careful explanation that the drug is being used to reduce estrogen drive and is not being used for breast cancer.

Alternative routes of delivery of tamoxifen or selective estrogen receptor modulators (SERMS) may be possible by the transcutaneous route to reduce side effects by avoiding transhepatic passage. This approach has shown some promise using a gel containing 4-hydroxy tamoxifen applied to the breast morning and night (26). A placebo-controlled trial of this gel showed efficacy in cyclic mastalgia, particularly in the late luteal phase of the cycle, and showed a clear blunting of the luteal peak of cyclic breast pain (Fig. 6-1). It is clear that these series of studies of SERMS and the prevention studies confirm the active therapeutic role of these agents in benign conditions of the breast. These new agents are currently not licensed in the treatment of breast pain, and are awaiting further safety data as it is a novel formulation of tamoxifen.

A recent randomized study compared a novel antiestrogen ormeloxifine with danazol and showed that the new agent, which has predominantly antagonist actions, was as effective as danazol but with fewer side effects (27). Pain was assessed by VAS pain scores and ormeloxifine (Centchroman) produced a reduction in median pain scores from 7 at baseline to 2 at 12 weeks.

The relationship of the menstrual cycle in cyclic breast pain was further demonstrated by a randomized trial of the luteinizing hormone-releasing hormone (LHRH) agonist goserelin (Zoladex), which abolishes the menstrual cycle and thus removes the normal fluctuation in estradiol and progesterone. This large placebo-controlled trial of women with cyclic mastalgia treated with Zoladex for 6 months showed significant reduction in breast pain (28). The patients were then followed off treatment for 6 months and the breast pain gradually returned as did menstruation.

In a different approach, Ingram et al. (29) studied isoflavones derived from red clover to determine whether this phytoestrogen could relieve mastalgia. The 18 patients in the trial underwent a 2-month, single-blinded, placebo run-in phase, after which they received either placebo, isoflavone 40 mg, or isoflavone 80 mg. Pain scores for the final single-blinded month and the final double-blinded month were compared. In the placebo group, there was a 13% reduction, for the 40 mg/day group it was 44%, and for

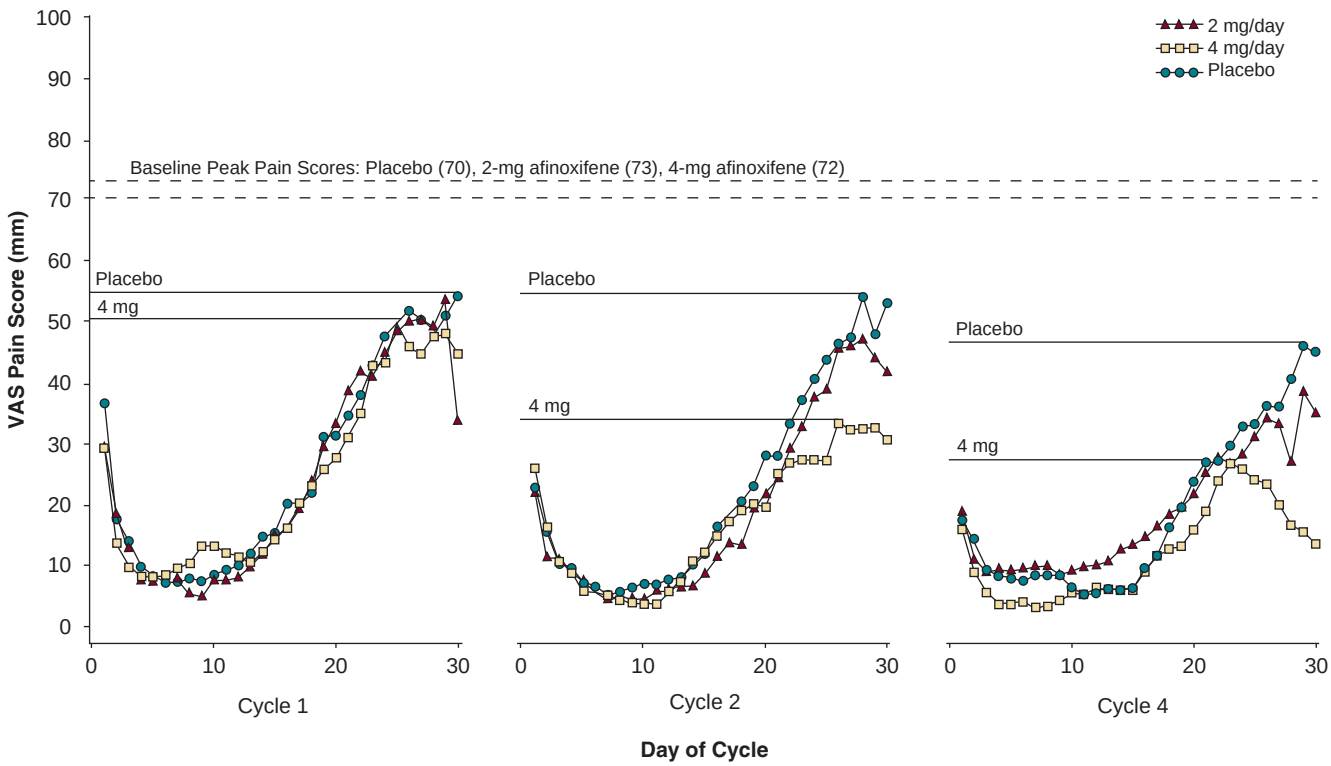

FIGURE 6-1 Effect of topical 4-hydroxy tamoxifen gel on cyclical mastalgia. Randomized trial of 4-hydroxy tamoxifen gel (2 and 4 mg vs. placebo gel) applied to the breast for breast pain. Note the clear cyclical pattern of pain and the reduction of the peak luteal pain in cycle 4 by the 4-mg preparation. (From Mansel R, Goyal A, Nestour EL, et al. and the Afimoxifene [4-OHT] Breast Pain Research Group. A phase II trial of Afimoxifene [4-hydroxytamoxifen gel] for cyclical mastalgia in premenopausal women. *Breast Cancer Res Treat* 2007;106[3]:389–397, with permission.)

the 80 mg/day group it was 31%. No major side effects were reported, but the study needs repeating with larger numbers to determine the true efficacy of isoflavones.

ALTERNATIVE APPROACHES

Acupuncture has been used for the treatment of premenstrual syndrome with some improvement of symptoms, but a recent study from the Mayo Clinic showed that pain scores measured on a 10-point brief inventory scale showed a clinically meaningful improvement in 67% of patients with the worst pain (30). The authors have suggested a randomized trial is required to confirm the findings, but this would be difficult to blind from the patient and placebo responses would be difficult to evaluate. At Guy's Hospital in an open pilot study, applied kinesiology was used in 88 women with self-rated moderate or severe mastalgia present for more than 6 months. This technique uses a type of pressure massage and is a hands-on technique based on improving lymphatic flow. Using self-rated pain scores, there was improvement in 60% and complete resolution in 18%, but as with the acupuncture trials, this trial was not blinded, and the response may have been due to placebo effects.

A randomized trial of *Vitus agnus-castus* extract (castor oil, Mastodynon) showed a modest fall in VAS scores on the plant extract (54% compared with 40% on placebo), with few side effects (Mastodynon).

Ghent et al. (31) investigated the effect of iodine replacement in women with breast pain in three different studies, one of which was a randomized, double-blinded, placebo-controlled trial. The rationale was that iodine deficiency in Sprague-Dawley rats led to mammary epithelial hyperplasia and carcinoma. Participants were treated for 6 months with aqueous molecular iodine 0.07 to 0.09 mg/kg daily, or placebo composed of an aqueous mixture of brown vegetable dye and quinine. Pain improvement occurred in 11 of 33 (33%) of the placebo group and 15 of 23 (65%) of those given iodine. No side effects were reported. More recently Kessler (32) studied supraphysiologic doses of iodine in cyclic mastalgia and reported that approximately 40% of patients obtained more than 50% reduction in breast pain on 3 to 6 mg iodine daily compared with 8% on placebo.

EXTRA MAMMARY PAIN

Pain originating within the thorax or abdomen and referred to the breast area is managed by treatment of the underlying condition. Pain that originates from the thoracic wall (Tietze's syndrome or costochondritis) and localized specific tender areas in the breast (trigger spots) can be managed by injection of steroid and local anesthetic. More recently, nonsteroidal analgesics have been used as topical gel applications and their use is supported by a large randomized trial of 108 women with both cyclic and noncyclic pain, which showed significant reduction in breast pain by diclofenac gel at 6 months compared with placebo gel (reduction in pain measured on visual analog scale from 0 = no pain to 10 = intolerable pain; cyclic 5.87 with diclofenac vs. 1.30 placebo; noncyclic 6.33 diclofenac vs. 1.12 placebo, $p < .001$) (33).

ROLE OF SURGERY

Severely distressed nonresponders to drug therapy may ask for mastectomy. This drastic step should not be undertaken before a full psychiatric assessment has been sought because without careful selection, surgical intervention will damage body image without achieving pain relief. Even after careful psychiatric assessment, excisional surgery should very rarely be undertaken because clinical experience has shown that pain reduction is achieved in only a small number of patients. This is not surprising because the etiology of breast pain is poorly understood, and there are causes of pain that lie outside the breast tissue. In the author's experience the focus on pain will often move to body image after mastectomy and this leaves an unhappy patient who still complains of breast pain, which is clearly therapeutic failure.

A recent overview has considered the role of drugs in the treatment of mastalgia. Srivastava et al. considered the range of drugs available but concluded that the only effective drugs were tamoxifen, bromocriptine, and danazol (34). Many of the studies considered were rejected for poor design or methodology.

The precise mechanisms behind many of the symptomatic presentations of benign breast change remain unclear, but the various hypotheses have been summarized in a review by Santen and Mansel (35).

MANAGEMENT SUMMARY

- The essentials of treatment of women with breast pain are excluding serious underlying pathologic processes, making a diagnosis, and communicating this to the patient to reassure the majority. Only a small proportion (<10%) have problems of such severity and duration that specific treatment is necessary.
- If moderate or severe pain has been present for less than 6 months, a high probability exists of spontaneous remission after reassurance, and no specific treatment should be given.
- In women older than 35 years of age who have not had mammography within the past 12 months and are presenting with a new symptom, mammography should be carried out to exclude abnormalities that may be unrelated to the breast pain.
- The initial approach to therapy should include analgesics, including nonsteroidal antiinflammatory agents, and dietary modifications, although these may work principally through placebo effects.
- The small group with severe, prolonged pain resistant to the above measures should be encouraged to keep a pain chart and return after 6 weeks. If the pain persists, treatment should be started with either tamoxifen or danazol. The former has fewer side effects and can be very effective. Although not licensed specifically for treatment of mastalgia, tamoxifen can be prescribed.
- Treatment should be given at a dosage of 10 mg per day for 3 months. If this achieves pain relief, the dose can be further reduced to 10 mg on alternate days for a further 3 months. For the few who do not respond, a higher dosage of 20 mg per day should be given.
- The very few who do not respond to this treatment should be switched to danazol or goserelin for 4 months.

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CHAPTER 7

Abnormalities of the Breast in Pregnancy and Lactation

Richard B. Wait and Holly S. Mason

CHAPTER CONTENTS

Breast disease during pregnancy and lactation can represent a clinical and diagnostic dilemma for the clinician due to the significant change to the breast parenchyma from hormone-related hypertrophy and increased vascularity. These changes affect the clinical breast examination as well as alter the efficacy of the currently available imaging modalities. Added to this is the need to balance concern for the mother with concern for the fetus. Breast cancer remains one of the most common types of cancer to be diagnosed during pregnancy or in the lactational period (1) (see Chapter 67); benign breast disease, however, is even more prevalent during this period. It is critical for the physician to remain as diligent in the evaluation of any breast abnormality in the pregnant or lactating patient as one would in any other woman. This chapter reviews the current state of the diagnosis and treatment of benign breast disease during pregnancy and lactation.

EVALUATION

Clinical Breast Examination

During the course of pregnancy, pregnancy-related hormones (estrogen, progesterone, and prolactin) cause breast tissue to undergo significant changes that lead to increased volume and density (see Chapter 1). During the first trimester, the ratio of fatty tissue to glandular tissue decreases; as the volume of glandular tissue increases, so does the overall volume of the breast. As the pregnancy progresses, these changes intensify and make the evaluation of any breast abnormality more difficult. It is preferred, therefore, for the pregnant patient to have a baseline clinical breast examination during the first trimester before these changes have occurred. As the number of women who become pregnant during their fourth decade increases, it is likely that more women will present already having had a baseline mammogram before becoming pregnant. A prior mammogram and any other imaging study obtained before pregnancy may help facilitate the evaluation of a new mass.

The pregnant patient who presents with a new mass or physical finding should be evaluated and followed very closely. If observation is chosen after completion of the appropriate workup (described later in this chapter), a short interval follow-up examination is indicated because delay in examination may allow pregnancy-related changes (such as an increase in volume or nodularity) to obscure the physical finding. Because the pregnant patient does not undergo the cyclic hormonal changes that the nonpregnant patient experiences, persistence of a mass after a short interval warrants further attention (Fig. 7-1). Ultimately, it is the responsibility of the clinician who identifies a breast mass to rule out a pregnancy-associated breast cancer.

Diagnostic Imaging Issues in Pregnancy and Lactation

When evaluating a pregnant patient, consideration must be given to minimizing exposure of ionizing radiation to the fetus. For this reason, ultrasonography is an ideal first option in the evaluation of a breast mass in this patient population. Ultrasound is a reliable means of differentiating a fluid-filled structure (cyst) versus a solid mass. It can assess the margins and shape of a solid mass or identify shadowing, which may help differentiate a benign mass (e.g., lymph node or adenoma) from a malignancy. Ultrasound can easily guide aspiration of a cyst or percutaneous biopsy of a suspicious mass. An important benefit of ultrasound is that it is less affected by pregnancy-related changes than is mammography. Ultrasound can have 100% sensitivity for identifying malignancy as seen in multiple studies, and high specificity rates are seen as well (Table 7-1). For these reasons, ultrasound is the optimal first imaging study employed for a pregnancy-related breast mass.

The use of mammography in this patient population, on the other hand, remains controversial. There is concern over the potential for exposure of the fetus to ionizing radiation but, with proper abdominal shielding, exposure to the fetus is considered negligible (5). A second issue affecting the use of mammography, however, is the potential for lowered sensitivity owing to the increased density of the pregnant breast and the decrease in adipose tissue-to-breast parenchyma ratio (6), although this is not universally seen

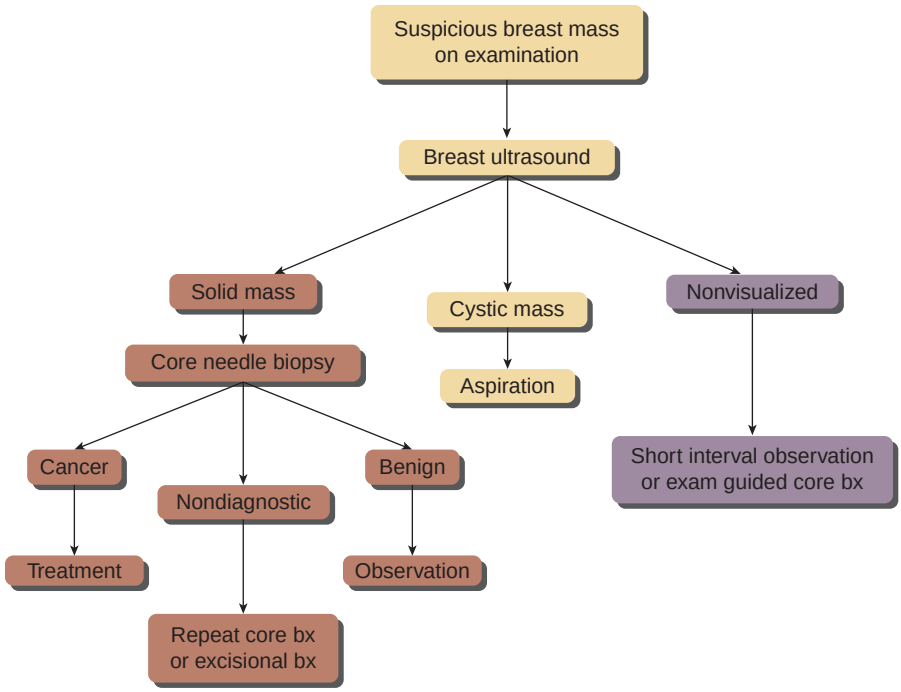

FIGURE 7-1 Flow diagram for management of clinically suspicious breast masses during pregnancy.

(3,7). Yang et al. (2) documented that a malignancy was visualized in 18 of 20 patients (90%) with breast cancer despite the breast density issue. The lactating patient can improve the quality of the mammographic study by emptying her breast either by nursing or pumping immediately prior to the study. In general, mammography should not be the primary imaging tool if there is a suspicious physical examination finding in a pregnant patient. If a patient has a suspicious discrete mass on examination that is not visible on ultrasound, tissue diagnosis with percutaneous biopsy can be performed. Mammography is more useful in the lactating patient or in the newly diagnosed pregnant patient to assess for calcifications or extent of disease.

Magnetic resonance imaging (MRI) of the breast has been used increasingly in the evaluation and treatment of breast cancer. At this time, however, it has not been well studied in the pregnant patient. Pregnancy-associated changes alter the ratio of parenchyma to adipose tissue, causing increased flow and permeability (8). In addition, gadolinium (the contrast agent used in breast MRI) crosses the placenta and, therefore, is a pregnancy category C drug. It is advised to wait until after first trimester if breast MRI is judged to be absolutely necessary (9). Gadolinium uptake in lactating breast tissue can mimic malignancy, however, and result in a false-positive study result (8). MRI is currently not indicated in the pregnant or lactating patient for these reasons.

Tissue Biopsy in the Pregnant and Lactating Patient

Percutaneous biopsy has become the standard of care for tissue diagnosis of any breast mass or imaging abnormality in any patient. Surgical incisional or excisional biopsy for diagnosis necessitates an incision and there is a potential need to return for additional surgery if the biopsy reveals malignancy. Each operation contains risks to both the patient and the fetus that should be minimized if possible. Thus, the clinician must protect the fetus while ensuring appropriate treatment for the patient. A secondary benefit to percutaneous biopsy over surgery for diagnosis should be minimal disruption of the ductal structures of the breast

TABLE 7-1

Sensitivity and Specificity of Ultrasonography and Mammography in Pregnant Women or Lactating Women

Author	*No. of Patients*	*Imaging Study*	
		Ultrasound (Sensitivity/Specificity)	*Mammography (Sensitivity/Specificity)*
Yang et al. (2)	23	100%/NR	90%/NR
Robbins et al. (3)	134	100%/86%	100%/93%
Ahn et al. (4)	22	100%/NR	86.7%/NR

Specificity data are not available in all studies (NR = not reported). There are currently no data on the sensitivity of breast MRI in the pregnant patient.

to facilitate successful lactation. An in-depth discussion of the risks and benefits of biopsy needs to be held with the patient to allow for informed consent.

For many years, fine-needle aspiration biopsy (FNAB) was thought to be the best method of percutaneous tissue diagnosis. In the pregnant or lactating patient, the hormone-mediated hyperproliferation of ductal cells can, however, result in a false-positive diagnosis in the hands of an inexperienced cytopathologist (10). In addition, FNAB can miss the intended target, causing a false-negative result. Percutaneous core biopsy can be more accurate and will provide the cellular architecture needed for a more definitive diagnosis. Excisional biopsy should be undertaken only when there is a lack of concordance between clinical suspicion, imaging result, and percutaneous biopsy result (Fig. 7-1). If an excisional biopsy is intended in the pregnant patient, surgery should be carefully planned to minimize the risk to the fetus from anesthesia, including fetal monitoring if indicated. Local anesthesia alone is the preferred method in these cases.

Care must be taken in this patient population to minimize complications. Gestational or lactational breast tissue is hypervascular, and meticulous hemostasis is mandatory with any intervention to prevent hematoma formation. Breast milk provides a good culture medium for bacteria and, therefore, efforts must be made to minimize the risk of infection. To prevent milk stasis after a biopsy, the lactating patient should either nurse or express milk regularly. If infection should develop, appropriate antibiotics should be administered.

The development of a milk fistula, a tract between a lactiferous duct and the skin, is a potential complication of any percutaneous or surgical intervention. The risk of milk fistula, whether from FNA, core biopsy, or excision, is not well documented, although case reports exist in the literature. Some clinicians suggest breast binding as a means of facilitating cessation of milk leakage, but this is not likely to succeed. Bromocriptine, a dopamine agonist that decreases prolactin levels, can be used to treat a milk fistula, but it is not routinely recommended. Cessation of lactation will allow the fistula tract to heal, and remains the only reliable method to control a milk fistula (11). If possible, the patient should stop lactation 1 week before the biopsy to minimize this risk.

CLINICAL PROBLEMS

Inflammatory and Infectious Problems in Pregnancy

Breast milk represents a lactose-rich culture medium and, thus, inflammatory or infectious problems remain the most common issues for the pregnant patient (12). Milk stasis, or poor emptying of milk from the breast, results from ineffective suckling, restriction of frequency of feeds, or blockage of milk ducts (13). Poor infant attachment to the breast can lead to cracking of the nipple epithelium, which is thought to allow bacteria to enter the breast in a retrograde direction via the terminal ducts, and it has been shown to be a risk factor for mastitis. Milk stasis provides a medium for bacterial growth and injury to the nipple, with subsequent bacterial translocation. This can then lead to a generalized infection (mastitis) with fever, redness, and tenderness, and it may also result in a breast abscess. *Staphylococcus aureus* is the most common organism (Table 7-2) and usually it can be treated with oral antibiotics (14). Other known risk factors for mastitis include advanced maternal age, low parity, difficulty breast-feeding, or employment outside the home (15). It is most important to continue the expression of breast milk to allow for complete emptying of the breast and symptom relief. Education concerning proper emptying, positioning of the infant, and nipple hygiene should be a key component to prevent future episodes of mastitis (13).

TABLE 7-2

Organisms Found in Mastitis or Breast Abscess (in order of frequency)

Staphylococcus aureus
S. epidermidis
Streptococcus (alpha, beta, and nonhemolytic)
Escherichia coli
Candida (rare)

From World Health Organization. *Mastitis: causes and management.* Geneva, Switzerland: WHO/FCH/CAH/00.13; 2000.

A breast abscess will not resolve with antibiotics alone, however, and further intervention is necessary. Ultrasound will help differentiate mastitis from a breast abscess. Repeated aspiration can be successful and it can avoid a disfiguring incision and drainage (16). Aspirate cultures should be taken to ensure appropriate antibiotic coverage. Skin and parenchymal biopsies should be considered to rule out inflammatory breast cancer if no improvement is seen. Despite concerns of the risk to the infant from bacterial contamination in the breast milk, the World Health Organization currently does not recommend cessation of breast-feeding in the presence of a breast abscess (13).

Management of Breast Masses in Pregnancy and Lactation

Most solid masses in the pregnant or lactating patient are benign lesions, such as fibroadenomas and hamartomas, and often predate the pregnancy. Any cause for a breast mass in the nonpregnant woman can also exist in pregnancy or the postpartum period.

Lactating adenomas are the most common cause of breast masses in this patient population and may arise secondary to hormones associated with pregnancy and lactation and are thought to be related to tubular adenomas, fibroadenomas, or hyperplasia (17). Biopsy can determine if a mass is a true lactating adenoma or is caused by lactational change in a preexisting fibroadenoma. Most of these lesions will involute once lactation has stopped, although excision may be required for those that do not. Hemorrhage or infarction will occur in 5% of lactating adenomas owing to vascular insufficiency seen occasionally in pregnancy-induced proliferative breast tissue (18).

Galactoceles are milk-filled cysts, which are thought to occur because of ductal obstruction during lactation. These usually present as tender masses; ultrasound can differentiate a galactocele from a solid mass. Asymptomatic patients can safely be observed. Local breast care, including ice packs and breast support, may help alleviate the discomfort, although aspiration provides the greatest likelihood of symptom relief (12). Rarely, galactoceles can become infected, but they can be effectively treated with repeated aspiration or drain placement in addition to appropriate antibiotics (16).

TABLE 7-3

Frequency of Pathology Types of Pregnancy-Related Breast Masses

Pathology	*Collins et al. (20)*	*Son et al. (6)*	*Slavin et al. (17)*
All nonpregnancy benign neoplasms[a]	4/19	2/29	18/30
All pregnancy-related benign neoplasms	14/19	18/29	12/30
[b]Infection		9/29	
Benign or fibrocystic breast tissue	1/19		

[a]Tubular adenoma, fibroadenoma, hamartoma, adenofibroma, lipoma, papilloma, phyllodes tumor.
[b]Lactating adenoma, lobular hyperplasia, galactocele or other changes "coincident with pregnancy."

Localized breast infarction can occur in the pregnant or lactating breast and often results in a palpable mass that must be differentiated from breast cancer (19). Other benign breast lesions, such as fibroadenomas, lipomas, and papillomas, can occur in these patients and, overall, are just as likely to be the cause of a breast mass as pregnancy-related lesions (6,17,20) (Table 7-3).

Bloody Nipple Discharge

The presence of bloody nipple discharge creates significant patient anxiety because of its association with breast cancer. In the nonpregnant patient, the evaluation of bloody nipple discharge has been well described (see Chapter 6). The workup in the pregnant or lactating patient remains controversial because of the issues with imaging as previously discussed. As in the nonpregnant population, most cases of bloody nipple discharge are of benign etiology.

Bloody nipple discharge can occur as a result of the epithelial proliferation and new capillary formation that occurs during the second and third trimesters (12). A careful clinical breast examination should be performed to identify if the discharge is from a single duct or multiple ducts as multiple-duct discharge is likely to be of physiologic etiology. The location of the draining duct should be carefully documented. The use of cytology is controversial due to low sensitivity rates that can be seen even in the nonpregnant, nonlactating patient (21). Cytology that shows benign ductal cells or is a "nondiagnostic evaluation" should not preclude further evaluation. If the examination does not reveal a palpable mass, retroareolar ultrasound can be undertaken. If retroareolar ultrasound is negative, imaging with mammography and ductography can be performed to identify the lesion location, which then should be biopsied. Terminal duct excision remains an option if all other diagnostic studies are negative, but potential difficulty with postoperative lactation should be discussed with the patient as part of the informed consent.

MANAGEMENT SUMMARY

- Most problems related to the breast in the pregnant or lactating patient are of benign origin; a thorough clinical and imaging evaluation is mandatory, however, to rule out malignancy.
- Ultrasound remains the imaging technique of choice for initial evaluation because of both its safety and sensitivity.
- Percutaneous core biopsy is the preferred method to obtain a tissue diagnosis of a solid mass, although FNA remains an acceptable option. Although not the preferred method of diagnosis, surgical excision may be appropriate in certain circumstances. Surgical excision of a biopsy-proved benign mass should be deferred either until pregnancy or lactation has been completed or until the risk to the fetus and mother can be minimized.
- Infectious or inflammatory problems remain a common cause of breast pathology during the pregnant or lactational period. Repeated aspiration with antibiotic therapy is an acceptable means of treating an abscess. If incision and drainage is undertaken, biopsy of the abscess wall is a reasonable undertaking for histologic evaluation and elimination of malignancy as a possible cause of the abscess.
- The management of bloody nipple discharge remains controversial. It is paramount to utilize imaging to identify the source, but terminal duct excision may be required for accurate diagnosis.

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CHAPTER 8

Management of Gynecomastia

Glenn D. Braunstein

CHAPTER CONTENTS

Benign proliferation of the glandular tissue of the male breast constitutes the histologic hallmark of gynecomastia, which, if sufficiently great, appears clinically as palpable or visual enlargement of the breast. This condition, which is exceedingly common, may (a) be a sign of a serious underlying pathologic condition, (b) cause physical or emotional discomfort, or (c) be confused with other breast problems, most significantly carcinoma.

PREVALENCE

Breast glandular proliferation commonly occurs in infancy, during puberty, and in older age. It has been estimated that between 60% and 90% of infants exhibit the transient development of palpable breast tissue owing to estrogenic stimulation from the maternal–placental–fetal unit. This stimulus for breast growth ceases as the estrogens are cleared from the neonatal circulation, and the breast tissue gradually regresses over a 2- to 3-week period, but may persist longer. Although population studies have shown that the prevalence of pubertal gynecomastia varies widely, most have indicated that 30% to 60% of pubertal boys exhibit gynecomastia, which usually begins between 10 and 12 years of age, with the highest prevalence between 13 and 14 years of age (corresponding to Tanner stage III or IV of pubertal development), followed by involution that is usually complete by age 16 to 17 years (1). The percentage of men who exhibit gynecomastia increases with advancing age, with the highest prevalence found in the 50- to 80-year age range (Fig. 8-1). The prevalence of the condition in men ranges between 24% and 65%, with the differences between series being accounted for by the defining criteria and by the population studied (2).

PATHOGENESIS

No inherent differences appear to exist in the hormonal responsiveness of the male or female breast glandular tissue (3). The hormonal milieu, the duration and intensity of stimulation, and the individual's breast tissue sensitivity determine the type and degree of glandular proliferation. Under the influence of estrogens, the ducts elongate and branch, the ductal epithelium becomes hyperplastic, the periductal fibroblasts proliferate, and the vascularity increases. This histologic picture is found early in the course of gynecomastia and is often referred to as the *florid stage*. Acinar development is not seen in the male because it requires the presence of progesterone in concentrations found during the luteal phase of the menstrual cycle (3). Androgens exert an antiestrogen effect on rodent breast cancer models and the human MCF-7 breast cancer cell line; they are thought to antagonize at least some of the effects of estrogens in normal breast tissue (4). Accordingly, gynecomastia is usually considered to represent an imbalance between the breast-stimulatory effects of estrogen and the inhibitory effects of androgens. In fact, alterations in the estrogen-to-androgen ratio have been found in many of the conditions associated with gynecomastia. Such alterations can occur through a variety of mechanisms (Table 8-1; Fig. 8-2).

In men, the testes secrete 95% of the testosterone, 15% of the estradiol, and less than 5% of the estrone produced daily. Most of the circulating estrogens are derived from the extraglandular conversion of estrogen precursors by extragonadal tissues, including the liver, skin, fat, muscle, bone, and kidney (Fig. 8-2). These tissues contain the aromatase enzyme that converts testosterone to estradiol and androstenedione, an androgen primarily secreted by the adrenal glands, to estrone. Estradiol and estrone are interconverted in extragonadal tissues through the activity of the 17-ketosteroid reductase enzyme. This enzyme is also responsible for the interconversion of testosterone and androstenedione. When androgens and estrogens enter the circulation, either through direct secretion from gonadal tissues or from the sites of extragonadal metabolism, most are bound to sex hormone-binding globulin (SHBG), a protein derived primarily from the liver and one that has a greater affinity for androgens than for estrogens. The non-SHBG sex hormones circulate either in the free or unbound state or are weakly bound to albumin. These fractions are able to cross the plasma membrane of target cells and are bound to steroid receptors. Testosterone and dihydrotestosterone bind to the same hormone-responsive element. Each also binds to the hormone-responsive element of the appropriate genes, resulting in the initiation of transcription and hormone

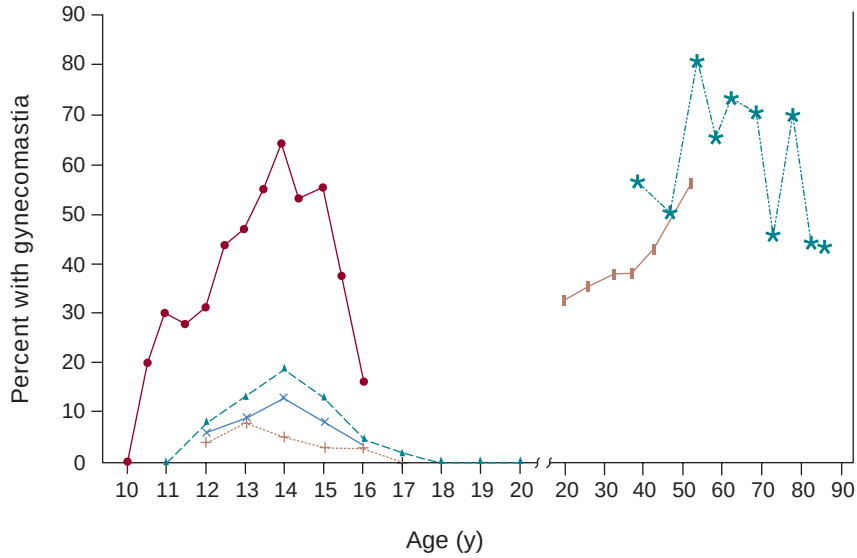

FIGURE 8-1 Prevalence of gynecomastia at various chronologic ages. Data were derived from multiple population studies. (Adapted from Braunstein GD. Pubertal gynecomastia. In: Lifshitz F, ed. *Pediatric endocrinology.* New York: Marcel Dekker, 1996:197–205, with permission.)

TABLE 8-1

Conditions Associated with Gynecomastia and Their Primary Pathophysiologic Mechanisms

Physiologic
- Neonatal
- Pubertal
- Aging

Pathologic
- Idiopathic
- Drug induced (see Table 8-2)
- Increased serum estrogen
  - Increased aromatization (peripheral and glandular)
    - Sertoli cell (sex cord) tumors
    - Testicular germ cell tumors
    - Leydig cell tumors
    - Adrenocortical carcinoma
    - Hermaphroditism
    - Obesity
    - Hyperthyroidism
    - Liver disease
    - Testicular feminization
    - Refeeding after starvation
    - Primary aromatase excess
  - Displacement of estrogen from sex hormone-binding globulin
    - Spironolactone
    - Ketoconazole
  - Decreased estrogen metabolism
    - Cirrhosis
  - Exogenous sources
    - Topical estrogen creams and lotions
    - Ingestion of estrogen
    - Tree tea or lavender oils
- Eutopic hCG production
  - Choriocarcinoma
- Ectopic hCG production
  - Lung carcinoma
  - Liver carcinoma
  - Gastric carcinoma
  - Kidney carcinoma
- Decreased testosterone synthesis
  - Primary gonadal failure, congenital
    - Anorchia
    - Klinefelter's syndrome
    - Hermaphroditism
    - Hereditary defects in testosterone synthesis
  - Primary gonadal failure, acquired
    - Viral orchitis
    - Castration
    - Granulomatous diseases (including leprosy)
  - Testicular failure owing to hypothalamic or pituitary disease
  - Androgen resistance owing to androgen receptor defects

Other
- Chronic renal failure
- Chronic illness
- Spinal cord injury
- Human immunodeficiency virus
- Enhanced breast tissue sensitivity

hCG, human chorionic gonadotropin.
Adapted with permission from Mathur R, Braunstein GD. Gynecomastia: pathomechanisms and treatment strategies. *Horm Res* 1997;48:95–102.

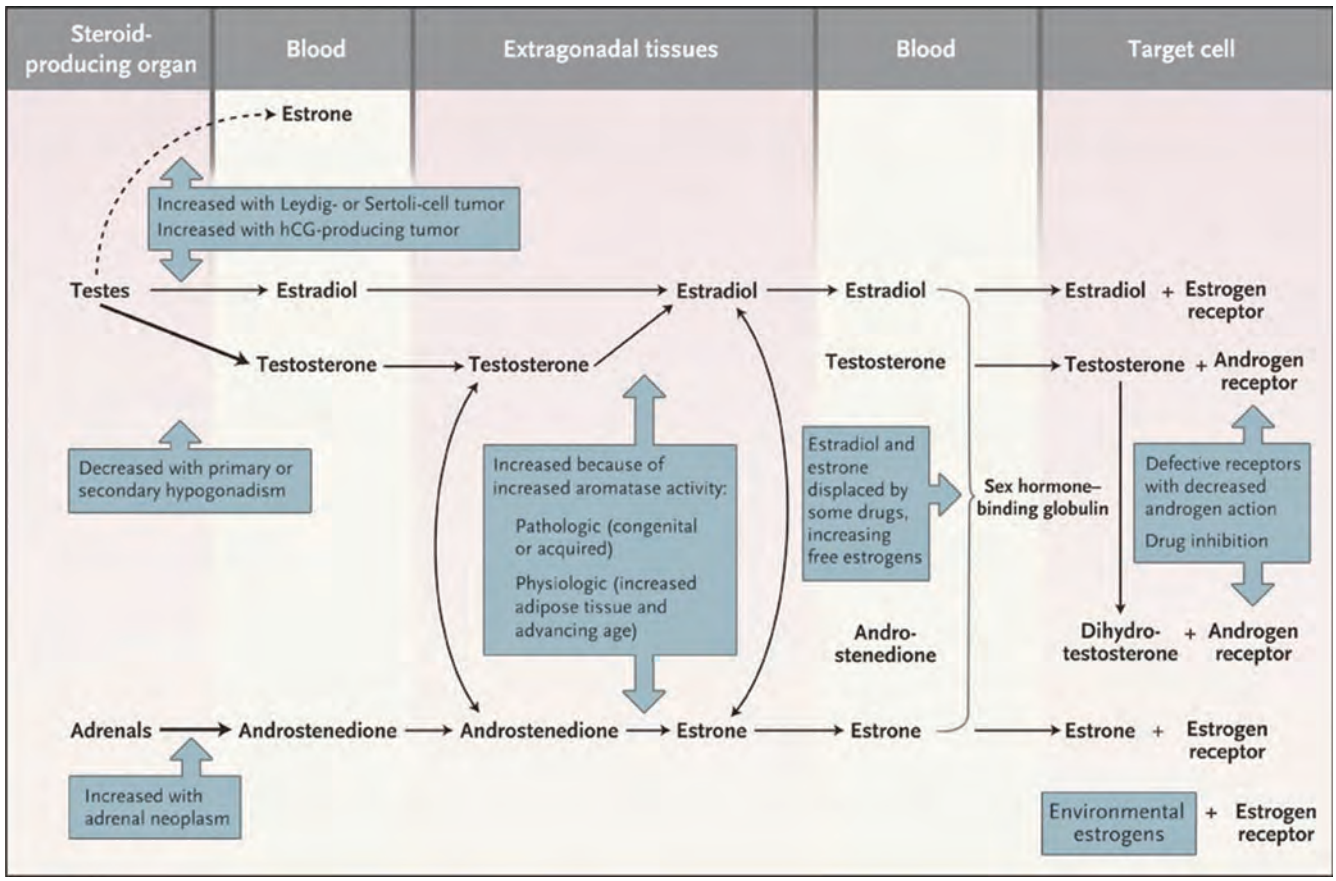

FIGURE 8-2 Pathways of estrogen and androgen production, action, and metabolism, and pathologic and physiologic changes that alter the pathways. (Adapted from Braunstein GD. Gynecomastia. *N Engl J Med* 2007;357:1229–1237, with permission.)

action. A similar sequence of events occurs after the binding of estradiol or estrone to the estrogen receptor (5).

From a pathophysiologic standpoint, an imbalance between estrogen and androgen concentrations or effects can occur as a result of abnormalities at several levels (Table 8-1; Fig. 8-2). Overproduction of estrogens from testicular or adrenal neoplasms or enhanced extraglandular conversion of estrogen precursors to estrogens can elevate the total estrogen concentration. Such extraglandular conversion can occur directly in the breast tissue. Indeed, increased aromatization of androgens to estrogens has been noted in pubic skin fibroblasts from some patients with idiopathic gynecomastia (6). Elevations of the absolute quantity of circulating free estrogens can occur if estrogen metabolism is slowed or if SHBG-bound estrogens are displaced from the protein. Conversely, decreased secretion of androgens from the testes—caused primarily by defects in the testes or secondary to loss of tonic stimulation by pituitary gonadotropins, enhanced metabolic degradation of androgens, or increased binding of androgens to SHBG—results in decreases in free androgens that could antagonize the effect of estrogens on the breast glandular tissue. As noted previously, androgen and estrogen balance depends not only on the amount and availability of free androgens and estrogens but on their ability to act at the target tissue level. Thus, defects in the androgen receptor or displacement of androgens from their receptors by drugs with antiandrogenic effects (e.g., spironolactone) result in decreased androgen action and, hence, decreased estrogen antagonism at the breast glandular cell level. Finally, the inherent sensitivity of an individual's breast tissue to estrogen or androgen action may predispose some persons to development of gynecomastia even in the presence of apparently normal concentrations of estrogens and androgens.

ASSOCIATED CONDITIONS

Tables 8-1 and 8-2 list the various conditions and drugs that have been associated with gynecomastia. Although the list is relatively long, almost two-thirds of the patients have either pubertal gynecomastia (approximately 25%), drug-induced gynecomastia (10% to 20%), or no underlying abnormality detected (idiopathic gynecomastia, approximately 25%). Most of the remainder have cirrhosis or malnutrition (8%), primary hypogonadism (8%), testicular tumors (3%), secondary hypogonadism (2%), hyperthyroidism (1.5%), or renal disease (1%) (2). For most pathologic conditions, alterations in the balance between estrogen and androgen levels or action occur through several of the pathophysiologic mechanisms outlined in Table 8-1 and Figure 8-2. One of the best examples is the gynecomastia associated with spironolactone. This aldosterone antagonist inhibits the testicular biosynthesis of testosterone, enhances the conversion of testosterone to the less potent androgen androstenedione, increases the aromatization of testosterone to estradiol, displaces testosterone from SHBG (leading to an increase in its metabolic clearance rate), and binds to the androgen receptors in target tissues, thereby acting as an antiandrogen (7). For an in-depth discussion of

the pathophysiology of gynecomastia associated with each of the conditions listed in Tables 8-1 and 8-2, the reader is referred to several reviews (2,3,5,7–15).

EVALUATION

Most patients with gynecomastia are asymptomatic, with the condition detected during a physical examination. Patients with recent onset of gynecomastia owing to drugs or one of the pathologic conditions noted in Tables 8-1 and 8-2, however, may present with breast or nipple pain and tenderness. Approximately 10% to 15% of patients recall a history of breast trauma just before or at the time of discovery of the breast enlargement (15). It is unclear whether breast trauma itself causes gynecomastia. It is likely that, in many patients with an antecedent history of trauma, the breast irritation from the trauma actually led to the discovery of preexisting gynecomastia. Although half of patients have clinically apparent bilateral gynecomastia, histologic studies have shown that virtually all patients have bilateral involvement (16). This discrepancy may be explained by asynchronous growth of the two breasts and differences in the amount of breast glandular and stromal proliferation.

Gynecomastia must be differentiated from other conditions that cause breast enlargement. Although neurofibromas, dermoid cysts, lipomas, hematomas, and lymphangiomas may enlarge portions of the breast, these abnormalities are usually easily distinguished from gynecomastia on historical or clinical grounds. The two conditions that are most important to differentiate are pseudogynecomastia and breast carcinoma. *Pseudogynecomastia* refers to enlargement of the breasts owing to fat deposition rather than to glandular proliferation. Patients with this condition often have generalized obesity and do not complain of breast pain or tenderness. In addition, the breast examination should allow the correct diagnosis (Fig. 8-3). The breasts are examined while the patient is lying on the back with hands behind the head. The examiner places a thumb on one side of the breast and the second finger on the other side. The fingers are then gradually brought together without more than superficial pressure being applied to the skin. Patients with gynecomastia have a rubbery or firm disc of tissue that extends concentrically out from the nipple and that either is easily palpated or offers some resistance to the apposition of the fingers, whereas those with pseudogynecomastia exhibit no such mound of tissue, and no resistance is felt as the fingers are brought together (10). Alternatively, flat palpation with the finger can be used to detect the glandular tissue.

Differentiation of gynecomastia from breast carcinoma usually can be accomplished through careful physical examination. Carcinoma of the breast in men is usually eccentric in location and unilateral (rather than subareolar and bilateral) and is hard or firm, whereas gynecomastia tends to be rubbery to firm in texture. Patients with carcinoma may also exhibit skin dimpling and nipple retraction; they are more likely to have a nipple discharge (10%) than are patients with gynecomastia and may present with axillary lymphadenopathy (15,17). If the two conditions cannot be differentiated on clinical grounds, then mammography, fine-needle aspiration (FNA) for cytologic examination, or core or open biopsy should be done. There is no increased risk of breast cancer in men with gynecomastia followed for 20 or more years (18). Although some epidemiological studies have failed to find an association between Klinefelter's syndrome and breast cancer, the largest study found a 19.2-fold increased incidence compared to the general male population (19).

After a clinical diagnosis of gynecomastia has been made, several causes should be investigated through a thorough history and physical examination. A careful history of medication use is essential, specifically regarding ingestion of the drugs listed in Table 8-2. A history of liver or renal disease, especially if the patient has been receiving hemodialysis for

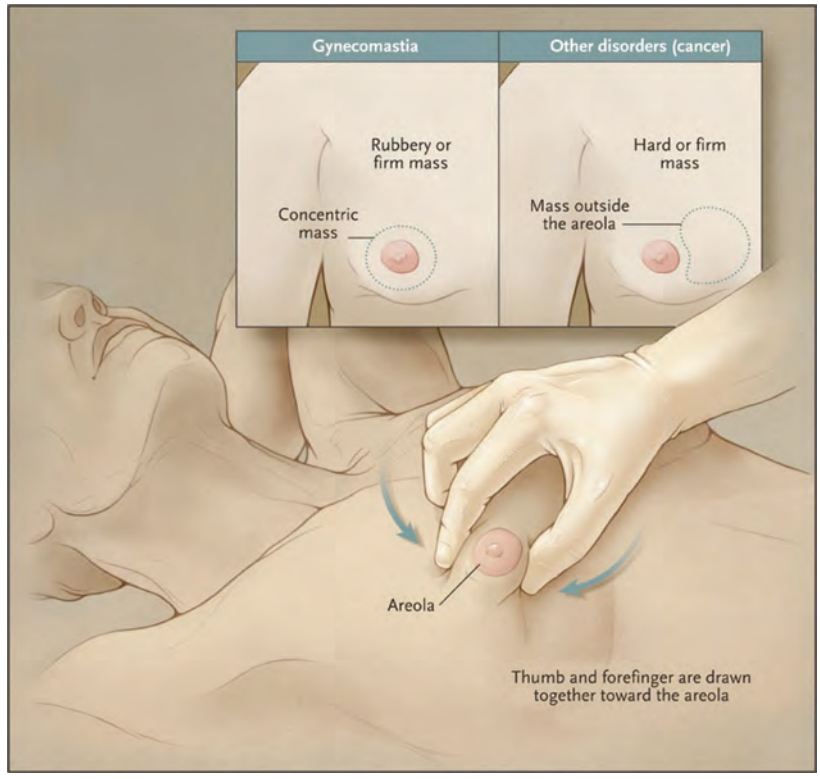

FIGURE 8-3 Differentiation of gynecomastia from pseudogynecomastia and other disorders by physical examination. (From Braunstein GD. Gynecomastia. *N Engl J Med* 2007;357:1229–1237, with permission.)

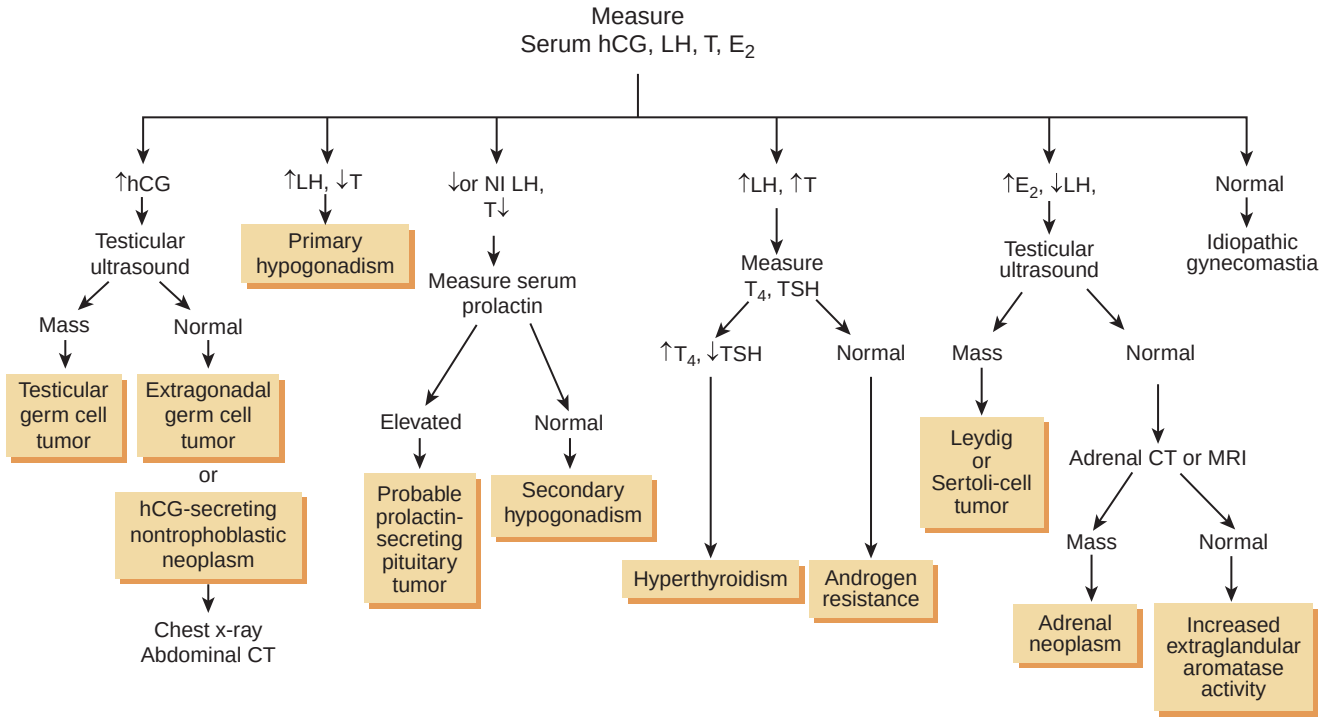

FIGURE 8-4 Algorithm providing interpretation of serum hormone levels and recommendations for further evaluation of patients with gynecomastia. CT, computed tomography; E_2, estradiol; hCG, human chorionic gonadotropin; LH, luteinizing hormone; MRI, magnetic resonance imaging; NI, normal; T, testosterone; T_4, thyroxine; TSH, thyroid-stimulating hormone. (From Braunstein GD. Gynecomastia. *N Engl J Med* 1993;328:490–495, with permission.)

the latter, may point to the underlying cause. A history of weight loss, tachycardia, tremulousness, diaphoresis, heat intolerance, and hyperdefecation, with or without the presence of a goiter, raises the possibility of hyperthyroidism. The patient should be evaluated for the signs and symptoms of hypogonadism, including loss of libido, impotence, decreased strength, and testicular atrophy. A careful examination for abdominal masses, which may be present in nearly one-half the patients with adrenocortical carcinoma, and a meticulous examination for testicular masses are essential parts of the evaluation.

The next step depends on the results of the clinical evaluation. If any of the drugs listed in Table 8-2 have been ingested, they should be discontinued and the patient reexamined in 1 month. If the drug was the inciting agent, then a decrease in breast pain and tenderness should occur during that time. If the patient is of pubertal age and has an otherwise negative general physical and testicular examination, he probably has transient or persistent pubertal gynecomastia. Reexamination at 3-month intervals should determine whether the condition is transient or persistent. At this time, medical or surgical therapy should be considered. If, during routine clinical examination, an adult is found to have asymptomatic gynecomastia without the presence of underlying disease, biochemical assessments of liver, kidney, thyroid function, and testosterone should be performed. In a patient with normal results, no further tests are necessary, but he should be reevaluated in 6 months. Conversely, if the gynecomastia is of recent onset or if the patient complains of pain or tenderness, additional studies—including measurements of serum concentrations of human chorionic gonadotropin (hCG), estradiol, testosterone, and luteinizing hormone—should be done, although the diagnostic yield is often low (20).

The algorithm outlined in Figure 8-4 can be used to discern the underlying abnormality, if any, that is responsible for the breast enlargement (6). An elevated level of hCG in the serum indicates the presence of a testicular or nongonadal germ cell tumor or, rarely, a nontrophoblastic neoplasm that secretes the hormone ectopically. Testicular ultrasonography should be done, and, if no testicular mass is found, a chest radiograph and abdominal computed tomographic scan or magnetic resonance imaging (MRI) study should be performed in an effort to localize an extragonadal hCG–producing tumor. Most nontrophoblastic tumors that secrete the hormone are bronchogenic, gastric, renal cell, or hepatic carcinomas. An elevated serum concentration of luteinizing hormone associated with a low testosterone level is indicative of primary hypogonadism, whereas a low testosterone level and a low or normal luteinizing hormone level suggest secondary hypogonadism owing to a hypothalamic or pituitary abnormality. Serum prolactin concentration should be determined in this situation to rule out a prolactin-secreting pituitary adenoma, which can cause hypogonadotropic hypogonadism. Elevated serum concentrations of luteinizing hormone and testosterone are found with hyperthyroidism and in patients with various forms of androgen resistance caused by androgen receptor disorders. Thyroid function tests can distinguish between these conditions.

If an elevated serum estradiol level is found along with a normal or suppressed concentration of luteinizing hormone, testicular ultrasonography is indicated to rule out a Leydig cell, Sertoli cell, or sex cord testicular tumor. If the ultrasonogram is negative, a computed tomographic scan or MRI scan of the adrenal glands should be done to detect an estrogen-secreting adrenal neoplasm. If both the testes and

adrenal glands appear normal, the increased estradiol level is probably caused by enhanced extraglandular aromatization of estrogen precursors to estrogens. In this situation, estrone levels are often relatively higher than estradiol concentrations. Finally, if all of these endocrine measurements are normal, the patient is considered to have idiopathic gynecomastia.

PREVENTION

Two situations exist in which gynecomastia can be prevented. The first is in patients who require a medication. Avoidance of the drugs listed in Table 8-2 decreases the risk for drug-induced breast stimulation. Also, not all the therapeutic agents in the drug groups listed in the table cause

TABLE 8-2

Drugs Associated with Gynecomastia

Hormones
Androgens and anabolic steroids (**F**)
Chorionic gonadotropin (**G**)
Estrogens and estrogen agonists (**G**)
Growth hormone (**G**)

Antiandrogens or Inhibitors of Androgen Synthesis
Bicalutamide (**G**)
Cyproterone (**G**)
Flutamide (**G**)
Gonadotropin-releasing hormone agonists (**G**)
Nilutamide (**G**)
5α-Reductase inhibitors (**G**)

Antibiotics
Ethionamide (**P**)
Isoniazid (**P**)
Ketoconazole (**G**)
Metronidazole (**P**)
Minocycline (**P**)

Antiulcer Medications
Cimetidine (**G**)
Lansoprazole (**P**)
Omeprazole (**F**)
Rabeprazole (**P**)
Ranitidine (**P**)

Cancer Chemotherapeutic Agents
Alkylating agents (**F**)
Cyclosporine (**P**)
Methotrexate (**P**)
Thalidomide (**P**)
Combination chemotherapy (**F**)

Cardiovascular Drugs
Amiodarone (**P**)
Amlodipine (**P**)
Captopril (**P**)
Clonidine (**P**)
Digoxin (**P**)
Diltiazem (**P**)
Enalapril (**P**)
Felodipine (**P**)
Methyldopa (**P**)
Nifedipine (**F**)
Reserpine (**P**)
Spironolactone (**G**)
Verapamil (**F**)

Psychoactive Agents
Aripiprazole (**P**)
Clozapine (**P**)
Diazepam (**P**)
Duloxetine (**P**)
Fluoxetine (**P**)
Haloperidol (**P**)
Olanzapine (**P**)
Paroxetine (**P**)
Perphenazine (**P**)
Phenothiazine (**P**)
Prochlorperazine (**P**)
Quetiapine (**P**)
Resperidone (**F**)
Sulpiride (**P**)
Thioridazine (**P**)
Trifluperazine (**P**)
Venlafaxine (**P**)
Ziprasidone (**P**)

Drugs of Abuse
Alcohol (**F**)
Amphetamines (**P**)
Heroin (**F**)
Marijuana (**P**)
Methadone (**F**)

Other
Auranofin (**P**)
Diethylpropion (**P**)
Domperidone (**P**)
Etretinate (**P**)
Fibrate (**P**)
Gabapentin (**P**)
Highly active antiretroviral therapy (HAART)
  Efavirenz (**F**)
  Indinavir (**P**)
  Stavudine (**P**)
Metoclopramide (**P**)
Penicillamine (**P**)
Phenytoin (**P**)
Pregabalin (**P**)
Statins (**P**)
Sulindac (**P**)
Theophylline (**P**)

Levels of evidence: Good (**G**), systematic review of randomized controlled trials, or randomized placebo-controlled trials, or prospective cohort studies with or without concurrent controls plus good pathophysiological explanation; Fair (**F**), retrospective studies, or case-control studies, or case series with good pathophysiological explanation; Poor (**P**), isolated case reports.
Adapted from Deepinder F, Braunstein GD. Drug-induced gynecomastia: an evidence-based review. *Expert Opin Drug Saf* 2012;11:779–795.

gynecomastia to the same extent. For example, when considering the use of a calcium channel blocker in an older man, the clinician should remember that nifedipine has been associated with the highest frequency of gynecomastia, followed by verapamil, with diltiazem having the lowest association (7,14). Among the mineralocorticoid antagonists, spironolactone, but not eplerenone is strongly associated with gynecomastia (14,21). Similarly, the incidence of gynecomastia in patients receiving histamine receptor or parietal cell proton pump blockers is highest with cimetidine, then ranitidine, and least with omeprazole (7,14). The second area of prevention occurs among patients with prostate cancer who are about to receive monotherapy with antiandrogens. Numerous studies have shown that prophylactic administration of the antiestrogen tamoxifen is superior to either the aromatase inhibitor anastrozole or low-dose breast irradiation (22,23).

TREATMENT

Discontinuation of the offending drug or correction of the underlying condition that altered the estrogen–androgen balance results in regression of gynecomastia in recent-onset breast growth. As was noted, histologic studies of the breast tissue from men with gynecomastia have shown a marked duct epithelial cell proliferation, inflammatory cell infiltration, increase in stromal fibroblasts, and enhanced vascularity early in the course of the disorder. It is during this proliferative, or florid, stage that patients may complain of breast pain and tenderness. This stage persists for a variable period, but usually lasts less than a year and is followed by spontaneous resolution or enters an inactive stage. There is a reduction in the epithelial proliferation, dilatation of the ducts, and hyalinization and fibrosis of the stroma (16,24). The inactive stage is usually asymptomatic. This histologic picture predominates in men whose gynecomastia is detected during a routine physical examination. When considering therapeutic approaches, it is important to appreciate that, after the inactive stage is reached, the gynecomastia is unlikely spontaneously to regress and is also unlikely to respond to medical therapies. Another important factor to consider is that most gynecomastia regresses spontaneously. Indeed, pubertal gynecomastia develops in a large proportion of boys, but very few exhibit persistent breast glandular enlargement. Similarly, in a group of patients with gynecomastia from various causes, 85% of untreated patients had spontaneous improvement (15). This finding emphasizes the difficulties in assessing the response to any medical intervention.

The indications for therapy are severe pain, tenderness, or embarrassment sufficient to interfere with the patient's normal daily activities. The objectives of surgery are to flatten the chest, eliminate the inframammary fold, align the two nipple-areola complexes, and conceal or contain the scars (25). Surgical removal of the breast glandular and stromal tissue has been the mainstay of interventional therapy. Subcutaneous mastectomy through a periareolar incision with contouring of the breast by suction-assisted lipectomy and ultrasound-assisted liposuction to remove the subglandular adipose tissue are currently the surgical procedure that are usually performed (25). These techniques should be used as primary therapy in patients with long-standing gynecomastia and as definitive therapy in patients who fail to respond to a series of medical therapies.

Three types of medical therapy—androgens, antiestrogens, and aromatase inhibitors—have been tested in patients with gynecomastia. Because this condition has a high frequency of spontaneous regression, the decision of when to treat is often difficult. It is also difficult to assess the use of most medications that have been tried, given the small sample sizes and nonblinded, uncontrolled designs of most studies. Nevertheless, with the exception of early pubertal gynecomastia that has been present for less than 3 months, a trial of medical therapy for patients with moderate to severe symptoms is recommended (26).

Testosterone administration has not been shown to be more effective than placebo in patients with pubertal or idiopathic gynecomastia and it carries the risk of exacerbating the condition by being aromatized to estradiol (15). Micronized testosterone has, however, been shown in a double-blind, placebo-controlled trial to reduce the prevalence of gynecomastia in men with liver cirrhosis after 6 months of therapy (26). Dihydrotestosterone, a nonaromatizable androgen, given either by injection or percutaneously, has been followed by a reduction in breast volume in 75% of patients, with complete resolution in approximately 15% (26). Responders had a decrease in breast tenderness within 1 to 2 weeks without side effects. The androgenic progestogen danazol has also been tried in uncontrolled trials and a single placebo-controlled study, with the latter showing a complete resolution in 23% of patients who received danazol and only a 12% response in those given placebo (26). Although the investigators believed that this drug was safe and well tolerated, other studies using danazol to treat other conditions have noted side effects, including edema, weight gain, acne, nausea, and muscle cramps.

The three antiestrogens that have been tested are clomiphene citrate, tamoxifen, and raloxifene. Response rates of 36% to 95% have been reported for clomiphene citrate, but two of the three systematic studies indicate that less than one-half of patients had a decrease in breast volume of 20% or more or were satisfied with the results (26). No side effects were noted by the investigators when the drug was used in dosages of 50 to 100 mg/day orally. In other settings, the drug has been associated with gastrointestinal distress and visual problems. Tamoxifen, given in dosages of 10 mg orally twice a day, has been studied in several uncontrolled as well as randomized, double-blind studies (26–28). Partial response is found in approximately 80% of the patients studied and complete regression noted in up to 60% of the patients. None of the studies has reported major side effects that are clearly medication-related from tamoxifen given in these doses, and, in view of its safety, the author usually recommends a 3-month trial of the drug for patients with painful gynecomastia. Raloxifene was reported to be partially effective in treating 10 patients with pubertal gynecomastia, but additional studies are needed to assess the true effectiveness of this drug (27).

The aromatase inhibitor testolactone has been given to a small number of patients with pubertal gynecomastia for up to 6 months at a dose of 450 mg/day orally without side effects (29). The authors of this uncontrolled study report a decrease in breast size after 2 months of therapy, but insufficient data currently exist to recommend this drug as a first-line agent. Anecdotal reports of the use of more potent members of this class of medications, such as anastrozole or letrozole, showed some benefit in individual patients (26). A study that examined anastrozole in a large group of patients with pubertal gynecomastia in a randomized, double-blind, placebo-controlled trial failed, however, to show a beneficial effect over placebo (30). In addition, anastrozole was found to be inferior to tamoxifen for preventing gynecomastia in patients with prostate cancer receiving antiandrogen monotherapy (22,23).

MANAGEMENT SUMMARY

- Gynecomastia, with its concentric enlargement of tissue radiating from beneath the nipple–areolar complex, needs to be differentiated from pseudogynecomastia (fatty breasts), cancer, and less common lesions.
- For a lesion that is unilateral, eccentric, or hard, breast cancer must be excluded through mammography or FNA, core, or open biopsy.
- Medications known to be associated with gynecomastia should be stopped or switched to another agent less likely to cause the problem. Breast pain and tenderness should remit within 1 month if the drug was the etiologic factor.
- If the patient is pubertal, a careful general physical and testicular examination should be performed and, if negative, the patient given reassurance, and seen again in 3 months.
- For breast enlargement that is of recent onset, is painful or tender, and hyperthyroidism or liver, adrenal, or testicular abnormalities are not present on physical examination, the clinician should measure serum concentrations of hCG, luteinizing hormone, estradiol, and free testosterone to differentiate among the pathologic causes of gynecomastia.
- If no reversible underlying cause is found and the patient has pain or tenderness or experiences embarrassment over the gynecomastia, a trial of medical therapy with tamoxifen or plastic surgical removal should be offered.

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CHAPTER 9

Pathology of Benign Breast Disorders

Laura C. Collins and Stuart J. Schnitt

CHAPTER CONTENTS

The term *benign breast disorders* encompasses a heterogeneous group of lesions that may present as a palpable mass, a nonpalpable abnormality detected on breast imaging studies, or an incidental microscopic finding. Some are discrete lesions, such as fibroadenoma and intraductal papilloma, but a large number of benign breast biopsies exhibit a mixture of microscopic changes affecting the terminal duct lobular units. The two major goals in the pathologic evaluation of a benign breast biopsy are (a) to distinguish benign lesions from *in situ* and invasive breast cancer, and (b) to assess the risk of subsequent breast cancer associated with the benign lesion(s) identified.

BENIGN BREAST DISEASE AND BREAST CANCER RISK: NONPROLIFERATIVE LESIONS, PROLIFERATIVE LESIONS WITHOUT ATYPIA, AND ATYPICAL HYPERPLASIAS

It has been known for many years that some benign breast lesions are more highly associated with breast cancer than others. Two types of studies have evaluated this relationship. In the first type, the prevalence of benign alterations

TABLE 9-1

Categorization of Benign Breast Lesions According to the Criteria of Dupont, Page, and Rogers (3)

Nonproliferative
- Cysts
- Papillary apocrine change
- Epithelial-related calcifications
- Mild hyperplasia of the usual type

Proliferative lesions without atypia
- Moderate or florid ductal hyperplasia of the usual type
- Intraductal papilloma
- Sclerosing adenosis
- Fibroadenoma
- Radial scar

Atypical hyperplasia
- Atypical ductal hyperplasia
- Atypical lobular hyperplasia

in breasts with cancer was compared with their prevalence in breasts without cancer (1). While these studies demonstrated that some benign lesions are more common in cancer-containing breasts, the histologic coexistence of certain benign breast lesions with breast cancer is not sufficient to establish that those benign lesions impart an increased cancer risk.

More recent studies have evaluated the subsequent risk of developing breast cancer in patients who have had a benign breast biopsy and for whom long-term follow-up is available (2–6). In these studies, histologic sections of the benign biopsies were reviewed, and the type of benign lesions present were recorded and related to the risk of breast cancer. In some of these studies, it was also possible to study the interaction of the histologic findings with other factors, such as family history of breast cancer, time since biopsy, menopausal status, and other factors in determining cancer risk. The results of these studies have provided important information regarding the risk of breast cancer associated with benign breast lesions and this information is useful in patient treatment, counseling, and follow-up. These studies have further indicated that terms such as *fibrocystic disease, chronic cystic mastitis*, and *mammary dysplasia* are not clinically meaningful because they encompass a heterogeneous group of processes, some physiologic and some pathologic, with widely varying cancer risks.

The seminal study evaluating benign breast disease and cancer risk is the retrospective cohort study of Dupont et al. (3,7). In their study, the slides of benign breast biopsies from more than 3,000 women in Nashville were reviewed, and the histologic lesions present were categorized using strictly defined criteria (3,7) into one of three categories: nonproliferative lesions, proliferative lesions without atypia, and atypical hyperplasias (Table 9-1). The risk of developing breast cancer was then determined for each of these groups. This system provides a pragmatic, clinically relevant approach to benign breast lesions and has been supported by a consensus conference of the College of American Pathologists (8). Studies from other groups have largely confirmed the initial observations of the Nashville group and have extended these findings by providing important new information regarding benign breast disease and breast cancer risk (2–6) (Table 9-2).

Nonproliferative Lesions

Nonproliferative lesions, as defined by Dupont and Page (3), include cysts, papillary apocrine change, epithelial-related calcifications, and mild hyperplasia of the usual type.

Cysts are fluid-filled, round-to-ovoid structures that vary in size from microscopic to grossly evident (Fig. 9-1). *Gross cysts*, as defined by Haagensen (9), are those which are sufficiently large to produce palpable masses. Cysts are derived from the terminal duct lobular unit. The epithelium usually consists of two layers: an inner (luminal) epithelial layer and an outer myoepithelial layer. In some cysts, the epithelium is markedly attenuated or absent; in others, the lining epithelium shows apocrine metaplasia, characterized by granular eosinophilic cytoplasm and apical cytoplasmic protrusions ("snouts").

Papillary apocrine change is characterized by a proliferation of ductal epithelial cells in which all of the cells show apocrine features as described above. *Epithelial-related calcifications* are frequently observed in breast tissue and may be seen in normal ducts and lobules or in virtually any pathologic condition in the breast. It should be noted that calcifications may also be seen in the breast stroma as well as in blood vessel walls. *Mild hyperplasia of the usual type* is defined as an increase in the number of epithelial cells within a duct that is less than four epithelial cells in depth. In this type of hyperplasia, the epithelial cells do not cross the lumen of the involved space.

TABLE 9-2

Relative Risk of Breast Cancer According to Histologic Criteria of Benign Breast Disease in Four Studies Using the Criteria of Dupont, Page, and Rogers (3)

Study	*Study Design*	*Histologic Category*		
		Nonproliferative[a]	*Proliferative without Atypia*[a]	*Atypical Hyperplasia*[a]
Nashville (3)	Retrospective cohort	1	1.9 (1.9–2.3)	5.3 (3.1–8.8)
Nurses' Health Study (2)	Case-control	1	1.5 (1.2–2.0)	4.1 (2.9–5.8)
Breast Cancer Detection Demonstration Project (4)	Case-control	1	1.3 (0.8–2.2)	4.3 (1.7–11.0)
Mayo Clinic (5)	Retrospective cohort	1.3 (1.15–1.41)	1.9 (1.7–2.1)	4.2 (3.3–5.4)

[a]Numbers in parentheses represent 95% confidence intervals.

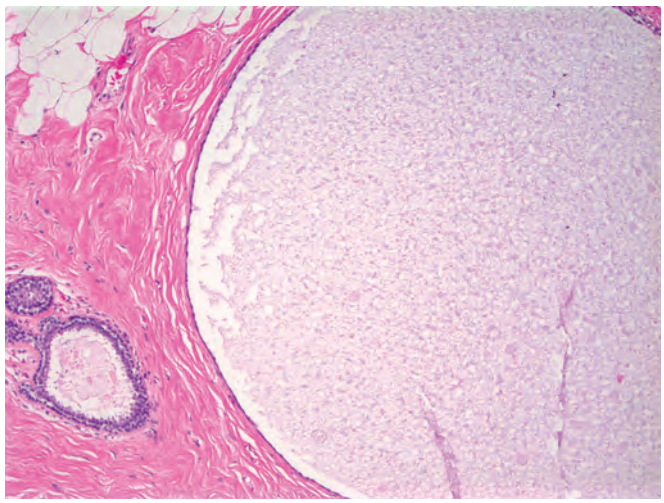

FIGURE 9-1 Cyst characterized by a large, dilated space filled with secretory material and lined by a flattened epithelial cell layer.

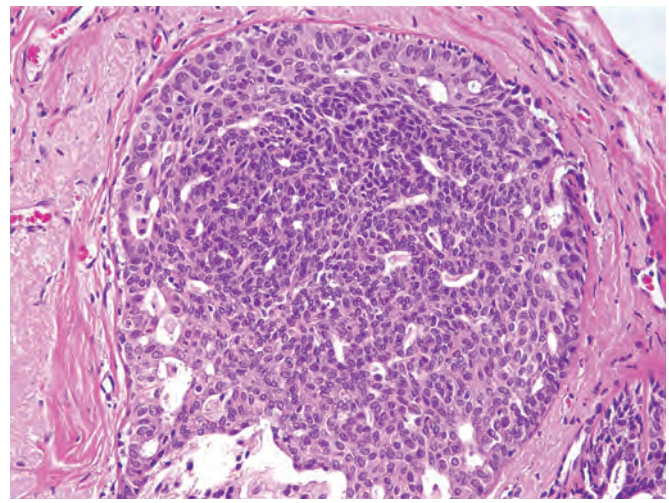

FIGURE 9-2 **Usual ductal hyperplasia.** A proliferation of cytologically benign epithelial cells fills and distends the duct. The nuclei vary in size, shape, and placement. The spaces within the duct are also variable in size and contour.

In the original study of Dupont and Page (3), 70% of the biopsies showed nonproliferative lesions. The risk of subsequent breast cancer among these patients was not increased, compared with that of women who have had no breast biopsy (relative risk [RR] 0.89), even in patients with a family history of breast cancer (in a mother, sister, or daughter). The only group of patients in the nonproliferative category with an increased risk of developing breast cancer was that with gross cysts plus a family history of breast cancer. The relative risk with gross cysts alone was 1.5, but was 3.0 in patients with gross cysts and a family history. It should be noted that, although Dupont and Page initially included fibroadenomas among the nonproliferative lesions, the results of a subsequent study by these investigators indicated a higher relative risk for breast cancer among patients with fibroadenoma than for patients with nonproliferative lesions (10). As a result, fibroadenomas are now included among the proliferative lesions without atypia (see the section on fibroadenomas).

Proliferative Lesions without Atypia

Included within the group of proliferative lesions without atypia are *usual ductal hyperplasia* (11) (also known as *moderate or florid hyperplasias of the usual type*), *intraductal papillomas, sclerosing adenosis,* and *radial scars* (3). As noted above, *fibroadenomas* are now included in this category as well. Women who have had a benign breast biopsy showing proliferative lesions without atypia, as defined previously, have a mildly elevated breast cancer risk, approximately 1.5 to 2.0 times that of the reference population (*intraductal papillomas, radial scars,* and *fibroadenomas* are discussed elsewhere in this chapter).

Usual ductal hyperplasias are intraductal epithelial proliferations more than four epithelial cells in depth. They are characterized by a tendency to bridge and often distend the involved space. The proliferation may have a solid, fenestrated or papillary architecture. If spaces remain within the duct lumen, they are irregular and variable in shape. These spaces are often slit-like and arranged around the periphery of the proliferation, with their long axes parallel to the basement membrane. The cells comprising this type of proliferation are cytologically benign and variable in size, shape, and orientation, and they often are arranged in a "swirling" pattern (Fig. 9-2). It is sometimes possible to discern multiple distinct cell populations, including epithelial cells, metaplastic apocrine cells, and myoepithelial cells (11).

Sclerosing adenosis is usually an incidental finding, but may present as a mammographic abnormality (microcalcifications, distorted architecture) or a mass lesion (also known as *nodular adenosis* or *adenosis tumor*). This lesion is composed of distorted epithelial, myoepithelial, and sclerotic stromal elements arising in association with the terminal duct lobular unit. This lobulocentric pattern is key to the correct diagnosis of sclerosing adenosis and its variants, and is best appreciated at low power microscopic examination (Fig. 9-3). The epithelium in sclerosing adenosis may undergo apocrine metaplasia, and is then referred to as *apocrine adenosis*. The apocrine metaplastic cells may show cytologic atypia, raising the differential diagnosis of invasive carcinoma if the lesion is examined at high microscopic power without accounting for the lobulocentric architecture appreciated at low power (12). Sclerosing adenosis may also be involved by atypical lobular hyperplasia, lobular carcinoma *in situ*, atypical ductal hyperplasia, or ductal carcinoma *in situ* (DCIS). Perineural "pseudoinvasion" may be present in approximately 2% of sclerosing adenosis cases and should not be confused with invasive carcinoma. Because of the distorted glandular pattern of sclerosing adenosis, this lesion may be confused with a low-grade invasive carcinoma, particularly tubular carcinoma. In contrast to the lobulocentric pattern of sclerosing adenosis, tubular carcinoma is infiltrative in nature, however, and does not conform to the normal breast ductal and lobular microanatomy. Although sclerosing adenosis is composed of distorted, elongated, or obliterated glands and tubules, tubular carcinoma is composed of angulated tubules with open lumens. The stroma of sclerosing adenosis is fibrotic or sclerotic compared with the desmoplastic stroma of invasive carcinoma. Importantly, as opposed to tubular carcinoma, sclerosing adenosis contains myoepithelial cells, which may be highlighted by immunohistochemistry.

Atypical Hyperplasias

Atypical hyperplasias have been defined as proliferative lesions of the breast that possess some, but not all, of the features of carcinoma *in situ* and are classified as either ductal

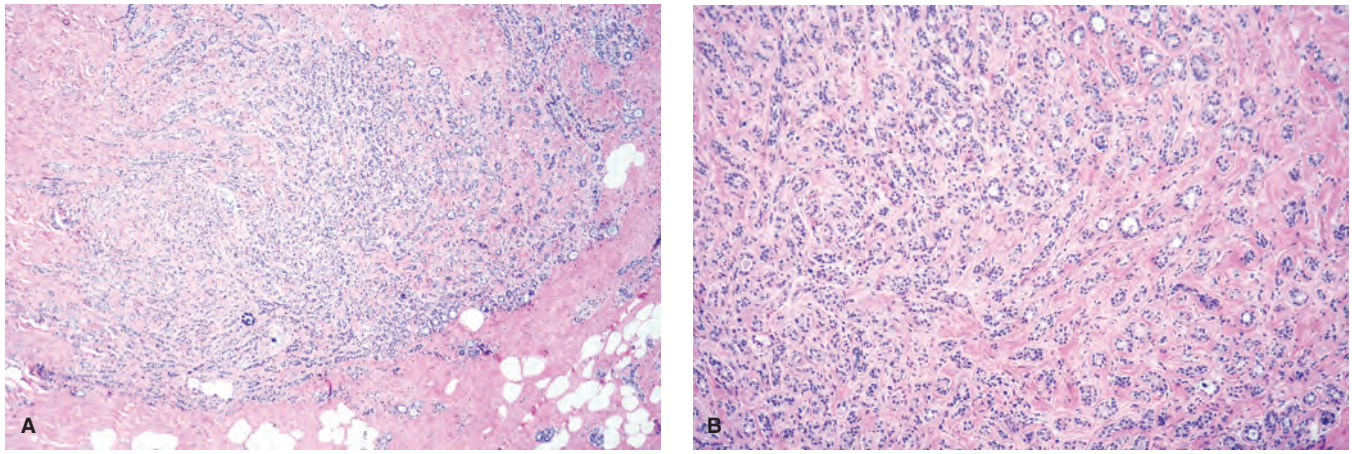

FIGURE 9-3 **Sclerosing adenosis. (A)** Low-power view demonstrates a lobulocentric proliferation of epithelial and stromal elements with scattered calcifications. **(B)** Higher-power view reveals glands and cords of epithelial cells entrapped in fibrotic stroma. The cells are cytologically benign, but the pattern simulates that of an invasive carcinoma.

or lobular type (3,7). *Atypical ductal hyperplasias* (ADH) are lesions that have some of the architectural and cytologic features of low-grade DCIS, such as nuclear monomorphism, regular cell placement, and round regular spaces, in at least part of the involved space. The cells may form tufts, micropapillations, arcades, bridges, solid, and cribriform patterns (11). A second cell population with features similar to those seen in usual ductal hyperplasia is also typically present (Fig. 9-4).

Atypical lobular hyperplasia (ALH) is composed of cells identical to those found in lobular carcinoma *in situ* (LCIS). These cells are monomorphic, evenly spaced, and dyshesive, with round or oval, usually eccentric nuclei and pale cytoplasm often with intracytoplasmic vacuoles (Fig. 9-5). Although criteria for the distinction between ALH and LCIS differ among experts, we utilize the criteria proposed by Page and Anderson (13) and diagnose ALH when the characteristic cells are present but less than one-half of the acini of a lobular unit are filled, distorted, or distended. In addition to involving lobular units, the cells of atypical lobular hyperplasia may also involve ducts (14).

It is important to note that with the increasing use of mammographic screening, atypical hyperplasias are being diagnosed more frequently than in the past. For example, when a biopsy is performed because of a palpable mass, atypical hyperplasia is seen in only about 2% to 4% of cases (3). In contrast, atypical hyperplasia was identified in 12% to 17% of biopsies performed because of the presence of mammographic microcalcifications (15).

Women who have had a benign breast biopsy that demonstrates atypical hyperplasia are at a substantially increased risk for developing breast cancer, approximately 3.5 to 5.0 times that of the reference population. Some studies have suggested that the risk associated with ALH is greater than that associated with ADH (2,7), but others have

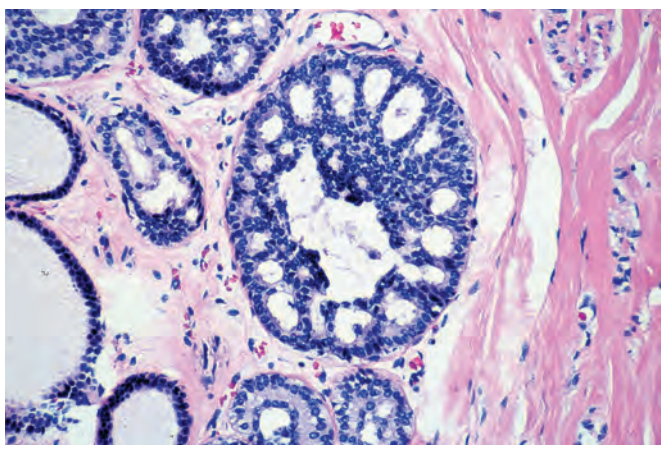

FIGURE 9-4 **Atypical ductal hyperplasia.** Near the center of this space is a proliferation of relatively uniform epithelial cells with monomorphic, round nuclei similar to those seen in low-grade ductal carcinoma *in situ*. However, these cells comprise only a portion of the proliferation within the space.

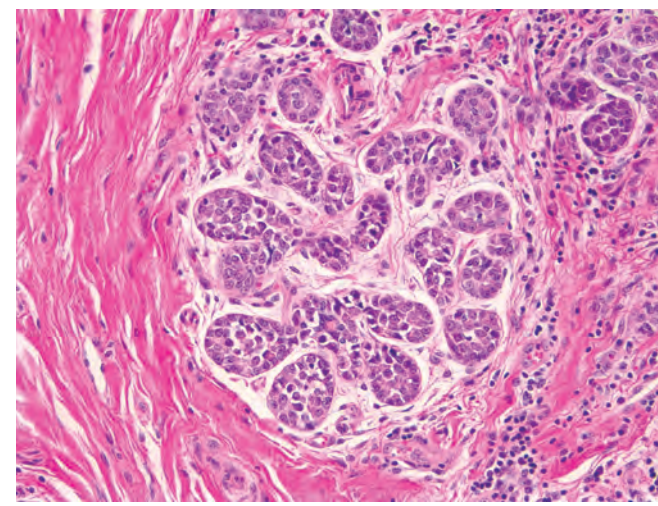

FIGURE 9-5 **Atypical lobular hyperplasia.** The acini of this lobule contain a proliferation of small uniform cells, which are dyshesive, and are identical to the cells that comprise lobular carcinoma *in situ*. However, the acini are not distended by this cellular proliferation.

TABLE 9-3

Relative Risk of Breast Cancer According to Type of Atypical Hyperplasia

Study/Reference	*All Atypical Hyperplasia*[a]	*Atypical Ductal Hyperplasia*[a]	*Atypical Lobular Hyperplasia*[a]
Nashville (7)	5.3 (3.1–8.8)	4.7 (2.5–8.9)	5.8 (3.0–11.0)
Nashville (88)	—	—	3.1 (2.3–4.3)
Nurses' Health Study (2)	4.1 (2.9–5.8)	3.1 (2.0–4.8)	5.5 (3.3–9.2)
Mayo Clinic (16)	3.9 (3.0–4.9)	3.8 (2.5–5.6)	3.7 (2.5–5.3)

[a]Numbers in parentheses represent 95% confidence intervals.

not (16) (Table 9-3); at the present time this issue remains unresolved. Patients whose biopsies showed ALH involving both lobules and ducts had a higher relative risk of developing cancer (RR 6.8) than those with either ALH alone (RR 4.3) or those with only ductal involvement by atypical lobular hyperplasia (RR 2.1) (14).

Columnar Cell Lesions and Flat Epithelial Atypia

Lesions of the breast characterized by enlarged terminal duct lobular units lined by columnar epithelial cells are being encountered increasingly in breast biopsies performed because of mammographic microcalcifications. Some of these lesions feature banal columnar cells in either a single layer (columnar cell change) or showing stratification and tufting, but without complex architectural patterns (columnar cell hyperplasia). In other columnar cell lesions, the lining cells exhibit cytologic atypia, most commonly of the low-grade, monomorphic type. Such lesions were included among lesions originally categorized by Azzopardi as "clinging carcinoma" (monomorphic type) (17), and were more recently included among lesions designated *flat epithelial atypia (FEA)* (11) (Fig. 9-6). The role of columnar cell lesions and, in particular, FEA in breast tumor progression is still emerging. FEA commonly coexists with well-developed examples of ADH, low-grade DCIS, and tubular carcinoma (11). These findings, in conjunction with the results of recent genetic studies (11), suggest that FEA is a neoplastic lesion that may represent either a precursor to, or the earliest morphologic manifestation of, DCIS. The few available clinical outcome studies suggest, however, that the risk of progression of FEA to invasive cancer is extremely low, lower even than that associated with ADH or ALH, supporting the notion that categorizing such lesions as *clinging carcinoma* and managing them as if they were fully developed DCIS will result in overtreatment of many patients (11). Additional studies are needed to better understand the biological nature and the level of subsequent breast cancer risk associated with these lesions.

Factors Modifying Breast Cancer Risk in Women with Biopsy-Proven Benign Breast Disease

A number of factors appear to modify the breast cancer risk associated with biopsy-proven benign breast disease, including a family history of breast cancer, time since biopsy, menopausal status, and the appearance of the background breast tissue.

Family History

There is general agreement that the presence of a family history of breast cancer in a first-degree relative (mother, sister, or daughter) is associated with a slight increase in the breast cancer risk in women with proliferative lesions without atypia (3–7). The influence of family history on breast cancer risk in women with atypical hyperplasia is less clear, however. Dupont et al. (3,7) reported that the risk among patients with both atypical hyperplasia and a family history of breast cancer was twice that of women with atypical hyperplasia without a family history. Similarly, in a study conducted by the Breast Cancer Detection Demonstration Project (BCDDP), the presence of a positive family history substantially increased the breast cancer risk among women with atypical hyperplasia (4). In a recent update of the Nurses' Health Study (6) and in a recent study from the Mayo Clinic (5), the presence of a positive family history was not, however, associated with a further increase in breast cancer risk among women with atypical hyperplasia (Table 9-4). Additional studies are needed to clarify this important issue.

Time since Biopsy

Information regarding the relationship between time since benign breast biopsy and breast cancer risk is available from several studies. In the Nashville study, women with prolifera-

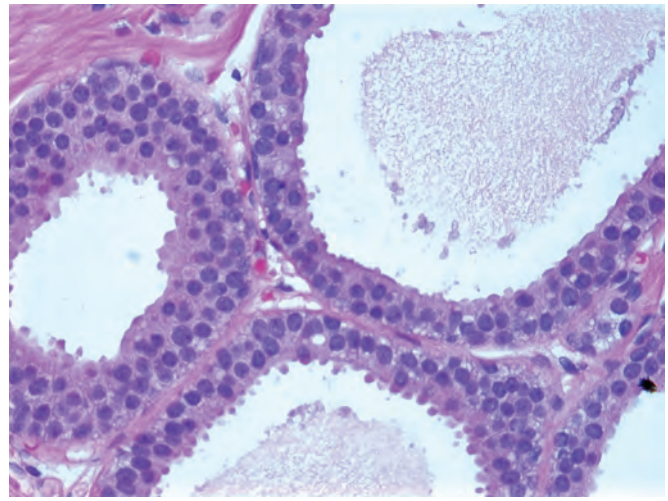

FIGURE 9-6 **Flat epithelia atypia.** The normal epithelial cells in the acini of this terminal duct are replaced by a population of columnar epithelial cells with round, monomorphic nuclei.

TABLE 9-4

Effect of Family History of Breast Cancer on Relative Risk of Breast Cancer

Study	*Proliferative without Atypia*		*Atypical Hyperplasia*	
	No Family History[a]	*Family History*[a]	*No Family History*[a]	*Family History*[a]
Nashville (3)	1.5 (1.2–1.9)	2.1 (1.2–3.7)	3.5 (2.3–5.5)	8.9 (4.8–17.0)
Nurses' Health Study (6)	1.5 (1.1–2.1)	2.5 (1.6–3.7)	4.3 (2.9–6.0)	5.4 (3.0–9.6)
Breast Cancer Detection Demonstration Project (4)	1.7 (0.9–3.2)	2.6 (1.0–6.4)	4.2 (1.4–12.0)	22.0 (2.3–203)
Mayo Clinic (5)	1.6 (~1.4–2.0)[b]	2.2 (~1.5–3.0)[b]	3.0 (~1.7–4.9)[b]	4.0 (~2.0–7.0)[b]

[a]Numbers in parentheses represent 95% confidence intervals.
[b]95% confidence intervals estimated from Figure 2 in Ref. (5).

tive lesions without atypia who remained free of breast cancer for 10 years after their benign breast biopsy were at no greater breast cancer risk than women of similar age without such a history. In addition, the breast cancer risk among women with atypical hyperplasia was greatest in the first 10 years after the benign breast biopsy (RR 9.8) and fell to a relative risk of 3.6 after 10 years (18). In contrast, in an analysis of data from the Nurses' Health Study, the breast cancer risk among women with proliferative lesions without atypia was similarly elevated before *and* after 10 years following the benign breast biopsy (RR 1.4 and 1.6, respectively). In addition, the risk associated with atypical hyperplasia was higher after 10 years (RR 5.2) than in the first 10 years after the benign breast biopsy (RR 3.3) (2). Similarly, in the Mayo Clinic study, an excess breast cancer risk was seen among women with biopsy-proven benign breast disease for at least 25 years after the benign breast biopsy (5). Among patients with atypical hyperplasia, the relative risk was persistently elevated beyond 15 years (16). More data are needed to clarify further the relationship between time since biopsy and breast cancer risk for women with benign breast disease, particularly for women with atypical hyperplasia.

Menopausal Status

The risk of breast cancer among women with atypical hyperplasia appears to be influenced by the patient's menopausal status. In the BCDDP study, premenopausal women with a biopsy showing atypical hyperplasia were at a substantially higher breast cancer risk (RR 12, 95% CI 1.0–68) than postmenopausal women with that diagnosis (RR 3.3, 95% CI 1.1–10) (4). In the Nurses' Health Study, the breast cancer risk associated with atypical hyperplasia as a group was similar in premenopausal and postmenopausal women (RR 3.9 and 3.8, respectively). Among premenopausal women, however, the risk associated with ALH was greater than the risk associated with ADH (RR 7.3 and 2.7, respectively). In contrast, the risk associated with ALH and ADH were similar in postmenopausal women (RR 3.4 and 4.0, respectively) (2). Of note, in both the BCDDP study and the Nurses' Health Study, the breast cancer risk among women with proliferative lesions without atypia did not vary according to menopausal status.

Another issue of clinical importance is the influence of postmenopausal hormone replacement therapy on the risk of breast cancer in women with biopsy-proven benign breast disease. Clinical follow-up studies have shown that women who take hormone replacement therapy are at increased risk for developing breast cancer (19). The use of hormone replacement does not, however, appear to further increase the risk in women with proliferative breast disease without atypia or in those with atypical hyperplasia. In an analysis from the Nurses' Health Study among women with proliferative lesions without atypia, the relative risks of breast cancer were similar for those women who never used postmenopausal hormones, who were past users, and who were current users (RR 1.6, 2.1, and 1.9, respectively). Similarly, among women with atypical hyperplasia, the relative breast cancer risks were not significantly different for those who had not used hormone replacement, for past users, and for current users (RR 3.4, 3.0, and 2.5, respectively) (20). Thus, the available data suggest that the use of hormone replacement therapy does not further increase the breast cancer risk among women with a history of biopsy-proven benign breast disease, even among those with atypical hyperplasia.

Background Breast Tissue

A study from the Mayo Clinic has suggested that the presence of lobular involution in the background breast tissue of a benign breast biopsy is associated with a significant decrease in the risk of breast cancer. Furthermore, in that study the presence of lobular involution modified the risk in women with proliferative lesions without atypia and in those with atypical hyperplasia. For example, the relative risk for the development of breast cancer was 7.8 (95% CI 3.6–14.8) for women with atypical hyperplasia without involution in the background breast tissue and 1.5 (95% CI 0.4–3.8) for those with both atypical hyperplasia and complete involution of the background breast tissue (21). Similar results have recently been reported for women enrolled in the Nurses' Health Study (22).

Laterality of Risk

Breast cancers that develop among women with atypical hyperplasia may occur in either breast. Overall, approximately 60% of cancers that develop in women with atypical hyperplasia occur in the ipsilateral breast; an excess of ipsilateral cancers is seen particularly in the first 10 years after the benign breast biopsy (2,5). Among women with ADH, about 55% of cancers occur in the ipsilateral breast (2,5,7). Among those with ALH, about 60% to 70% of the cancers occur in the ipsilateral breast (2). These observations suggest that the concept that atypical hyperplasias represent only risk indicators is overly simplistic and that, in at least some instances, these lesions may act as direct (albeit nonobligate) precursors to invasive breast cancer (23).

Consistency of Histologic Classification

The foregoing data provide compelling evidence that breast cancer risk varies with the histologic category of benign breast disease. They further indicate that the risk among women with biopsy-proven benign breast disease is influenced by other factors as well. To counsel individual patients properly, an understanding of the difference between relative risk and absolute risk is necessary. The *relative risk* for breast cancer represents the incidence of breast cancer among women within a certain subpopulation divided by the incidence of breast cancer in the reference population. The magnitude of the relative risk is highly dependent on the breast cancer incidence in both the study group and the reference population. In contrast, a woman's *absolute risk* of breast cancer is her probability of developing breast cancer during some specified time period. For example, although the relative risk for patients with atypical hyperplasia and a family history of breast cancer in the study of Dupont and Page was 8.9, only 20% of patients in this group had developed breast cancer 15 years after their benign biopsy. Eight percent of patients with atypical hyperplasia but no family history, 4% of patients with proliferative lesions without atypia, and 2% of women with nonproliferative lesions developed breast cancer in 15 years (3).

Given the apparent clinical importance of distinguishing among the various types of benign breast disease, the ability of pathologists to categorize accurately and reproducibly such lesions and to distinguish them from carcinoma *in situ* is a matter of legitimate concern. A study by Schnitt and colleagues suggests that with standardization of histologic criteria among pathologists, interobserver variability in the diagnosis of proliferative breast lesions can be reduced. In that study, six experienced breast pathologists were instructed to use standardized diagnostic criteria (i.e., those of Page et al.) for categorizing a series of proliferative breast lesions. Complete agreement among all six pathologists was observed in 58% of the cases and all but one pathologist arrived at the same diagnosis in 71% (24). The results of this study and others like it indicate that, although the use of standardized histologic criteria improves interobserver concordance in the diagnosis of proliferative breast lesions, even under these circumstances some lesions defy reproducible categorization, particularly the distinction between ADH and limited examples of low-grade DCIS.

Some authors have advocated that qualitative criteria should be supplemented by quantitative criteria to aid in the distinction between ADH and low-grade DCIS. For example, Page et al. (7) require that all of the features of low-grade DCIS be uniformly present throughout at least two separate spaces before DCIS is diagnosed. Lesions that have the qualitative features of low-grade DCIS that do not fulfill this quantitative criterion are categorized as ADH. Tavassoli and Norris (25) have suggested that the risk of breast cancer associated with very small foci of low-grade DCIS (i.e., less than 2 mm) is similar to that of ADH; therefore, they classify lesions that fulfill the qualitative criteria for low-grade DCIS but that are less than 2 mm in size as ADH. The most recent WHO working group did not endorse one approach over another; rather, it pointed out that quantitative criteria are meant to provide "pragmatic guidelines to prevent the overdiagnosis of small low-grade lesions as DCIS," thereby avoiding overtreatment of patients with minimal or equivocal lesions (11).

Newer Methods to Assess Breast Cancer Risk

There is currently an active effort to determine if biological markers in benign breast biopsies might be useful in predicting breast cancer risk, either alone or in combination with histopathology (26). A variety of biomarkers have been studied in this regard including estrogen receptor (ER), angiogenesis, p53 expression, HER2/neu expression, transforming growth factor (TGF)-β receptor II, and cyclooxygenase-2 (COX-2), among others.

In a study of ER expression in benign breast tissue, Khan et al. (27) found that the odds ratio for breast cancer in women with ER positive benign epithelium was 3.2 in comparison with women with ER negative benign breast tissue. In contrast, Gobbi et al. (28) found no significant differences in ER expression in usual-type hyperplasias of women who subsequently developed breast cancer compared with those who did not. Shabban et al. (29) have suggested that the ratio of ERα to ERβ in hyperplasias of the usual type is an important determinant of breast cancer risk. In that study, in women with hyperplasias of the usual type who developed invasive breast cancer the ERα-to-ERβ ratio was significantly higher than in those who did not develop breast cancer (29).

In a small pilot study, Guinebretiere et al. (30) found that increased angiogenesis in benign breast biopsies was associated with a significantly increased breast cancer risk, independent of the presence of atypical hyperplasia. Heffelfinger et al. (31) have also shown that some benign proliferative breast lesions are associated with angiogenesis in the surrounding stroma and that stromal vascularity associated with normal breast epithelium is greater in breasts with invasive cancer than in breasts without cancer. Finally, Viacava et al. (32) have demonstrated higher microvessel density counts in association with usual and atypical ductal hyperplasias than in association with normal mammary glandular structures.

One study has suggested that p53 protein accumulation in benign breast tissue was associated with an increased breast cancer risk (RR 2.6), even after adjustment for other breast cancer risk factors (33). However, a second study from the same group did not substantiate these findings; rather the combination of p53 protein accumulation and p53 nucleotide changes was associated with a nonsignificant fivefold increase in breast cancer risk (34). No significant association was found between HER2/neu protein expression in benign breast tissue and increased breast cancer risk in one study (33), whereas in another study HER2/neu gene amplification in benign breast tissue, as determined by the polymerase chain reaction, was associated with an increase in breast cancer risk, particularly among women with coexistent proliferative breast disease (35).

In another study, women with hyperplasia that showed loss of expression of TGF-β receptor II were found to have a greater risk of breast cancer than those whose hyperplasia showed prominent expression of this receptor protein (36). Recently, Visscher et al. (37) reported that higher levels of COX-2 expression in atypical hyperplasias were associated with greater breast cancer risk.

Insulin-like growth factor receptor-1 (IGF1-R) has recently been evaluated in normal breast terminal duct lobular units. IGF1-R is thought to play a role in breast tumorigenesis and the finding of cytoplasmic distribution of this protein has been shown to be associated with a threefold increase in breast cancer risk (38). This risk is further increased when there is little or no associated membranous staining with IGF1-R, wherein the risk of developing breast cancer is 15 times that of those women not developing breast cancer (38). As with the aforementioned studies, validation of these findings is still needed.

A number of studies have also evaluated loss of heterozygosity, genomic copy number changes, and microsatellite instability in benign breast lesions. These studies have

shown that at least some examples of usual ductal hyperplasia and atypical hyperplasia exhibit a variety of genomic alterations (39,40). The clinical significance of these observations is not yet clear, however. Finally, studies to identify patterns of gene expression or protein expression either in the epithelium or in the stroma using expression profiling and proteomic technologies, respectively, are likely to provide important new insights into the molecular and genetic alterations involved in both neoplastic progression and breast cancer risk in women with benign breast lesions.

A number of follow-up studies evaluating benign breast disease and breast cancer risk have used diagnostic criteria other than those of the Nashville group for categorizing benign breast lesions (41,42). In some of these studies, information regarding the pathology findings in the benign breast biopsies was obtained from a review of the pathology reports only, without a slide review. In general, in these studies, proliferative lesions, particularly those categorized as atypical hyperplasia, have been associated with a higher breast cancer risk than other lesions, although the magnitude of this risk has varied among these studies. In a recent analysis of almost 12,000 women enrolled in the National Surgical Adjuvant Breast and Bowel Project breast cancer prevention (NSABP-P1) trial, women with a history of biopsy-proven "benign breast disease" had a fourfold greater risk of developing breast cancer than women without such a history. Information about the benign breast disease was obtained from review of pathology reports and no further details regarding the nature of the benign breast disease were reported (43).

In summary, the results of clinical follow-up studies indicate that most women who have a benign breast biopsy are not at increased risk for developing breast cancer. A substantially increased breast cancer risk is seen only in the small percentage of patients whose benign breast biopsies show atypical hyperplasia using strictly defined histologic and cytologic criteria. The role of biological and molecular markers to help assess breast cancer risk is not yet well defined but remains an area of active investigation.

SPECIFIC BENIGN LESIONS

Benign Neoplasms and Proliferative Lesions

Fibroadenomas

On gross examination, fibroadenomas are pseudoencapsulated and are sharply delimited from the surrounding breast tissue. They are usually spherical or ovoid, but may be multilobulated. When cut, the tumor bulges above the level of the surrounding breast tissue. The cut surface is most typically gray-white, and small, punctate, yellow-to-pink soft areas and slit-like spaces are commonly observed. Occasionally, the tumor has a gelatinous, mucoid consistency.

Microscopically, fibroadenomas have both an epithelial and stromal component. The histologic pattern depends on which of these components predominates. In general, the epithelial component consists of well-defined, gland-like and duct-like spaces lined by cuboidal or columnar cells with uniform nuclei. Varying degrees of epithelial hyperplasia are frequently observed. The stromal component consists of connective tissue that has a variable content of acid mucopolysaccharides and collagen (Fig. 9-7). In older lesions and in postmenopausal patients, the stroma may become hyalinized, calcified, or even ossified (ancient fibroadenoma). On rare occasions, mature adipose tissue or smooth muscle may comprise a portion of the stroma. The term *intracanalicular* has been used to describe tumors in which the stromal component compresses the glands into slit-like spaces, whereas *pericanalicular* tumors are those in which the rounded configuration of the glandular structures is maintained. In fact, these two patterns often coexist in the same lesion, and this distinction has no clinical significance.

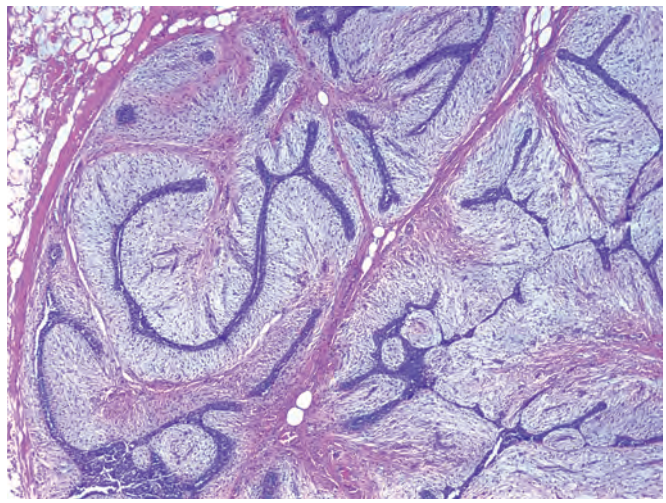

FIGURE 9-7 **Fibroadenoma.** The tumor is well circumscribed and is composed of benign glandular and stromal elements.

Complex Fibroadenomas: Fibroadenomas that contain cysts larger than 3 mm in diameter, sclerosing adenosis, epithelial calcifications, or papillary apocrine change have been designated complex fibroadenomas. In a review of almost 2,500 fibroadenomas, such changes were seen in 23% of the cases. In one clinical follow-up study, complex fibroadenomas were reported to be associated with a greater subsequent breast cancer risk than fibroadenomas that lack such changes (10).

Juvenile Fibroadenomas: Most fibroadenomas in adolescents and younger women are of the usual type seen in older patients. A few present a different clinical and pathologic picture and are termed *juvenile fibroadenomas*. This term, however, has been used by different authors to describe different lesions. Some authors use the term to refer to fibroadenomatous lesions that grow rapidly and may show venous dilatation in the overlying skin. Such lesions may clinically resemble virginal hypertrophy, and only surgical exploration will reveal a circumscribed tumor (44). Microscopically, juvenile fibroadenomas are more floridly glandular and have greater stromal cellularity than the more common adult-type fibroadenoma. Mies and Rosen (45) use the term *juvenile fibroadenomas* to refer to fibroadenomatous lesions that demonstrate severe epithelial hyperplasia which may border on carcinoma *in situ*. Nevertheless, these lesions behave in a clinically benign fashion.

Giant Fibroadenomas: Some tumors that are histologically typical fibroadenomas may attain great size. Several authors have used the terms *giant fibroadenoma* and *benign cystosarcoma phyllodes* synonymously, however, and have created considerable confusion regarding these entities. A lesion that has the microscopic appearance of a conventional fibroadenoma, but that is large, should still be classified as a fibroadenoma and may be treated adequately by enucleation. The major feature that distinguishes a cystosarcoma

phyllodes (preferably called a phyllodes tumor) from a giant fibroadenoma is the cellularity of the stromal component in the former (17). It must be noted, however, that the distinction between these two entities may be extremely difficult in some cases. Because juvenile fibroadenomas may attain great sizes, some authors consider them to be variants of giant fibroadenomas.

Infarction: Fibroadenomas may undergo partial, subtotal, or total infarction. Pregnancy and lactation are the most common predisposing factors. It has been postulated that a relative vascular insufficiency in the face of increased metabolic activity in the breast underlies this phenomenon (17).

Involvement of Fibroadenomas by Atypical Hyperplasia: Atypical hyperplasia of both ductal and lobular types may occasionally be found within a fibroadenoma. In a study of almost 2,000 fibroadenomas, atypical hyperplasia was found in 0.81% of the cases (46). Of note, in that study, the presence of atypia in a fibroadenoma did not predict for the presence of atypical hyperplasia in the surrounding breast tissue, nor was it associated with a significant increase in the risk of subsequent breast cancer.

Involvement of Fibroadenomas by Carcinoma: Infrequently, carcinoma occurs in association with a fibroadenoma. The most frequent type of carcinoma involving fibroadenomas is LCIS, but DCIS, invasive ductal, and invasive lobular carcinomas have also been observed. In almost half of the reported cases, the malignant tumor also involves the surrounding breast tissue. The prognosis of carcinoma limited to a fibroadenoma is excellent.

Adenomas

Adenomas of the breast are well-circumscribed tumors composed of benign epithelial elements with sparse, inconspicuous stroma. The last feature differentiates these lesions from fibroadenomas, in which the stroma is an integral part of the tumor. For practical purposes, adenomas can be divided into two major groups: tubular adenomas and lactating adenomas.

Tubular Adenomas

Tubular adenomas present in young women as well-defined, freely movable nodules that clinically resemble fibroadenomas. Gross examination reveals a well-circumscribed, tan-yellow, firm tumor. On microscopic examination, tubular adenomas are separated from the adjacent breast tissue by a pseudocapsule, and are composed of a proliferation of uniform, small tubular structures with a scant amount of intervening stroma. The tubules are composed of an inner epithelial layer and an outer myoepithelial layer, and resemble normal breast acini, both at the light and ultrastructural level. The tubular lumens often contain eosinophilic material. In some cases, this pattern is admixed with that of a fibroadenoma, suggesting a relationship between the two tumors.

Lactating Adenomas (Nodular Lactational Hyperplasia)

Lactating adenomas present as one or more freely movable masses during pregnancy or the postpartum period. They are grossly well circumscribed and lobulated, and on cut section appear tan and softer than tubular adenomas. On microscopic examination, these lesions have lobulated borders and are composed of glands lined by cuboidal cells with secretory activity, identical to the lactational changes normally observed in breast tissue during pregnancy and the puerperium. Although some authors believe that these lesions are the result of lactational changes superimposed on a preexisting tubular adenoma, others have suggested that they represent *de novo* lesions and are merely nodular foci of hyperplasia in the lactating breast.

O'Hara and Page (47) reviewed 42 breast adenomas that demonstrated lactational changes. They observed an overlapping spectrum of morphologic features in fibroadenomas with lactational changes and in lactating and tubular adenomas. These authors suggested that all these lesions may have a common pathogenesis.

Rarely, adenomatous tumors resembling dermal sweat-gland neoplasms are observed as primary lesions in the breast parenchyma (e.g., clear cell hidradenoma and eccrine spiradenoma) (11) or nipple (e.g., syringomatous adenoma) (11). Pleomorphic adenomas, histologically identical to those seen in the salivary glands and skin, have also been described in the breast (11). Although some of these lesions appear to arise from the breast tissue *de novo*, others appear to represent variants of intraductal papillomas.

Adenomas of the Nipple

Adenoma of the nipple has been described under a variety of names, including florid papillomatosis of the nipple ducts, subareolar duct papillomatosis, papillary adenoma of the nipple, and erosive adenomatosis of the nipple (11). It is not, strictly speaking, a true adenoma of the breast, because of its prominent stromal component.

On macroscopic examination, some adenomas of the nipple appear as solid, gray-tan, poorly demarcated tumors in the nipple and subareolar region; in other cases, no gross lesion is evident. Microscopically, the dominant feature is a proliferation of small gland-like structures. Solid and papillary proliferation of ductal epithelium is also usually evident; however, the papillary pattern may be inconspicuous or totally absent. In advanced lesions, glandular epithelium extends out onto the surface of the nipple. It is this phenomenon that results in the clinically apparent, reddish, granular appearance. Squamous epithelium frequently extends into the superficial regions of the involved ducts, sometimes with the formation of keratinaceous cysts. The lesions usually show considerable stromal fibrosis. This connective tissue may distort and entrap the epithelial elements, resulting in a pattern mimicking invasive carcinoma. The lesion is distinguishable from carcinoma by the preservation of a double layer of epithelium in the proliferating glands (an inner epithelial and outer myoepithelial cell layer), minimal nuclear atypia, absence of necrosis, and the overall low-power configuration. In problematic cases, immunohistochemical stains for myoepithelial cell markers may be of value in distinguishing a nipple adenoma (the glands of which are surrounded by myoepithelial cells) and invasive carcinoma (which lacks a myoepithelial cell component).

A few cases of carcinoma associated with adenomas of the nipple have been reported (48). In most cases, however, adenomas of the nipple are entirely benign. Reports of recurrence most likely represent cases in which the initial resection failed to remove the lesion completely.

Syringomatous Adenoma of the Nipple

Syringomatous adenoma of the nipple is an uncommon benign breast lesion similar in histologic appearance to eccrine syringoma of the skin. The usual clinical presentation is as a mass lesion in the region of the nipple–areola complex. Microscopic examination reveals an infiltrative pattern of epithelial islands that are angulated or comma shaped,

as well as tubular or solid in configuration. The glandular lumens are small or obliterated. Squamous metaplasia is usually present within a variable proportion of epithelial islands, which have an inconspicuous outer myoepithelial layer. The epithelial elements often "invade" into the smooth muscle of the nipple, mimicking invasive carcinoma (11).

It is important to distinguish syringomatous adenoma from the malignant lesions tubular carcinoma and low-grade adenosquamous carcinoma. The glandular structures of tubular carcinoma are mostly angulated with open lumens compared with the epithelial islands of syringomatous adenoma, which have smaller or absent lumens and often have characteristic "comma" or "tadpole" shapes. In addition, the glands of tubular carcinoma are composed of a single cell population as opposed to those of syringomatous adenoma, which have a variable amount of squamous metaplasia. Unlike syringomatous adenoma, tubular carcinoma often has associated DCIS. Low-grade adenosquamous carcinoma is virtually indistinguishable from syringomatous adenoma, but usually involves the deeper parenchyma of the breast. If low-grade adenosquamous carcinoma involves the nipple areola complex, the lesion may be impossible to distinguish from syringomatous adenoma.

Intraductal Papillomas

Intraductal papillomas can be divided into two major categories: solitary (central) papillomas and multiple (peripheral) papillomas.

Solitary (Central) Papillomas

Solitary intraductal papillomas are tumors of the major lactiferous ducts, most frequently observed in women 30 to 50 years of age. These lesions are generally less than 1 cm in diameter, usually measuring 3 to 4 mm. Occasionally, they may be as large as 4 or 5 cm. On gross examination, solitary intraductal papillomas are tan-pink, friable tumors within a dilated duct or cyst. A frankly papillary configuration may or may not be apparent. The tumor is usually attached to the wall of the involved duct by a delicate stalk, but it may be sessile. To identify the papilloma, the involved duct should be opened carefully, using a fine pair of scissors, until the tumor is exposed. Identification of the lesion may be facilitated by the placement of a suture at the end of the involved duct nearest the nipple. Randomly slicing through the excised tissue is not recommended because a small lesion might be missed.

Microscopically, these tumors are composed of multiple, branching, and interanastomosing papillae, each with a central fibrovascular core and a covering layer of cuboidal to columnar epithelial cells. A myoepithelial cell layer is often discernible between the epithelial cells and the connective tissue stalk (Fig. 9-8). In some areas, the complex growth pattern of the papillae results in the formation of glandlike spaces. Variable amounts of fibrosis can result in the entrapment of epithelial elements, producing a pseudoinfiltrative pattern. The lesion designated *ductal adenoma* appears to represent an extensively sclerotic variant of an intraductal papilloma (11). Florid epithelial proliferation is sometimes observed in intraductal papillomas. At times, the epithelial hyperplasia or fibrosis (or both) and the architectural distortion make it extremely difficult to distinguish between benign papilloma and papillary DCIS. Features helpful in making this distinction have been elucidated by Kraus and Neubecker (49) and by Azzopardi (17).

Several additional features of solitary intraductal papillomas deserve emphasis. Papillomas can undergo partial or total infarction, often accompanied by distortion of the adjacent, viable epithelium and production of a pattern that may simulate invasive carcinoma. Squamous metaplasia has been observed in intraductal papillomas. In some cases it accompanies infarction, but it has also been observed in the absence of infarction. This phenomenon may also result in a disturbing growth pattern that can be confused with carcinoma. Finally, some intraductal papillomas exhibit areas of atypia that range from foci resembling ADH to areas qualitatively similar to DCIS, most often low-grade. The classification of such lesions, particularly when the proliferation fulfills the qualitative criteria for the diagnosis of DCIS, varies among different authors. In general, the classification of such lesions has been based largely on the extent of the atypical proliferation within the papillary lesion. For example, Tavassoli uses the designation *atypical papilloma* if the atypical changes involve less than one-third of the

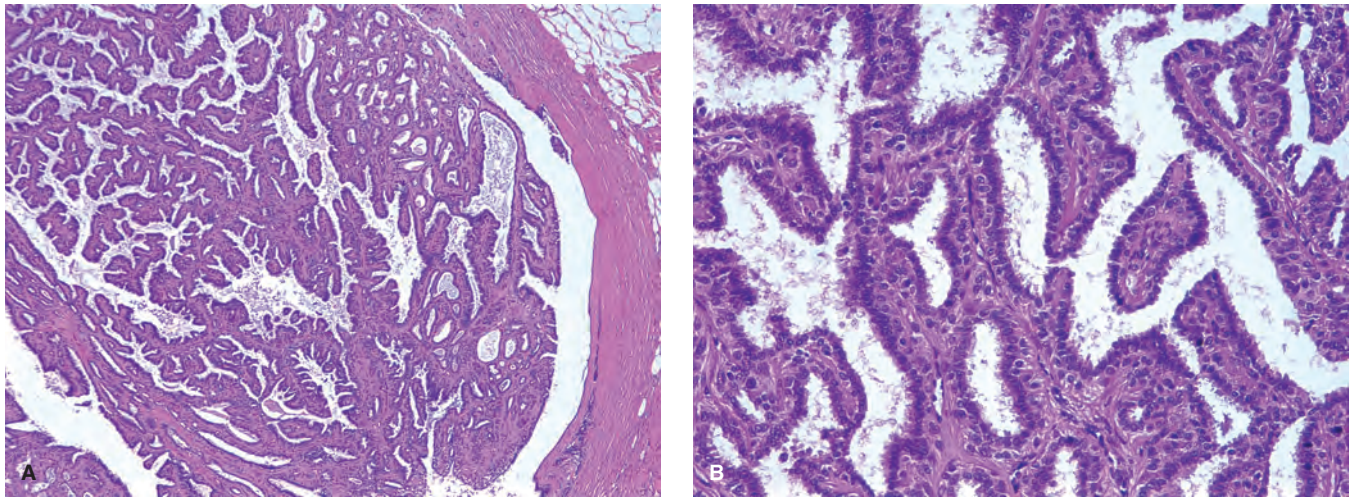

FIGURE 9-8 **Intraductal papilloma. (A)** Low-power view demonstrates the papillary lesion within a dilated duct. **(B)** Higher-power view demonstrates that the papillae are composed of fibrovascular cores covered by an epithelial cell layer (closer to the duct lumen) and a myoepithelial layer (closer to the cores).

papilloma and *carcinoma arising in a papilloma* when the atypical population of cells involves at least a third but less than 90% of the lesion (50). Page et al. (51) have stated that the presence of "any area of uniform histology and cytology consistent with non-comedo DCIS" within a papilloma that is more than 3 mm in size should be considered DCIS within a papilloma, whereas foci with the same qualitative features which measure 3 mm or less in size are classified as a papilloma with atypia. The most recent WHO Working Group recommended use of size/extent criteria as a pragmatic approach for distinguishing papillomas with atypia from papillomas with DCIS (11).

The clinical significance of atypia or DCIS in a papilloma is not well defined. Some authors have reported a substantially increased risk (7.5-fold) for the subsequent development of breast cancer, predominantly in the ipsilateral breast (51), whereas others have found that the level of breast cancer risk associated with papillomas with atypia was similar to that of patients with ADH elsewhere in the breast (four- to fivefold) and that the risk was approximately equal in both breasts (52). Breast cancer risk is reported to be particularly high (sevenfold) among women with multiple papillomas with atypia (52).

The risk of subsequent breast cancer and local recurrence does not appear to be related to the extent of atypia or DCIS within the papilloma. In fact, the most important consideration is the presence of atypia or DCIS in the surrounding breast tissue because this appears to be more closely related to the risk of recurrence than the qualitative features or extent of atypia within the papilloma itself (51,53).

Multiple (Peripheral) Intraductal Papillomas

Compared with solitary intraductal papillomas, multiple intraductal papillomas tend to occur in younger patients; they are less often associated with nipple discharge, are more frequently peripheral, and are more often bilateral. Most importantly, these lesions appear to be particularly susceptible to the development of carcinoma. In Haagensen's (9) series of 68 patients with multiple papillomas, simultaneous or subsequent carcinoma of the apocrine papillary and cribriform types was observed in 22 patients (32%). Another study in which surgically excised specimens from patients with intraductal papillomas were subjected to three-dimensional reconstruction confirms these observations (54). All 16 cases of multiple papillomas in the series were found to originate in the most peripheral portion of the duct system, the terminal duct lobular unit (TDLU). Furthermore, carcinoma was found to be associated with these multiple peripheral papillomas in six cases (37.5%). In contrast, no cases of carcinoma were found to be associated with solitary papillomas involving the large ducts. These findings suggest that peripheral papillomas, in contrast to solitary central papillomas, may be highly susceptible to malignant transformation.

Juvenile Papillomatosis (Swiss Cheese Disease)

This lesion occurs most commonly in adolescents and young women (with a mean age of 23 years), but has been seen in women up to 48 years of age. Patients typically present with a painless mass which, on physical examination, is circumscribed, easily movable, and is most often considered to be a fibroadenoma.

On gross pathologic examination, the lesions range in size from 1 to 8 cm. Multiple cysts of up to 1 cm in diameter are generally apparent. The microscopic features of juvenile papillomatosis are not unique to this entity, and are all components previously described as part of *fibrocystic disease*. The constellation of histologic features, however, forms a characteristic complex. These lesions appear to be well circumscribed, but not encapsulated, and are characterized by the following elements: duct papillomatosis, apocrine and nonapocrine cysts, papillary apocrine hyperplasia, sclerosing adenosis, and duct stasis. The epithelial proliferation in these lesions may be quite marked, and the cytologic and architectural features may approach those of DCIS.

Follow-up studies have suggested that juvenile papillomatosis is associated with an increased risk of breast cancer in the patient's female relatives, and that the patient herself may be at increased risk for developing carcinoma, particularly if the lesion is bilateral and the patient has a family history of breast cancer (55).

Microglandular Adenosis

Microglandular adenosis (MGA) is an uncommon lesion that may be found incidentally in breast tissue excised for other lesions, or it may present as a mass lesion. Most women in whom this lesion has been reported are older than 40 years of age, but patients as young as 28 years and as old as 82 years have been reported to have MGA (11). The importance of this lesion is that it may be mistaken for a well-differentiated (tubular) carcinoma on histological examination.

On gross examination, MGA has generally been described as an ill-defined area of firm, rubbery tissue. Microscopically, the lesion is characterized by a poorly circumscribed, haphazard proliferation of small, round glands in the breast stroma and adipose tissue. Unlike sclerosing adenosis, MGA does not have a lobulocentric, organoid configuration. As with tubular carcinoma, the glands are composed of a single cell layer and lack an outer myoepithelial layer. In contrast to tubular carcinoma, however, the glands are round (not angulated). The single layer of cuboidal epithelial cells has clear to slightly eosinophilic cytoplasm and small, regular nuclei, but the cells lack the apical secretory snouts that are characteristic of tubular carcinoma. The cells stain strongly for S100 protein, and the glands are surrounded by basement membrane material. Eosinophilic secretions are frequently present within the glandular lumina, and are periodic acid-Schiff (PAS) positive. When tubular carcinoma gland lumens contain material, it is usually calcified. As opposed to the desmoplastic stroma associated with tubular carcinoma, the stroma in MGA is typically composed of dense, relatively acellular collagen, which usually demarcates the lesion from the adjacent parenchyma. In some areas, the stroma is minimal and the proliferating glands lie exposed in adipose tissue (Fig. 9-9).

The relationship between MGA and either simultaneous or subsequent carcinoma has been addressed in several studies (56,57). A study by Koenig et al. (58) emphasized the potential importance of atypical MGA as a transitional form between typical MGA and carcinomas arising in this setting. More recent evidence suggests a molecular link between MGA and invasive carcinoma (59). Utilizing array CGH techniques on areas of MGA, atypical MGA and associated invasive carcinomas, Geyer et al. demonstrated that MGA is a clonal lesion with genetic aberrations similar to those found in associated atypical MGA and invasive carcinomas (59). The results of this study, taken together with those reported by others, suggest that some MGA lesions may represent nonobligate precursors to triple negative breast cancers. Further corroboration of these findings in larger studies is still needed.

At the present time, the recommended approach to the treatment of patients with MGA is complete, local excision

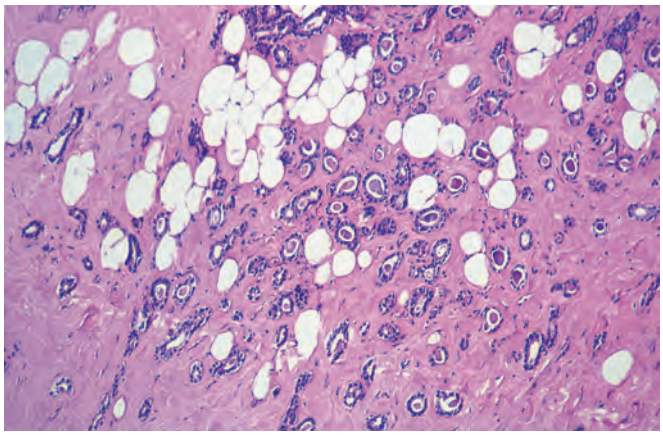

FIGURE 9-9 **Microglandular adenosis**. This adenosis is characterized by a haphazard proliferation of small glands composed of a single layer of epithelial cells. The glands are relatively rounded and many contain eosinophilic secretions in their lumens.

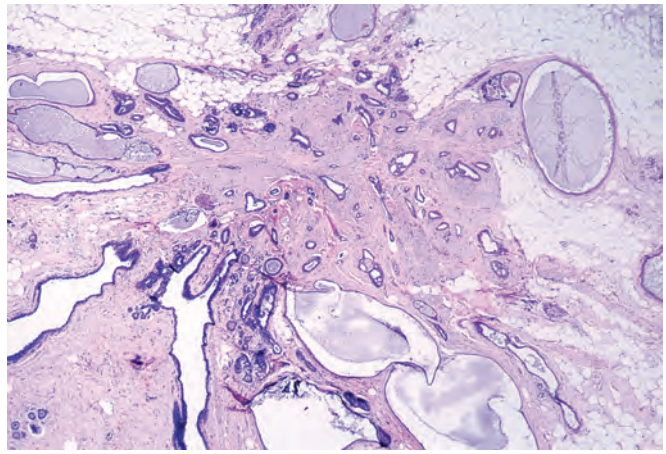

FIGURE 9-10 **Radial scar.** This lesion is characterized by a central fibroelastic core containing entrapped benign glands. Radiating from this core are ducts that show a variety of changes, including cysts and epithelial hyperplasia.

of the lesion and careful follow-up. Those with associated invasive carcinomas should be managed as for the stage of the invasive carcinoma.

Radial Scars

Radial scars were first recognized by Semb in 1928. The name *radial scar* was proposed in 1980, which was a translation of Hamperl's *strahlige narben* introduced in 1975. They have been described in the literature by a variety of other names, including sclerosing papillary proliferation, nonencapsulated sclerosing lesion, indurative mastopathy, and radial sclerosing lesion. The term *complex sclerosing lesion* is sometimes used for similar lesions larger than 1 cm in size or for those lesions with several fibroelastotic areas in close contiguity. The importance of these lesions is twofold. First, they may, on mammographic, gross, and microscopic examination, simulate breast carcinomas. Second, the relationship between the presence of radial scars and subsequent breast cancer has long been a matter of controversy (see discussion below).

Radial scars are most often incidental microscopic findings in breast biopsies performed for other indications (60,61). Some are sufficiently large to be detected mammographically where they appear as spiculated masses that cannot be reliably distinguished from carcinomas. The reported incidence of radial scars varies from 4% to 28% with more contemporary studies closer to the 5% to 7% range (61,62). Several studies have found radial scars to be bilateral and multicentric, with these frequencies reported to be as high as 43% and 67%, respectively (60). They are often multiple, with as many as 31 lesions having been observed in a single breast.

On gross examination, radial scars are irregular, gray-white, and indurated with central retraction—an appearance identical to that of scirrhous carcinoma. On microscopic examination, radial scars are characterized by a central zone of fibroelastosis from which ducts and lobules radiate, exhibiting various benign alterations, such as microcysts, apocrine metaplasia, and proliferative changes, such as florid hyperplasia and papillomas. Within the central area of fibroelastotic stroma, smaller entrapped ducts are present, which are often distorted or angular in appearance (Fig. 9-10). These ducts are lined by one or more layers of epithelium and an outer myoepithelial cell layer. The presence of these myoepithelial cells may be confirmed immunohistochemically with markers such as smooth muscle myosin heavy chain, p63, and calponin. Radial scars may be involved by atypical hyperplasia (either ductal or lobular), and LCIS, DCIS, or invasive carcinoma may rarely be present.

The relationship between radial scars and breast cancer has interested investigators for many years. The observation that the entrapped epithelial elements within the central zone of fibroelastosis in radial scars may mimic tubular carcinoma led several authors to postulate that radial scars represent an early phase in the development of some breast cancers (63). The presence of invasive, *in situ* carcinoma, or both in some radial scars has been cited as further support for the concept of their malignant potential (64). To define further the relationship between radial scars and breast cancer, Sloane and Mayers (64) reviewed 126 radial scars and complex sclerosing lesions. They found that carcinoma and atypical hyperplasia were more common in radial scars larger than 6 to 7 mm than in smaller radial scars and in radial scars in women older than 50 years than in younger women. The similarity in appearance between radial scars and some cancers, and the coexistence of *in situ* or invasive carcinoma within some radial scars, although of interest, does not, however, provide conclusive evidence of a relationship. Studies of the frequency of radial scars in women with breast cancer compared with those without cancer have, however, yielded conflicting results regarding their potential premalignant nature (65).

Until recently, the malignant potential of radial scars postulated in these observational reports had not been validated by clinical follow-up studies. The few available follow-up studies that existed were characterized by small patient numbers and lack of suitable controls. The results of one case-control study suggest that women with a biopsy-proven radial scar are at increased risk for subsequent breast cancer. In that study, the presence of a radial scar was associated with a twofold increase in breast cancer risk, independent of the histologic category of benign breast disease (61). Moreover, the presence of a radial scar further increased the breast cancer risk in women with other types of proliferative breast disease, particularly those with proliferative lesions without atypia. In a subsequent study, the increased breast cancer risk associated with radial scars was observed primarily in women over the age of 50 years and

was largely attributable to the category of coexistent proliferative breast disease. However, two recent studies have not shown an increase in breast cancer risk over and above that associated with the category of proliferative breast disease (62,66). Therefore, radial scars are probably best considered markers of generalized increased breast cancer risk. Given that *in situ* and invasive carcinomas appear to be more common in larger than smaller radial scars (64), the possibility that at least some radial scars represent direct cancer precursors must also be considered. In fact, these two possibilities are not mutually exclusive. Most authorities agree that the finding of radial scar on a core needle biopsy is an indication for excision (67).

The pathogenesis of radial scars is uncertain, as are the reasons for their association with an increased risk of breast cancer. It is attractive to postulate that a disturbance in the normal reciprocal stromal–epithelial interaction exists in radial scars. This may be a reflection of a more generalized perturbation of the interaction between stromal and epithelial cells in the breast, a phenomenon postulated to be important in breast cancer pathogenesis. Jacobs et al. (61) demonstrated by *in situ* hybridization that certain vascular stromal factors found in radial scars were similar to those in invasive carcinomas, raising the possibility that a similar disturbance in stromal–epithelial interactions is present in both lesions.

Granular Cell Tumor

Granular cell tumors are uncommonly found in the breast but, when present, simulate carcinoma on clinical, mammographic, and pathologic examination (68). These tumors occur more commonly in African American than white women, and typically appear between puberty and menopause, implicating some hormonal factor in their development. Granular cell tumors of the breast most commonly occur in the upper, inner quadrant in contrast to carcinomas, which occur most frequently in the upper, outer quadrant. Patients present with a palpable mass that may be associated with skin retraction or fixation to chest wall skeletal muscles. The similarity of granular cell tumors to carcinoma is also evident on mammographic examination, on which they resemble scirrhous carcinoma. Gross examination of the lesion reveals a gray-white to tan firm tumor that may be gritty when cut with a knife; these features further support the impression of carcinoma. Microscopically, these lesions are identical to granular cell tumors in other sites, consisting of a poorly circumscribed proliferation of cells in which the most characteristic feature is prominent granularity of the cytoplasm. On electron microscopic examination, these granules correspond to secondary lysosomes. The nuclei are small and uniform, and lack the features of malignant disease.

Granular cell tumors are almost invariably benign and are adequately treated by wide local excision. Rare cases of malignant granular cell tumors have been reported in both the breast and extramammary sites. Granular cell tumors were initially considered to be myogenic in origin (hence, their earlier designation as granular cell myoblastomas), but ultrastructural and immunohistochemical evidence supports a neurogenic origin for these tumors (68).

Fibromatosis

Fibromatosis of the breast, which is analogous to fibromatosis in other sites (e.g., desmoid tumors of the abdominal wall), is characterized by a locally invasive, nonencapsulated proliferation of well-differentiated spindle cells (69). These tumors have the capacity to recur locally if inadequately excised, but they do not metastasize. Although most cases are sporadic, mammary fibromatosis may be seen in association with familial adenomatous polyposis, Gardner's syndrome, or as part of a hereditary desmoid syndrome (69). There is also an association with prior trauma or surgery, particularly the presence of breast implants.

Patients typically present with a palpable mass which is sometimes associated with skin retraction or fixation to the underlying pectoral muscle. On mammography, these lesions are indistinguishable from carcinomas. Gross pathologic examination reveals an ill-defined, firm, gray-white lesion. Microscopically, fibromatoses consist of interlacing bundles of spindle-shaped cells surrounded by collagen. The cells show minimal to no cytologic atypia, and mitoses are only infrequently encountered. The proliferation tends to surround and entrap preexisting ducts and lobules without destroying them. Fibromatosis may exhibit keloid-like areas where collagen is increased, and the periphery of the lesion may be more cellular, with lymphocytic aggregates also present. The edges of the lesion infiltrate irregularly into the adjacent parenchyma. On electron microscopic and immunohistochemical examination, many of the tumor cells have the features of fibroblasts and myofibroblasts.

The proper treatment for fibromatosis consists of wide local excision. Although metastases have not been reported, lesions may recur locally.

MISCELLANEOUS BENIGN LESIONS

Lipomas

Lipomas consist of encapsulated nodules of mature adipose tissue. Although true lipomas occur in the breast, many lesions designated *lipoma* probably represent foci of fatty breast tissue without a true capsule. *Adenolipoma* is a term that has been applied to a benign fatty tumor of the breast containing entrapped lobular epithelial elements (17); however, such lesions are probably best considered hamartomas.

Vascular Lesions

Benign vascular lesions of the breast parenchyma are relatively uncommon and most often represent incidental microscopic findings. In a series of 550 mastectomy specimens from patients with breast carcinoma, the incidence of benign hemangiomas was 1.2% (70). Benign vascular lesions of the breast can be divided into four major categories: *perilobular hemangiomas, angiomatoses, venous hemangiomas,* and *hemangiomas involving the mammary subcutaneous tissue*. The major significance of these lesions is that they must be distinguished from angiosarcomas. Benign angiomatous lesions are almost always microscopic in size and lack interanastomosing channels, endothelial proliferation, and atypia. Complete excision is recommended for all vascular lesions of the breast. Atypical vascular lesions have been described in the skin of the breast and the mammary parenchyma in women who have been treated with conservative surgery and radiation therapy for breast cancer and these may represent precursors to angiosarcoma of the breast (71,72).

Pseudoangiomatous Stromal Hyperplasia

Pseudoangiomatous hyperplasia of the mammary stroma is a benign stromal proliferation that simulates a vascular lesion. The lesion is often seen as an incidental microscopic finding, but may present as a palpable mass. Microscopic examination reveals complex interanastomosing spaces, some of which have spindle-shaped stromal cells at their margins simulating endothelial cells. Occasionally, the myofibroblasts aggregate together into fascicular bundles that

may simulate a myofibroblastoma. Ultrastructural examinations have demonstrated that the spaces appear to be caused by separation and disruption of collagen fibers and that the associated spindle cells are myofibroblasts. The significance of this lesion is that it must be distinguished from a true vascular lesion, specifically, angiosarcoma.

Chondromatous Lesions

Chondromatous lesions of the breast are uncommon. Although chondromatous changes are most often seen in breast carcinomas and sarcomas, chondroid metaplasia may rarely be seen in fibroadenomas and intraductal papillomas. A few cases of *chondrolipoma* have also been reported, as has a single case of *choristoma* containing cartilage.

Leiomyoma

Leiomyomas of the breast are most often seen in the areolar region and rarely occur in the breast parenchyma (17). The histologic characteristics are the same as those of leiomyomas in other tissue.

Neural Lesions

Neurofibromas and neurilemmomas (schwannomas) are benign nerve sheath tumors. These lesions are most frequently seen in the breast in patients with neurofibromatosis and are most common in the areolar area.

Adenomyoepithelioma

Adenomyoepitheliomas are uncommon lesions considered variants of intraductal papilloma. They present as palpable masses that are grossly circumscribed. Microscopically, these lesions are usually multinodular and are composed of a combination of epithelial and myoepithelial elements. The myoepithelial cells may be polygonal or spindle shaped. These lesions are adequately treated by complete local excision (73). Lesions composed exclusively of myoepithelial cells *(myoepitheliomas)* have also been described (74).

Hamartoma

Hamartomas of the breast present as well-defined masses on physical examination and on mammography. Microscopically, these lesions are composed of an admixture of ducts, lobules, fibrous stroma and adipose tissue in varying proportions. Occasional lesions also contain smooth muscle *(myoid hamartomas)*. These lesions frequently go unrecognized by the pathologist because histologically they resemble other benign or physiologic changes in the breast.

Myofibroblastoma

Myofibroblastomas are uncommon benign mesenchymal tumors. These lesions are typically well circumscribed and are most often composed of a proliferation of relatively uniform-appearing spindle cells in a densely collagenized stroma. The cells comprising the tumor show features of myofibroblasts on ultrastructural and immunohistochemical examination.

Mucocele-Like Lesion

Mucocele-like lesions are composed of mucin-containing cysts that often rupture, with resultant extravasation of mucin into surrounding stroma. The mucoid character of these lesions is usually evident on gross examination. The epithelium lining these cysts can range from benign (including flat or cuboidal epithelium and hyperplasia, including papillary) to atypical ductal hyperplasia to DCIS. The distinction between mucocele-like lesion and mucinous (colloid) carcinoma may be difficult, particularly if there are epithelial cells floating within the mucin. Therefore, these lesions must be completely excised and carefully examined histologically (with multiple sections if necessary) to rule out the possibility of an invasive mucinous carcinoma.

Collagenous Spherulosis

Collagenous spherulosis is most often an incidental microscopic finding in breast tissue removed for another abnormality. This lesion appears to be more frequent in breasts containing sclerosing lesions (e.g., radial scar or sclerosed papilloma). Occasionally, collagenous spherulosis may calcify and present as mammographic microcalcifications. This lesion is characterized by aggregates of eosinophilic fibrillary or hyaline spherules, or both, which are surrounded by an inner myoepithelial layer and outer epithelial layers within the lobules. This arrangement gives rise to an appearance of a fenestrated or cribriform proliferation at low power microscopic examination. The spherules are composed of variable amounts of basement membrane-like material and type IV collagen and are positive for PAS and Alcian blue. This lesion is important to recognize because it must be distinguished from cribriform DCIS and adenoid cystic carcinoma.

REACTIVE/INFLAMMATORY LESIONS

Mammary Duct Ectasia (Periductal Mastitis)

Mammary duct ectasia occurs primarily in perimenopausal and postmenopausal women, and is characterized by dilatation of the subareolar ducts. Considerable controversy exists regarding the most appropriate name for this condition. This controversy has arisen because some authors consider ductal dilatation to be the primary event, whereas others consider the ectatic ducts to be the consequence of prior periductal inflammation.

Duct ectasia is a frequent pathologic finding in breast tissue obtained at autopsy and in surgically excised material. It has been observed on microscopic examination in 30% to 40% of women older than 50 years of age. Clinically evident disease, however, occurs much less frequently (75).

A wide spectrum of pathologic changes is observed in this condition. Cut section of the gross specimen often reveals dilated, thick-walled ducts that contain pasty, yellow-brown secretions. The intervening stroma may be fibrotic. On microscopic examination, some cases show prominent inspissation of lipid-rich material within ducts, accompanied by periductal inflammation. Rupture or leakage of these ducts results in release of this material into the adjacent stroma, with subsequent inflammation and fat necrosis. Plasma cells may be a prominent component of the periductal and stromal inflammatory infiltrate. It should be noted that many cases previously designated as plasma cell mastitis probably represent a stage in the evolution of duct ectasia. In other cases, the histologic picture is dominated by periductal fibrosis and ductal dilatation with minimal inflammation.

As alluded to earlier, the pathogenesis of this condition has not been fully established. Dixon et al. (75) suggested that the primary event is periductal inflammation and that duct ectasia is the ultimate outcome of this disorder. In support of this premise, they observed that inflammation around nondilated ducts predominates in younger patients with this condition, whereas duct dilatation and nipple retraction are more common in older patients (75). Thus,

their postulated sequence of events in the evolution of this disease was that periductal inflammation leads to periductal fibrosis, which subsequently results in ductal dilatation. This group of investigators has also suggested that periductal mastitis and duct ectasia may represent two separate entities, based on differences between women with these two disorders with regard to age, clinical history, and smoking history (76).

Squamous Metaplasia of Lactiferous Ducts (Recurrent Subareolar Abscess, Zuska's Disease)

Keratinizing squamous epithelium normally extends into the orifices of the lactiferous ducts for 1 to 2 mm. If these keratinizing cells extend deeper into the ducts, keratin production can result in ductal distention and eventual duct rupture, resulting in an intense inflammatory response and sterile abscess formation. Secondary bacterial colonization and infection may occur. A fistulous tract may also develop, typically opening at the edge of the areola. Appropriate treatment requires excision of the involved duct, which may also require excision of a portion of the nipple (77).

Fat Necrosis

The importance of fat necrosis is that it may closely simulate carcinoma, both clinically and on mammographic examination.

The macroscopic appearance of fat necrosis depends on its age. In early lesions, there is hemorrhage and indurated fat. With time, a rounded, firm tumor is formed. The cut surface of the lesion at this stage has a variegated, yellow-gray appearance with focal hemorrhage. Cavitation can subsequently occur, owing to liquefactive necrosis. The lesion may eventually be converted to a dense, fibrous scar or may remain a cystic cavity with calcification of its walls.

On microscopic examination, early lesions show cystic spaces surrounded by lipid-laden macrophages and foreign body-type giant cells with foamy cytoplasm (Fig. 9-11). A variable, acute inflammatory cell infiltrate may be present, and there may be focal hemorrhage. With time, there is fibroblastic proliferation with deposition of collagen. Scattered, chronic inflammatory cells are usually present, and focal hemosiderin deposition may be observed. Even in older lesions, scattered, foamy histiocytes and foreign body giant cells are usually discernible. A similar pathologic appearance may be seen after surgical trauma to the breast and after radiation therapy for carcinoma (see the section on pathologic changes associated with radiation therapy, below).

Reactions to Foreign Material

Foreign body-type granulomatous inflammation has been described following injection within the breast of a variety of substances, including paraffin and silicone. Clinically, these lesions generally appear as firm nodules that may be tender.

A variety of tissue reactions has been reported in association with mammary implants (78). One of these is the formation of a fibrous capsule in the surrounding tissue. In 10% to 40% of patients there is contracture of this capsule which results in breast tightness or firmness and deformation of the implant necessitating either capsulotomy or removal of the implant and the surrounding capsule. Histologic examination of the capsular tissue shows varying degrees of fibrosis, chronic inflammation, fat necrosis, granulation tissue, fibrin deposition, histiocytes, and foreign body giant cells, often with demonstrable silicone

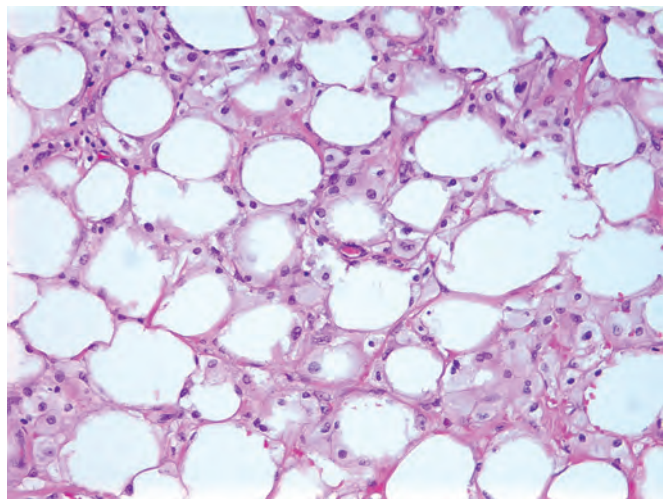

FIGURE 9-11 **Fat necrosis.** The fatty breast tissue is infiltrated by histiocytes containing foamy cytoplasm.

(and in some cases in which it has been used as part of the implant shell, polyurethane). In some cases, the capsule surrounding breast implants develops a cellular lining that histologically, immunohistochemically, and ultrastructurally resembles either normal synovium or synovium with papillary hyperplasia (proliferative synovitis) and has physiologic properties similar to synovium (78). This change has been variably described as *pseudoepithelialization, synovial metaplasia*, and *capsular synovial hyperplasia*. The factors associated with development of synovial-type metaplasia in this setting are not known. Some have suggested that this is a consequence of mechanical forces (e.g., micromotion and friction) between the implant and the surrounding tissue.

A more significant complication of prosthetic implants is the recently described implant-associated T-cell anaplastic large cell lymphoma (ALCL) (79). Patients present 1 to 23 years following implant placement (median time 8 years) with capsule-associated contracture or a late onset seroma. In the few reported cases, there does not appear to be a predilection for a particular implant type (i.e., saline vs. silicone; textured vs. smooth). Microscopic examination of the seroma fluid or the fibrous capsule reveals a relatively cohesive population of large, pleomorphic blasts. The vast majority of implant-associated ALCLs are ALK-negative (anaplastic large cell kinase-negative) (79). Removal of the implant is recommended once the diagnosis is established. Limited data suggest that this lymphoma is relatively indolent, though there are reports of cases with an aggressive clinical course (80).

Mondor's Disease (Phlebitis of the Thoracoepigastric Vein)

Mondor's disease, or phlebitis of the thoracoepigastric vein, has been considered to be rare (81). On pathologic examination, there is phlebitis and periphlebitis. The obliterative endophlebitis is associated with varying degrees of thrombosis, and the adventitia and media may be completely destroyed in advanced cases.

Pathologic Changes Associated with Radiation Therapy for Carcinoma

Breast-conserving surgery, followed by radiation therapy, is now a common treatment for patients with early-stage

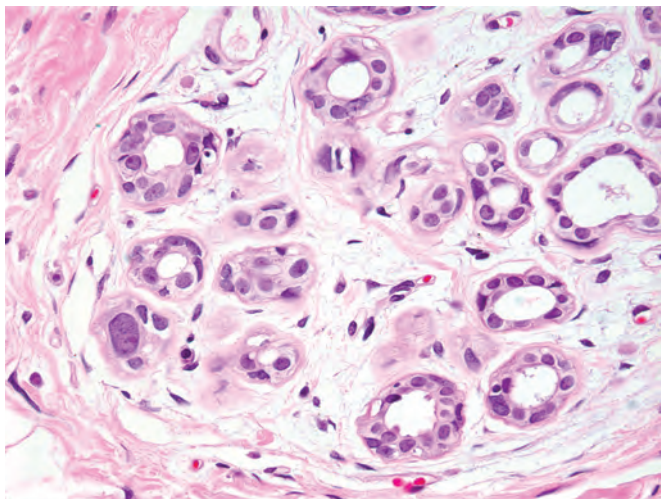

FIGURE 9-12 **Radiation effects.** This terminal duct lobular unit contains scattered enlarged epithelial cells with large, diffusely hyperchromatic nuclei. Cellular polarity is maintained and no evidence of cellular proliferation is present.

breast cancer. The effects of therapeutic doses of ionizing radiation on the skin of the breast have been well described, and are identical to the radiation-induced alterations occurring in skin from any irradiated site.

Fat necrosis can occur in the breast following local excision and radiation therapy for carcinoma. These lesions may be indistinguishable from carcinoma by clinical and radiographic examination, requiring complete histologic examination for accurate diagnosis. The most characteristic pathologic finding in breast tissue excised following primary radiation therapy for carcinoma is epithelial cell atypia in the TDLU, usually associated with varying degrees of lobular sclerosis and atrophy (82) (Fig. 9-12). These changes may be distinguished from carcinoma involving the TDLU by the preservation of polarity and cohesion, and by the absence of cellular proliferation and distention of the involved TDLU in areas of radiation-induced change. Similar epithelial changes have been described in patients treated with preoperative or neoadjuvant chemotherapy (83). Less frequently, epithelial atypia in large (extralobular) ducts, atypical fibroblasts in the stroma, and radiation-related vascular changes may be observed. Interestingly, stromal fibrosis, a characteristic feature of radiation effect in other organs, is so variable among both irradiated patients and nonirradiated control subjects that it is not, by itself, a reliable marker for radiation-induced injury in the breast.

Sarcoidosis

Involvement of the breast by sarcoidosis is rare, but when present, may clinically simulate a neoplasm. Histologically, the lesions consist of typical, noncaseating granulomas with varying numbers of giant cells present in the interlobular and intralobular connective tissue. A diagnosis of sarcoidosis should be made only after the exclusion of other causes of granulomatous inflammation, such as mycobacterial, fungal, and parasitic infections or reactions to foreign materials. Sarcoidosis should also be distinguished from *granulomatous mastitis*, a lesion in which the granulomas are associated with microabscesses and which may respond to corticosteroid therapy.

Lymphocytic Mastitis/Diabetic Mastopathy

Insulin-dependent diabetic patients occasionally develop breast masses that on histologic examination show a characteristic constellation of features. These include dense, keloid-like fibrosis, lymphocytic infiltrates in association with ducts and lobules (lymphocytic ductitis and lobulitis), lymphocytic vasculitis, and epithelioid fibroblasts in the stroma. Although the pathogenesis of this lesion is unknown, it may represent an autoimmune reaction. Similar histologic changes have been described in association with other autoimmune diseases, such as Hashimoto's thyroiditis and in patients with various types of autoantibodies in their serum (84).

IgG4-Related Sclerosing Mastitis

IgG4-related sclerosing mastitis is a benign disease process characterized by discrete, painless breast masses which may be unilateral or bilateral. These lesions are composed of dense lymphoplasmacytic infiltrates with lymphoid follicle formation, a prominent component of IgG4-positive plasma cells, stromal sclerosis, and lobular atrophy. Elevated serum levels of IgG4 are often present as well as the finding of similar lesions in other organs (85,86).

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SECTION III

Breast Imaging and Image-Guided Biopsy Techniques

CHAPTER 10

Breast Cancer Screening

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CHAPTER CONTENTS

INTRODUCTION

Until breast cancer can be prevented, regular screening programs are widely recommended for asymptomatic women. The rationale behind such programs is that early diagnosis through screening can possibly reduce mortality and morbidity more effectively than no screening at all. Nevertheless, even though breast cancer screening has been more thoroughly studied than any other type of cancer screening, questions remain about its overall benefits and potential harms.

Evaluating any screening program is challenging, and breast cancer screening in particular has been a topic of many controversies over the years. In this chapter, we review the general principles of cancer screening that women, clinicians, and health system administrators need to consider before undertaking a breast cancer screening program. We then describe the many modalities that have been studied for possible inclusion in screening programs, including screening mammography, ultrasound, magnetic resonance imaging, breast examination by clinicians, and breast self-examination by individual women. We also review published data from randomized, controlled trials, population studies, and meta-analyses regarding the effects of screening programs on mortality and their potential harms, including false positive and false negative results, overdiagnosis, radiation exposure, anxiety, and economic cost. We then look at data on screening issues in special populations, such as elderly women and women with genetic mutations. We conclude with suggestions on informed decision-making as individual women are the ones who must decide whether to undergo medical screening of any kind.

PRINCIPLES OF CANCER SCREENING

The goal of breast cancer screening is early detection of disease, to be followed by appropriate treatment. Screening tests differ from diagnostic tests insofar as screening identifies subgroups of people who have a high probability of

asymptomatic disease, while diagnostic tests are obtained in symptomatic patients. A positive screening result in an individual rarely provides direct evidence of disease; screening tests must be followed by diagnostic tests to determine whether disease is truly present.

When an apparently healthy population undergoes regular screening, medical professionals have an obligation to show that the benefits of screening outweigh the costs. As we discuss in more detail later in this chapter, a positive screening test result and a diagnosis of breast cancer brings anxiety and treatments with associated morbidities and costs. Screening tests should therefore be safe, with minimal side effects. The minimum requirements for establishing a safe, ethical, and cost-effective screening program involve three areas: the disease targeted by the program, the screening tests needed to detect the disease, and the features of the health care system needed to support the program (1). All the requirements for each of these areas are reviewed in further detail in the following material. If these requirements are not at least partially met, population-wide screening may be ineffective.

Disease Requirements

First, the disease must be serious, with significant morbidity or mortality. Second, an effective therapy for the disease must be available if it is detected as screening would obviously have no value if subsequent treatment would not be beneficial. Third, the natural history of the disease must be understood clearly enough to identify a significant window of opportunity during which the disease is detectable and detection would probably lead to a cure, or at least an effective treatment with less morbidity than the disease itself. Finally, the disease must not be too rare; if it is rare, we can expect an excess of false positive test results, which increases the cost and effort necessary to detect true positives.

Screening Test Requirements and Characteristics

First, a screening test must be reasonably easy and inexpensive to perform. Otherwise, the costs of large-scale screening in terms of time, effort, and money will be prohibitive. This is an important point to remember when considering the relative utility of the many screening modalities now available, as we will discuss in the next section. Second, the screening test must be safe and acceptable both to the individuals undergoing the screening and to their physicians. Finally, the level of accuracy of the screening test must be known and acceptable to the health care system, the physician, and the patient. Its sensitivity, specificity, positive predictive value, and other operating characteristics require careful assessment.

It is critical to understand the characteristics of a given screening test, as well as the interplay of its characteristics with those of the population screened and the clinicians who perform and interpret the test. We present a standard 2×2 table (Table 10-1) comparing the results of screening tests with the disease status of the individuals screened, along with a series of formulas to measure the sensitivity, specificity, and other performance features of the test. The next three paragraphs explain Table 10-1 in more detail.

A positive test result for a person who does not have the disease assessed by a test is called a false positive result while a negative result for a person who actually has the disease is called a false negative result.

Sensitivity refers to the ability of a screening test to detect a disease when it is present and is calculated as $a / (a + c)$. If a test is not sensitive, it will fail to detect disease in some people who actually have the disease; they appear in cell *c*.

Specificity refers to the ability of a screening test to indicate the absence of disease when no disease is present and is calculated as $d / (b + d)$. If a test is not specific, it will falsely indicate the presence of disease in some people who do not have the disease; they appear in cell *b*.

Another important parameter of a screening test is its predictive value, which may be either positive or negative. If a test result is positive, what is the probability that the person tested actually has the disease (i.e., true positive)? If the result is negative, what is the probability that the person does not have the disease (i.e., true negative)? The answers to these questions depend on the sensitivity and specificity of the screening test, as well as on the prevalence of the disease in the underlying population that undergoes screening. Positive predictive value (PPV) is calculated as $a / (a + b)$. Negative predictive value (NPV) is calculated as $d / (c + d)$, indicating the proportion of people with negative test results who are truly free of disease.

Health Care System Requirements

A screening program divides results into positives and negatives. Follow-up within a health care system must be available for everyone who has a positive result to confirm or rule out the presence of disease. Some follow-up testing can be expensive, time-consuming, and painful; it may even entail a degree of risk for the people who receive it. For example, estimates indicate that for every $100 U.S. dollars spent on breast cancer screening, an additional $33 are spent on subsequent diagnostic evaluations stemming from false positive results (2).

Before screening is undertaken, treatment should be available, accessible, and acceptable to people with disease. If a country's resources are too limited to provide treatment in an equitable manner, or if no effective treatment for a given disease is available, it makes no sense, either ethically or in terms of cost-effectiveness, to encourage screening when people in whom disease is actually detected must go untreated.

BREAST CANCER SCREENING MODALITIES

Screen-Film Mammography

Screen-film mammography (SFM) has historically been the standard modality used for breast cancer screening, and the technology studied in all major randomized controlled trials reporting mortality benefit from screening. SFM serves as both image receptor and display medium, thus, requiring images to be processed much like film-based photography prior to digital photography. SFM images need to be developed and fixed chemically, with an image rejection rate due to processing errors exceeding 20% (3). Repeat imaging due to processing errors results in increased examination time, increased patient exposure to ionizing radiation, and increased costs. Thus, full-field digital mammography (FFDM) has quickly replaced SFM, as it does not require chemical image processing and, by enabling real-time contrast and brightness correction, reduces the rate of image rejection due to processing errors.

Digital Mammography

Because SFM serves as both image receptor and display medium, the film must be processed before review, resulting in delayed interpretations and requiring additional resources

TABLE 10-1

Standard 2 × 2 Table Comparing Test Results and Disease Status of Subjects Tested, along with Formulas to Measure Test Characteristics

		TRUE DISEASE STATUS		
		Diseased	*Nondiseased*	*Total*
TEST RESULT	Positive	*a*	*b*	*a* + *b*
	Negative	*c*	*d*	*c* + *d*
	Total	*a* + *c*	*b* + *d*	*a* + *b* + *c* + *d*

Cells:

a = subjects with true positive test results
b = subjects with false positive test results
c = subjects with false negative test results
d = subjects with true negative test results

a + *b* = all subjects with positive test results
c + *d* = all subjects with negative test results
a + *c* = all subjects with disease
b + *d* = all subjects without disease

a + *b* + *c* + *d* = all study subjects

Associated formulas:

a / (*a* + *c*) = sensitivity
d / (*b* + *d*) = specificity
b / (*b* + *d*) = false positive error rate (alpha error rate, type I rate)
c / (*a* + *c*) = false negative error rate (beta error rate, type II rate)
a / (*a* + *b*) = positive predictive value
d / (*c* + *d*) = negative predictive value
[*a* / (*a* + *c*)] / [*b* / (*b* + *d*)] = (*a* / *b*) / [(*a* + *c*) / (*b* + *d*)] = likelihood ratio positive (LR+)
[*c* / (*a* + *c*)] / [*d* / (*b* + *d*)] = (*c* / *d*) / [(*a* + *c*) / (*b* + *d*)] = likelihood ratio negative (LR–)
(*a* + *c*) / (*a* + *b* + *c* + *d*) = prevalence

Adapted from Jekel JF, Katz DL, Elmore JG. *Epidemiology, biostatistics, and preventive medicine.* 2nd ed. Philadelphia: W.B. Saunders, 2001.

for image archiving. Full-field digital mammography (FFDM), in comparison to SFM, has been shown to have lower noise, higher contrast, and improved dynamic range (4). In addition, FFDM allows immediate display of digital images on a monitor without film processing, enabling more rapid interpretation (5). Moreover, FFDM makes the use of computer-aided detection (CAD) software, which recognize suspicious image patterns, a possibility.

Large clinical trials comparing FFDM to SFM have generally demonstrated similar accuracy overall, with slight improvements when FFDM is used in certain subpopulations(6–8). For example, the Digital Mammography Imaging Screening Trial (DMIST) compared the performance of FFDM to SFM in asymptomatic U.S. women, finding similar accuracy for breast cancer detection(9). However, FFDM was more accurate than SFM in three subpopulations: pre- or peri-menopausal women, women younger than age 50, and women with mammographically dense breast tissue. Given the growing evidence that FFDM is at least as useful as SFM for screening purposes, FFDM has progressively been adopted over SFM, especially in light of the potential efficiencies inherent in digital image transfer, interpretation, and archiving=(10).

Computer-Aided Detection

Computer-aided detection (CAD) has been found effective for improving the detection of malignancy when it is used in conjunction with both SFM and FFDM (11–13). CAD was initially developed to help radiologists identify small tumors that might otherwise be overlooked, and has been shown to detect 84% to 94% of small malignancies in SFM and FFDM, regardless of whether the malignancies present as masses or as calcifications (11,14,15). Moreover, CAD has been shown to have equal sensitivity for detecting malignancies in women regardless of breast density and histopathologic results (16). However, CAD is also associated with a high false positive rate of between 2 and 5 marks per screening case when the exams include four standard views (by either SFM or FFDM), which may potentially confound radiologic interpretation and lead to unnecessary diagnostic work-up (11,14,15,17). It is currently uncertain what effect the addition of CAD has had on patient outcomes such as mortality. Despite our lack of knowledge, CAD capabilities have become a standard feature of the latest generation of digital mammography workstations.

Ultrasound

Ultrasound serves as a critical adjunct diagnostic modality after abnormalities are noted during mammographic screening, and is increasingly used as a primary diagnostic modality for evaluating focal breast symptoms in women younger than age 40 (18,19). The use of ultrasound to screen asymptomatic women is also rapidly increasing, especially for women found to have extremely or heterogeneously dense breasts on mammography. Dense breast tissue reduces the sensitivity of screening mammography to detect malignancy, and is associated with an increased risk of breast cancer even after adjusting for associated risks such as age and body mass index (20–24). As of early 2013, legislation has been passed in the states of Connecticut, Texas, Virginia, New York, and California to mandate that women with mammographically dense breasts be informed that they may be at higher than average risk for developing cancer, and that they may benefit from supplemental screening tests such as whole-breast ultrasound (25).

Given the wide availability and relatively low cost of ultrasound, it will likely become the most common adjunct screening modality for asymptomatic women with dense breasts. However, current evidence for the effectiveness of ultrasound in breast cancer screening is scarce. To date, the largest trial comparing the addition of screening ultrasound to mammography in women with dense breasts and at least one other risk factor demonstrated a detection rate of 4.3 additional cancers per 1,000 women screened (26). Known as ACRIN 6666, this trial also found that the increased yield of detections came with an unfortunate increase in biopsy rates, from 2% of women screened with mammography alone to 5% of women screened with both mammography and ultrasound. Of the additional biopsies, only 7.4% were positive for cancer, suggesting a very high false positive rate. Because the screening exams studied in ACRIN 6666 were performed by subspecialty radiologists, it is uncertain what the rates of false positives and true positives would be for screening performed by community radiologists under real-world conditions (25). Moreover, no studies have demonstrated the clinical effectiveness of ultrasound screening in asymptomatic women with dense breasts who lack other risk factors.

Recently, automated whole-breast ultrasound (AWBU) was approved for medical use by the U.S. Food and Drug Administration (FDA). It enables the acquisition of ultrasound images of the breast without the need for a hand-held ultrasound exam (27). Early pilot data suggests that AWBU may provide high diagnostic accuracy and operator independence in whole-breast evaluation (28). However, no data from any large trials are currently available to indicate the rates of cancer detection, false positive results, unnecessary diagnostic follow-ups, or image-guided biopsies associated with AWBU.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) of the breast is more sensitive than mammography for identifying malignancies in women with a higher than average risk of breast cancer. Studies have found that the sensitivity of MRI for detecting cancer in this population ranges from 71% to 100%, in comparison to 16% to 40% for mammography (29–31). Currently, annual MRI screening is recommended for women with the gene mutations known as *BRCA1* and *BRCA2*, as well as women whose lifetime risk of breast cancer is higher than 25% (29). The latter group includes women with a strong family history of breast or ovarian cancer and women treated with radiation for Hodgkin disease. Using MRI to perform annual screening of women aged 35 to 54 years who carry the *BRCA1* mutation has been shown to be cost-effective, requiring $55,420 per year of life gained (after adjustment for quality of life) (32).

Insufficient data are available to assess the efficacy of annual MRI screening for women who have either personal histories of breast cancer, previous diagnoses of high-risk breast lesions (e.g., atypical ductal hyperplasia or lobular carcinoma *in situ*), or extremely dense breasts (29). Because the specificity of screening MRI is lower than that of mammography, its use may result in an increase in false positives and associated unnecessary diagnostic workups and image-guided biopsies. Studies suggest that 8% to 15% of all women who receive screening MRI are recalled for additional imaging evaluation, while 3% to 15% of all recipients of screening MRI will ultimately undergo breast biopsies (33 to 35). MRI remains an expensive technology, so its use for screening in the general population is unlikely to be covered by health insurance and will therefore require substantial out-of-pocket expenses for individual patients.

Digital Breast Tomosynthesis

While the sensitivity of FFDM is comparable to that of SFM, FFDM suffers from a masking effect caused by fibroglandular tissue lying directly above and below tumors in two-dimensional images. The masking problem can be partially overcome by digital breast tomosynthesis (DBT). This new technology, which has received approval by the FDA, uses a rotating camera that images the breast from various angles to create a three-dimensional view (36). DBT offers significant advantages over ultrasound and MRI in terms of cost, operation, and ease of use, as it has become an integrated component of the latest generation of digital mammography units (37).

Initial studies comparing DBT to FFDM demonstrated comparable sensitivity and specificity for detecting cancer (38–41). By eliminating the masking problem from screening mammography, adjunct DBT has been reported to produce a 30% to 40% reduction in call-back rates compared to FFDM alone (40–42). Because about 10% of U.S. women are recalled for additional views after screening mammography, DBT may offer substantial cost savings by reducing unnecessary diagnostic workups. As DBT is associated with an additional radiation dose equal to that of routine mammography, the use of adjunct DBT effectively doubles the radiation dose received by patients (43). The clinical and cost-effectiveness of DBT is currently under study in large clinical trials, but no results are available to date.

Molecular Breast Imaging

Molecular breast imaging includes several modalities that use nuclear medicine techniques in combination with radiopharmaceutical agents. Among them are breast-specific gamma imaging (breast scintigraphy) and positron emission mammography, two new technologies that have been approved by the FDA. Some physicians have begun to use molecular breast imaging either as an adjunct diagnostic modality for evaluating abnormalities found on screening mammography or in place of diagnostic MRI for patients with metallic implants or other contraindications for MRI (44). Anecdotally, some facilities also offer molecular breast imaging for screening high-risk patients and women with dense breasts. However, data on the clinical effectiveness of these techniques remain sparse. Nevertheless, as nuclear medicine technologies evolve, these devices may play an increasing role in breast cancer screening and diagnosis.

Clinical Breast Examination

Although screening mammography has been well studied, no research has evaluated clinical breast examination (CBE) by itself, without any other modalities, as a screening modality. The first randomized, controlled trial (RCT) to show breast cancer mortality reduction for combined mammography and CBE was the Health Insurance Plan (HIP) study in the 1960s (45). However, CBE and mammography were studied in combination and not separately. Subsequently, the Canadian National Breast Screening Study compared CBE plus mammography to CBE alone in women aged 50 to 59 years, with CBE conducted by trained health professionals whose performance was periodically evaluated and breast cancer mortality was found to be the same for women in both treatment groups (46). Overall, among the RCTs that evaluated the combination of mammography and CBE compared to usual care, adjunct CBE showed no incremental mortality benefit.

The quality of CBE performed by community clinicians might be less than that in an RCT, especially as the typical duration of an examination in the Canadian trial was 5 to 10 minutes per breast. CBE has also been studied in descriptive, population-based studies, the results of which suggest that it is less accurate than screening mammography. While the specificity may be high in the community, the sensitivity is likely much lower than what has been reported in published trials. For example, the specificity of CBE was 88% among specially trained clinicians in the Canadian trial during the first screening exam (47) and 99% in a U.S. community setting (48). Among women with breast cancer, a false negative CBE was less common in the trial on the first screening exam than in community settings: 17% (47) versus 43% (48), respectively. False negative CBEs result in false reassurance to patients that they do not have cancer, and can delay timely diagnosis and treatment.

Breast Self-Examination

Monthly breast self-examination (BSE) is frequently encouraged, but evidence for its effectiveness is weak (49,50). Research has shown that teaching BSE is not associated with reduced breast cancer mortality. One RCT randomly assigned female workers in Shanghai factories either to an intervention group that received instruction in BSE, with subsequent reinforcement, or to a control group with no intervention (51). After 10 years of follow-up, no difference in breast cancer mortality was found between groups. In addition, formal instruction and encouragement to perform BSE led to more breast biopsies and more diagnoses of benign breast lesions in the intervention group. In this group, the biopsy rate was 1.8%, compared with 1% in the control group. However, a major limitation of the study was that 40% of participants were younger than age 40 at enrollment, a population for whom screening has never been shown to be beneficial.

Case-control studies, nonrandomized trials, and cohort studies on the effectiveness of BSE have returned mixed results, which are difficult to interpret because of possible selection and recall bias. In the U.K. Trial of Early Detection of Breast Cancer, more than 63,500 women aged 45 to 64 years were invited to educational sessions on BSE. However, no difference in mortality was noted when the study sites were compared with other centers without organized BSE education (RR = 1.07; 95% CI, 0.93–1.22) (52). The Canadian National Breast Screening Study noted above also included a nested case-control study based on self-reported BSE, with results suggesting that well-performed BSE may be effective (53).

To improve women's accuracy in performing BSE, a device called the B-D Sensability™ Breast Self-Examination Aid (54) (previously called the Sensor Pad™) has been approved by the FDA. However, no evidence is available on its efficacy in reducing breast cancer mortality.

Thermography

Breast thermography, or digital infrared imaging, is based on the belief that the tissue surrounding a developing breast cancer has higher metabolic activity and vascular circulation compared to normal breast tissue. Supporters of this technology claim that increased regional surface temperature can be imaged and used as a means for identifying breast cancer (55). However, there is no substantial scientific evidence to give credence to this theory and this unproven technology is not endorsed by leading medical societies for breast cancer screening.

BENEFITS OF SCREENING—EFFECT ON BREAST CANCER MORTALITY AND CHALLENGES OF STUDYING SCREENING PROGRAMS

It is difficult to establish the value of a community-based screening program unless an RCT is conducted, as RCTs are less prone to bias than other types of study designs. An improvement in survival among women who have undergone breast cancer screening is often taken to imply that the test saves lives. However, association between receipt of screening and longer survival does not necessarily prove a cause-and-effect relationship, because a study might be limited by various forms of bias (Fig. 10-1) (1). *Selection bias* occurs when most participants in a screening program are healthier than average, so they will likely have a better overall rate of mortality. *Lead-time bias* occurs when screening detects a disease earlier in its natural history than would otherwise have happened, thereby lengthening the time between diagnosis and death. Nevertheless, having additional time during which the diagnosis is known seems unlikely to alter the natural history of the disease, so that no overall reduction in mortality will result. *Length bias* occurs when the full spectrum of a disease includes both indolent and aggressive cases, such that screening participants with less aggressive illness are likely to survive longer after diagnosis, regardless of the treatment they receive.

RANDOMIZED CLINICAL TRIALS OF SCREENING MAMMOGRAPHY

Summary of RCTs

Population-based randomized, controlled trials (RCTs) involving screening mammography have been conducted in North America and Europe with participation by nearly half a million women (46,56–66). These trials differ with regards to design, recruitment, participant characteristics, imaging protocols, management of control groups, compliance with assignment to screening and control group and analysis of outcomes (67). Almost all reported a mortality reduction for women screened by mammography.

Most randomized trials were not set up to specifically evaluate screening mammography for women less than 50 years of age, and the use of age 50 has been considered somewhat arbitrary. The recent AGE trial focused specifically on screening of women 40 to 49 years of age and found

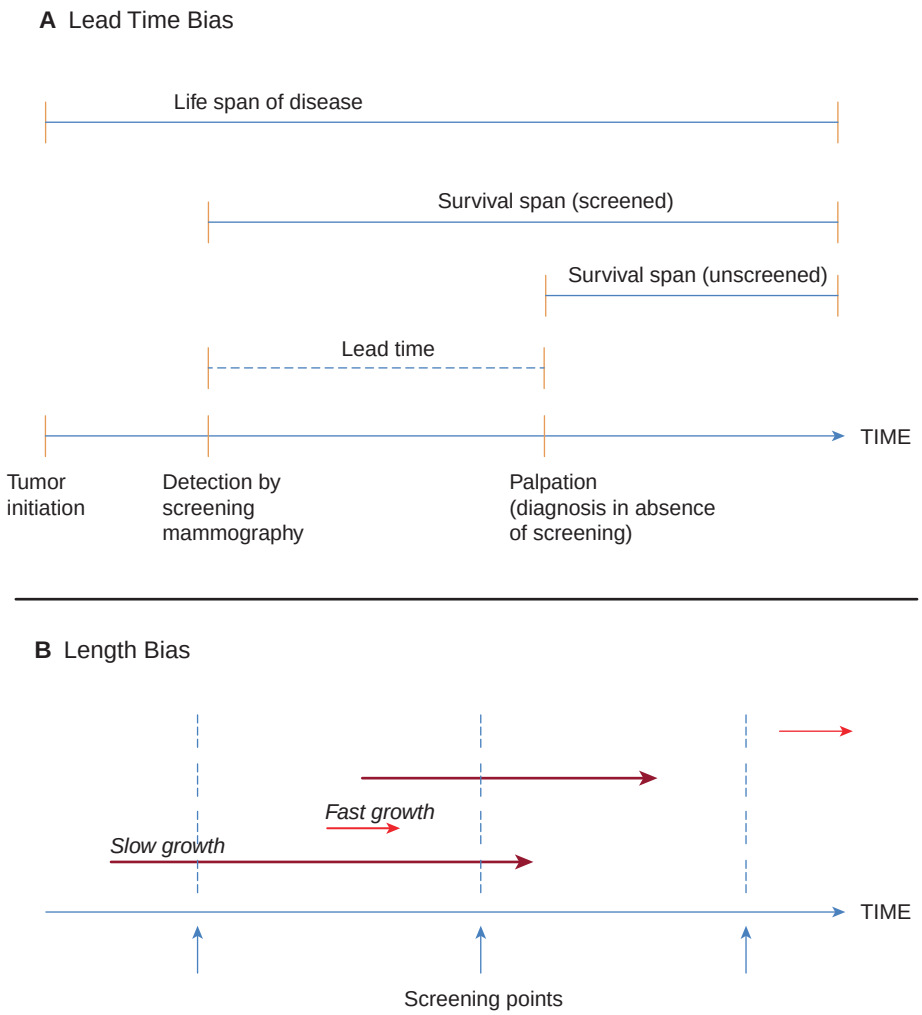

FIGURE 10-1 Lead-time **(A)** and length **(B)** bias. In part B, the length of the arrows represents the time required for the tumor to reach a palpable size. (From Institute of Medicine (IOM). *Mammography and beyond: developing technologies for the early detection of breast cancer: a non-technical summary*. The National Academies Press. http:// www.nap.edu/openbook.php?record_id=10107&page=7)

a small reduction in breast cancer mortality from screening (65). However, the reduction did not reach statistical significance. Thus, the effectiveness of routinely screening women 40 to 49 years of age remains controversial, with concern regarding whether or not the magnitude of benefit from routine screening sufficiently outweighs the harms of false positives and overdiagnosis.

Overview of Individual RCTs

The first RCT, the *Health Insurance Plan of Greater New York* (HIP), was met with great enthusiasm (45,66). In this trial conducted from 1963 to 1966, women aged 40 to 64 years at entry were randomized to screening versus no screening. While there were slight imbalances in the distribution of women between assigned arms with regards to both menopausal status and education, these did not favor the screening nor the control group. The sample size was 30,239 women in the study group and 30,256 women in the control group with the intervention being two-view mammography annually and clinical breast examination (CBE) every 3 years. As in many of the other subsequent RCTs, noncompliance was an issue, with approximately 35% of the invitation-to-screening cohort not attending the first screening. These women who did not attend their initial screening were not re-invited. In this early trial, screening mammography was not readily available outside of the clinical trial, as was often the case leading to contamination of the control groups in other subsequent RCTs. However, it is unclear whether CBE was performed with the same frequency in the two study arms. The follow-up duration for this study was 18 years with a relative risk of breast cancer death of 0.71 at 10 years, and at 0.77 at 15 years. Of note, the mammograms were performed with older equipment and may be of lower quality than current technologies (68). HIP also had differential exclusion between the intervention and control groups of women with a prior history of breast cancer.

The Malmo, Sweden study, which began in 1976, invited women aged 45 to 69 years for mammography screening (69,70). This trial had 21,088 women in the intervention and 21,195 women in the control group, with 74% of women invited to screen attending their first screen, and 70% attending rounds 2 to 5. The intervention was two-view mammography every 18 to 24 months for nine rounds. The control group received mammography at the end of the study, after year 14. It is thought that about 24% of all control women had at least one mammogram. This study had 12 years of follow-up with a subsequent relative risk of breast cancer death at 0.81 (0.62–1.07). This Malmo study, which is often referred to as MMST1 Mammography Screening Trial 1, is often combined with the MMST2 trial for many analyses.

The Swedish Two-County Trial (71–73), which began in 1977, enrolled women 40 to 74 years of age. The randomization was done through geographic clustering with

geographic units designed to be heterogeneous with regards to urban versus rural, population size, and socioeconomic factors. Women with preexisting breast cancer were excluded from both groups. This trial enrolled approximately 80,000 women to screening and just over 39,000 women in the control group from Ostergotland, Sweden, and approximately 39,000 women to screening and 18,000 in the control group from Kopparberg, Sweden. The intervention included one-view mammography every 2 years for women younger than 50 years and every 33 months for women 50 years and older. Contamination was much lower in this study compared to other RCTs; approximately 13% had mammograms as part of routine care, mostly in the later years of the study. The relative risk of breast cancer death for the screened population in the study was reported as 0.82 (0.64–1.05) in Ostergotland and 0.68 (0.52–0.89) in Kopparberg. Concerns have been raised about the randomization methods used as well as the analysis, which required correction for late performance of the control group mammography. However, the group from Sweden has performed subsequent meta-analysis that addressed many of these questions (70,71,74–76).

The Edinburgh (U.K.) Study, which commenced in 1976, enrolled women aged 45 to 64 years from 87 general practices (77). Patients were randomized by clustering based on physician practices. Some randomization assignments were changed after the study began and there was inconsistent recruitment of women within practices, perhaps according to physician judgment about the women's suitability for the trial. There were 28,628 in the intervention group and 26,015 women in the control group. The intervention consisted of two-view mammography and CBE initially followed by single-view mammography every 2 years for the duration of the trial. Compliance was 61% among those screened initially, and decreased to 44% by round 7. Contamination among the control group was not reported. Death was assessed by the Cancer Registry Data. The longest follow-up duration was 14 years, and the ultimate relative risk for the intervention group was 0.84 (0.63–1.12). The lower socioeconomic status and higher all-cause mortality in the control group compared with the screen group suggested inadequate randomization during the study.

The Canada National Breast Cancer Screening Study-1 (NBSS-1), which began in 1980, enrolled women aged 40 to 49 years who volunteered to participate (57). The sample size was 25,214 in the intervention group and 25,216 in the control group. The intervention consisted of annual two-view screening mammography and CBE for 4 to 5 years. Randomization was by blocks after CBE, stratified by the center and 5-year age groups. Compliance was initially 100% and decreased to 85.5% by the fifth screen. Contamination was noted in approximately one out of four women in the control group. The cause of death was ascribed to death certificates reviewed by a blinded panel and cross-referenced with Canadian Mortality Data Base, Statistics Canada. Follow-up over 13 years showed a relative risk of breast cancer death 0.97 (0.74–1.27). This and the later AGE trial are the only trials specifically designed to study women in their 40s. Of note, cancers diagnosed at entry in both of the study arms were included with a disproportionate number in the screened group compared with the control group. This study included evaluation of the technical quality of the mammograms and concerns have been expressed about the mammogram quality, the equipment standardization, and the radiologist's training. A mediolateral view was used in some of the early years for the screening arm instead of the mediolateral oblique view. This trial and the NBSS-2 differ from other RCTS in that women during this time period were also taking adjuvant hormone and chemotherapy following breast cancer therapy.

The Canada National Breast Cancer Screening Study-2 (NBSS-2), which also began in 1980, enrolled women 50 to 59 years of age who volunteered to participate (46). The sample size was 19,711 in the screened group and 19,694 in the control group with the intervention being annual two-view screening mammography and CBE. The control group received annual CBE. As in NBSS-1, all participants in both the control and intervention groups of NBSS-2 were pre-screened and instructed in breast self-examination. In the intervention group, compliance started at 100% and decreased to 87% by the fifth screen. In the control group, compliance initially began at 100% and fell to 85% by screen five. Contamination was lower in this study than in NBSS-1, involving 17% of the control group. There was 11 to 16 years of follow-up, with a relative risk of breast cancer death of 1.02 (0.78–1.33) for the intervention group. The cause of death was ascribed to death certificates that were reviewed by a blinded panel as well as a review with the Canadian Mortality Data Base, Statistics Canada. This trial compared one screening modality to another and does not include an unscreened control group. It also received similar criticisms and reviews as the NBSS-1 study. The quality of the CBE performed at the 15 Canadian centers involved in NBSS-1 and NBSS-2 was likely much higher than that performed in the general community (78).

The Stockholm (Sweden) Study, which commenced in 1981, enrolled women aged 40 to 64 years (79). Patients were randomized based on the birth date; specifically, by day of month. There were two sub-trials with a significant imbalance in the second with approximately 500 more women in the screened group than the control group. The sample size declined from approximately 40,000 to 38,000 in the intervention group and rose from nearly 20,000 to 21,000 in the control group. The intervention consisted of a single-view mammogram every 24 to 28 months. The control group received mammograms during the fifth year. Contamination was noted in approximately one out of four women in the control group. Compliance was 82% screened, and the relative risk of breast cancer death among those screened was 0.80 (0.53–1.22). The follow-up duration was 8 years and the cause of death was obtained by linking to the Swedish Cause of Death Registry. Some concerns have been raised about the randomization of this study, patient exclusions, and the delay in control group mammograms. Inclusion of these data in the Swedish meta-analysis addressed some of these questions (71–73).

The Gothenburg, Sweden Trial, which began in 1982, invited women aged 39 to 59 years old (63,80). The randomization method was complex, with women clustered randomly by their day of birth within their birth year for the older group (50 to 59 years old) and by individual for the younger group (39 to 49 years old). The ratio of study to control varied by the year depending on the mammogram availability. Women with a previous breast cancer diagnosis were excluded from the trial. The sample size included approximately 20,724 women in the screened group and 28,809 women in the control group. The intervention group received an initial two-view mammogram and then a single-view mammogram every 18 months, up to four screens in total. In addition, exams in the later years were double read by two radiologists. The control group received one screening exam approximately 3 to 8 months after the final screen in the study group. Women were followed up to 12 to 14 years. The relative risk of breast cancer death for screened women aged 39 to 59 years was 0.79 (0.58–1.08) in the initial evaluation and 0.77 (0.60–1.00) in the follow-up. The cause of death

was assessed by the Swedish Cause of Death Registry and also an independent endpoint committee. The interpretation of this study is complicated by the delay in performance of mammograms in the control group and by the unequal numbers of women in the invited and control groups.

The AGE Trial enrolled women aged 39 to 41 years from 1991 to 1997, and included 160,921 women (65). Women were randomized to screening with annual two-view mammography until age 48, or usual care for the control group. Patients were randomized based on lists of general practitioners in geographically defined areas of England, Wales, and Scotland; however, the allocation was concealed. Those women who were not invited to the study received usual care. The follow-up method was the intention-to-treat; although all women aged 50 years and older would be offered screening by the National Health Services (NHS). The follow-up duration was 10.7 years and the relative risk of breast cancer death was 0.83 (0.66–1.04). The cause of death was assessed by the NHS central register. The level of contamination of the study groups were not provided, and 70% or fewer women attended screening across the trial. To note, while this trial did not produce statistically significant results, its findings are similar to those of the other RCTs.

Meta-Analyses and Reviews of RCT Data

Meta-analyses of the RCTs have been published by different authors using varying analytic methods, with some authors excluding specific trials due to concerns about quality of the data (50,81–84). In general, most meta-analyses show a reduction in breast cancer mortality with mammography screening among women 40 to 74 years of age, with the greatest absolute risk reduction seen among the older age cohorts. The four trials conducted in Sweden comparing mammography with usual care demonstrated a 9 to 32% reduction in risk of breast cancer death among those screened (56,73). One meta-analysis found little change in the effectiveness of screening mammography in reducing breast cancer mortality after adjusting for differences in patient randomization and adherence to imaging protocols across the trials (Fig. 10-2) (85).

A meta-analysis of RCTs conducted for the U.S. Preventive Services Task Force in 2009, shown in Table 10-2, found that the number needed to invite to screen for 10 years to avoid or delay one death from breast cancer was 1,904 for women in their 40s, 1,339 for women in their 50s and 377 for women in their 60s (81). The meta-analysis demonstrated a pooled relative risk for breast cancer mortality for screening women aged 39 to 49 years of 0.85 (95% CI: 0.75–0.96), indicating a 15% reduction in breast cancer mortality favoring screening. Screening women aged 50 to 69 years was associated with an even lower pooled relative risk for breast cancer mortality of 0.68 (95% CI: 0.54–0.87) (81).

Additional analyses by six Cancer Intervention and Surveillance Modeling Network (CISNET) groups reported that screening every 2 years maintained the majority of the benefit of annual screening with almost half the false-positive results (82). This same group reported that starting biennial screening at age 40 years (vs. age 50 years) reduced

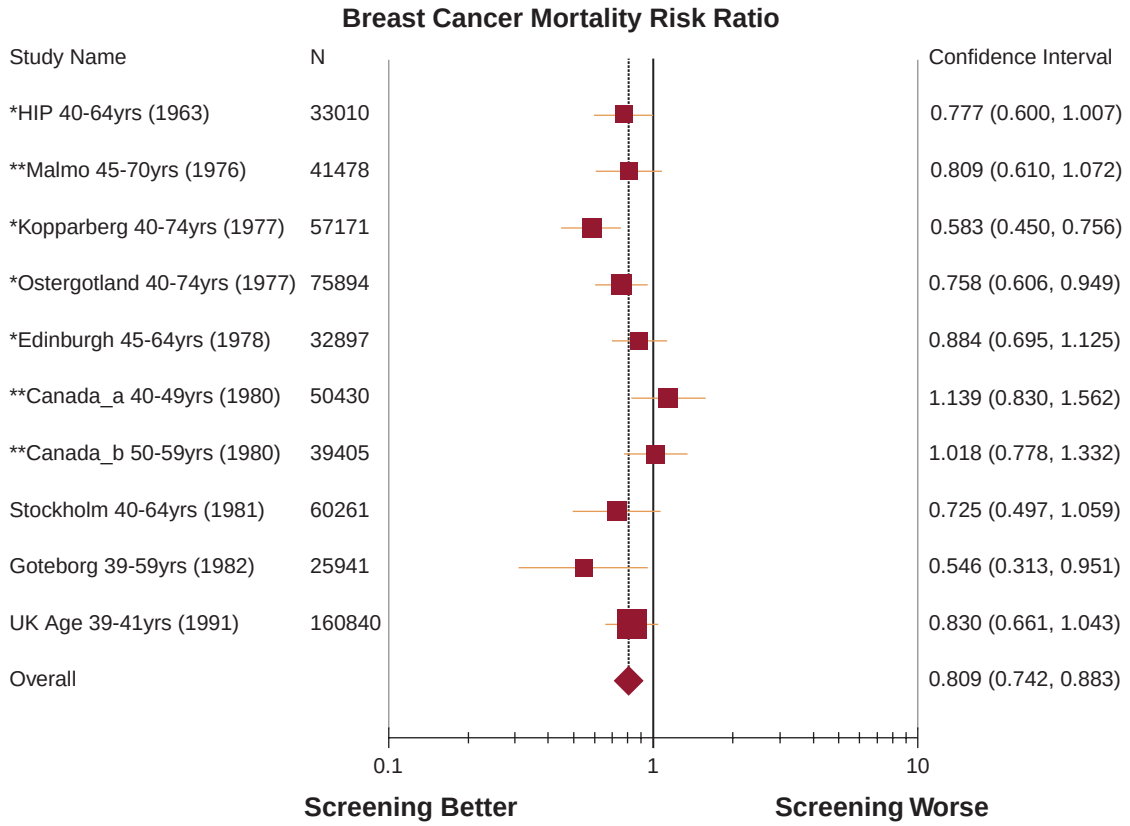

FIGURE 10-2 Example results of a meta-analysis of randomized clinical trials of breast cancer screening. (From Glasziou P, Houssami N. The evidence base for breast cancer screening. *Prev Med* 2011;53(3).)

TABLE 10-2

Summary of Meta-Analyses of Relative Risk for Breast Cancer Mortality from Mammography Screening Trials for All Ages

Age (Years)	*Number of Included Trials*	*RR for Breast Cancer Mortality (95% CrI)*	*NNI to Prevent 1 Breast Cancer Death (95% CrI)*
39–49	8*	0.85 (0.75–0.96)	1,904 (929–6,378)
50–59	6†	0.86 (0.75–0.99)	1,339 (332–7,455)
60–69	2‡	0.68 (0.54–0.87)	377 (230–1,050)
70–74	1§	1.12 (0.73–1.72)	Not Available

*Health Insurance Plan of Greater New York, Canadian National Breast Screening Study-1, Stockholm, Malmo, Swedish Two-County (two trials), Gothenburg, Age.
†Canadian National Breast Screening Study-2, Stockholm, Malmo, Swedish Two-County (two trials), Gothenburg.
‡Malmo and Swedish Two-Country (Ostergotland).
§Swedish Two-Country Trial (Ostergotland).
CrI, credible interval; NNI, number needed to invite to screening; RR, relative risk.
Adapted from Nelson HD, Tyne K, Naik A, et al. Screening for breast cancer: an update for the U.S. Preventive Services Task Force. *Ann Intern Med* 2009;151(10):727–737, W237–W742.

breast cancer mortality by an additional 3%, consumed more health care-related resources, and yielded more false-positive results (82).

An independent U.K. panel was convened to evaluate the benefits and harms of breast screening with a report published in 2012, which concluded that the U.K. breast screening programs confer "significant benefit and should continue." (84) This report describes the results of many of the different meta-analyses and includes a detailed description and review of published data on the topic of overdiagnosis. They report that, for every 10,000 U.K. women aged 50 years invited to screening for the next 20 years, 43 deaths from breast cancer would be prevented and 129 cases of DCIS and invasive breast cancer would be overdiagnosed; in other words, they estimate that there will be one breast cancer death prevented for about every three overdiagnosed cases identified and treated. They estimate that just over 1% of UK women invited to begin screening every year would have an overdiagnosed cancer in the next 20 years.

COMMENTS ON OTHER BENEFITS OF SCREENING

It should be noted that RCTs may underestimate the true benefits of mammographic screening, as mortality reduction is assessed among all women invited to be screened rather than those who actually participated in screening (86). Moreover, beyond mortality reduction, there are other potential benefits of mammographic screening including decreased patient morbidity from less invasive therapies for cancers detected at earlier stages (87). Cancers detected by mammography are statistically more likely to be treated with breast conservation surgery (56% vs 32%) and less likely to receive adjunct chemotherapy (28% vs 56%) (88,89). Women undergoing screening mammography, therefore, experience decreased morbidity by less frequently undergoing mastectomy and complete axillary node dissection, and are provided a wider choice of treatment options than women with cancers who do not undergo routine screening mammography (87). The U.S. preventive services task force (USPSTF) did not consider the increased morbidity associated with treating more advanced stage disease among women not routinely screened during the development of their recommendations.

POTENTIAL HARMS OF SCREENING

False Positive Results and Additional Interventions

Clinicians face the challenge of minimizing the number of women who are unnecessarily called back for diagnostic follow-up after a screening exam while maximizing the likelihood of detecting all potentially lethal cancers. This situation can be compared to the performance of a home smoke detector—you don't want an alarm sounding on a daily basis with no fire, nor do you want to miss an alarm triggered by smoke from a true fire.

Most women who are screened for breast cancer are free of disease. In the United States, approximately one in 10 women who are screened with mammography receive false positive results and are recalled for additional testing, even though they do not have breast cancer (90,91). The availability of prior test results for comparison can help to reassure radiologists that a lesion has been stable over time, and such availability has been associated with lower false positive rates (92). Increased breast density has been associated with lower sensitivity and specificity of screening mammography, with hormone therapy affecting density and, thus, interpretation. However, there are no specific guidelines or protocols for short-term suspension of hormone therapy (in order to optimize mammographic accuracy) that have been shown to be effective (93).

Most data on false positive results in breast cancer screening refer to rates per mammogram instead of rates per woman over the lifespan. This approach ignores the fact that many women undergo screening over a period of decades, and thus could receive 10, 20, or more exams during their lives. A retrospective study published in 1998 highlighted this problem by quantifying the cumulative risk of receiving false positive results. The study followed women who were continually enrolled in a U.S. health plan for 10 years. At the end of this period, one-third of the women who participated in breast cancer screening had received at least one abnormal result requiring additional evaluation, even though none of these women actually had breast cancer (2).

Furthermore, this same study found that the false positive rate associated with mammography was higher than that associated with CBE. The authors estimated that the cumulative risk of receiving at least one false positive result after 10 mammograms was 49.1% (95% CI, 40.3–64.1; see Fig. 10-1),

while the cumulative risk after 10 CBEs was only 22.3% (95% CI, 19.2–27.5). False positive results among study participants led to 870 outpatient appointments, 539 diagnostic mammograms, 186 ultrasound examinations, and 188 biopsies. In one patient, a false positive mammogram prompted a biopsy that resulted in cellulitis, requiring hospitalization for surgical debridement and intravenous antibiotic therapy. The same study also estimated the cumulative rate of breast biopsies, finding that among women without breast cancer, 18.6% (95% CI, 9.8–41.2) underwent biopsies after 10 mammograms and 6.2% (95% CI, 3.7–11.2) underwent biopsies after 10 CBEs. In terms of cost effectiveness, as the authors noted, every $100 spent on initial screening corresponded to an additional $33 spent to evaluate false positive results.

A subsequent study that modeled data from the same cohort of women found that the likelihood of a false positive mammogram varied widely based on characteristics of the women screened, the screening modality used, and the radiologist who interpreted the exam (94). The cumulative risk of receiving at least one false positive result by the ninth mammogram actually varied from 5% to 100%, with increasing risk independently associated with four patient variables (younger age; higher number of previous breast biopsies; family history of breast cancer; current estrogen use) and three radiology variables (longer time between screening; failure to compare the current mammogram with previous mammograms; individual tendency to interpret mammograms as abnormal). The single risk factor most strongly associated with false positive results was the last: the tendency of individual radiologists to find abnormalities on screening.

False positive rates may vary substantially from country to country. One report noted that the recall rate in the United States after screening mammography was twice as high as the rate in the United Kingdom, yet the rate of cancers detected was essentially the same in both countries (95). Another review of 32 community-based screening programs returned similar findings, noting that North American programs appear to interpret a higher percentage of mammograms as abnormal than do programs from other geographical regions, even though rates of cancer detection are similar (except that more cases of ductal carcinoma *in situ* are reported in North America) (96). This review also noted that the percentage of abnormal mammograms varies widely around the world (1.2%–15%), as does the PPV of abnormal mammograms (3.4%–48.7%) and of biopsies (5%–85.2%). Similar variability was noted for other outcomes, including the percentage of cases diagnosed as ductal carcinoma *in situ* (4.3%–68.1%) and the percentage diagnosed with minimal disease (14.0%–80.6%). The large percentage of mammograms judged abnormal in North American screening programs had a negative association with PPV (both $p < .001$) and a positive association with both the frequency of diagnoses of ductal carcinoma *in situ* ($p = .008$) and the number of such cases diagnosed per 1000 screens ($p = .024$). Factors that might explain such international discrepancies are summarized in Table 10-3. A woman's estimated risk of having at least one false positive screening mammogram, according to the total number of screening mammograms performed, is detailed in Figure 10-3.

Most studies on false-positive exams predate the widespread use of such modalities as CAD and MRI in breast screening programs, where the false positive rates may be even higher.

TABLE 10-3

Possible Explanations for the Variability in the Abnormal Interpretation Rate Noted among Published Studies of Screening Mammography

Characteristics of the population screened
Age (e.g., percentage of women <50 yr of age)
Initial versus subsequent screening examination
Presence of risk factors for breast cancer
Presence of breast symptoms
Self-referral versus physician referral
Features of the mammography examination
Equipment type and year
One or two views of each breast
Single or double readings
Technician training
Features of physicians interpreting the mammogram
Experience of the physician
Level of personal comfort with ambiguity
Individual thresholds to label film as abnormal
Features of the health care system
Malpractice concerns
Financial incentives
Private versus academic/public programs
Different stated goals for the percentage of mammograms judged abnormal and positive predictive value
Quality control and auditing procedures
Variability of definitions used to calculate outcomes

From a table in Elmore JG, Nakano CY, Koepsell TD, et al. International variation in screening mammography interpretations in community-based programs. *J Natl Cancer Inst* 2003;95(18):1384–1393.

False Negative Results and False Sense of Security

No medical test is perfect. All the screening modalities that we have discussed can return negative results even when breast cancer is present, either because a lesion was missed by the radiologist or clinician, or because no lesion was visible or palpable on examination. For example, if screening mammography has a sensitivity of 80%, then 20% of mammograms of women who will be diagnosed with breast cancer within 1 year will be interpreted as negative. These women, as well as their primary care physicians, would mistakenly be reassured by such false negative results. To counteract any false sense of security, mammography reports in the United States increasingly note the limitations of the examination and the potential impact of breast density on missed lesions; they also encourage women to seek evaluation if they personally note breast abnormalities despite negative findings on mammography.

Radiation Exposure

Radiation exposure is a known risk factor for developing breast cancer, as documented in observations of women who survived the atomic bombing of Hiroshima and Nagasaki and women who received therapeutic radiation treatments for the chest and upper body (97). Younger age at exposure and higher levels of exposure carry the greatest risk (98,99). Because mammography exposes women to radiation, various efforts have been proposed to minimize harm. These include reducing the amount of radiation required for screening, developing radiation-free screening modalities, and identifying subpopulations that might have heightened vulnerability to radiation (100,101).

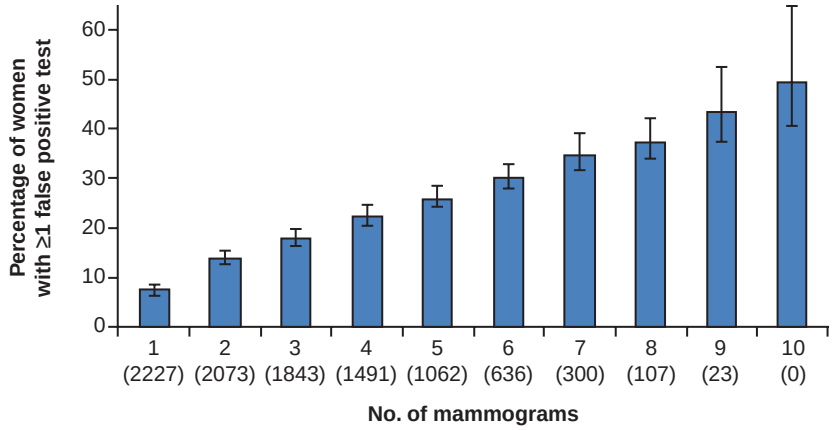

FIGURE 10-3 A woman's estimated risk of having at least one false positive screening mammogram, according to the total number of screening mammograms performed. NOTE: Numbers in parentheses denote numbers of women with at least that many mammograms. I bars indicate 95% confidence intervals. (From Elmore JG, Barton MB, Moceri VM, et al. Ten-year risk of false positive screening mammograms and clinical breast examinations. *N Engl J Med* 1998;338(16):1089–1096.)

In the United States, the mean glandular dose for screening mammography is 1 to 2 mGy (100–200 mrad) per view, which amounts to 2 to 4 mGy (200–400 mrad) per standard two-view examination (97,102). Discussions of the appropriate age to initiate screening often consider the increased lifetime exposure to radiation associated with screening young women.

Discomfort, Anxiety, and Distress

Compression of the breasts is required during mammography in order to create uniform breast density, improve image resolution, and reduce radiation dose. A systematic review of studies examining physical pain and discomfort associated with mammography demonstrates that while most women experience some physical discomfort, few considered the transient pain as a deterrent from screening (103). Pain was often associated with patients' menstrual cycles and anticipation of pain rather than the actual compression itself (103).

In general, women do not react well to hearing that their screening mammogram is "abnormal" and that they might have breast cancer. In such situations, women typically experience a heightened sense of their risk of cancer. Further, when media campaigns publicize that "one in eight women will be diagnosed with breast cancer," some women may misinterpret this message to mean that one in eight women will die of breast cancer. They may also be unaware that a 40-year-old woman is much less likely to be diagnosed with breast cancer than a 60-year-old woman.

Women who receive clear communication of negative mammography results have minimal anxiety about screening (104). Several studies, however, show at least transient levels of anxiety to persistent levels of anxiety for women who are recalled after screening for further diagnostic evaluation (104). One survey of women 3 months after screening mammography found that about one-quarter of those who initially received an abnormal result were still experiencing worry that affected their mood or functioning, even though subsequent testing had already ruled out a cancer diagnosis (105). Such worry and anxiety may have long-term effects. A systematic review of false positive mammograms found that anxiety after receiving a false positive result is associated with more frequent receipt of future screening mammograms (106).

Overdiagnosis

Overdiagnosis of breast cancer refers to the diagnosis of a neoplasm that would never become clinically apparent without screening before a patient's death from other causes (107). Because cancers that will progress cannot be distinguished with certainty from those that will not, any tumor identified by screening is usually treated with surgery and possibly with radiation, chemotherapy, and hormonal therapy. In some cases this regimen might constitute overtreatment because it confers no benefit unless the tumor will actually progress.

Autopsy studies that note breast tumors in women who died of causes unrelated to breast cancer provide some information on the possible rate of underlying breast cancer in the asymptomatic population. An overview of seven autopsy studies found a median prevalence of 1.3% for undiagnosed invasive breast cancer (range 0%–1.8%) and 8.9% for undiagnosed ductal carcinoma *in situ* (range 0%–14.7%) (108,109).

It is difficult to determine the proportion of cancers that are overdiagnosed by existing screening programs. Randomized screening trials might provide the best estimates, but such data are challenging to interpret and not available for all studies. Population-based studies have reported estimates derived from comparing groups with screening against groups without. However, unbiased estimates are possible only if both groups are identical except for screening status. Achieving this level of equivalence is daunting, considering that populations may differ in time, geography, culture, and use of hormone therapy, while investigators may differ in their analyses and handling of the various kinds of bias that affect research outcomes (110,111).

Another method of looking for overdiagnosis would be to conduct an observational, population-based comparison of breast cancer incidence rates before and after the adoption of screening. In the absence of overdiagnosis, we would expect to see a rise in the incidence of breast cancer after screening is adopted, followed by a decrease below the prescreening level, with cumulative incidence remaining stable. However, available findings are more suggestive of the presence of overdiagnosis, as breast cancer incidence rates have historically increased after the initiation of screening, without a compensatory drop in later years (112–117).

The magnitude of overdiagnosis of breast cancer due to screening is controversial, with reported estimates ranging from 7% to 50% of all breast cancer cases possibly being "overdiagnosed." (110,111,118–120) While the precise extent remains debatable, it is highly improbable that no overdiagnosis occurs.

SCREENING CONSIDERATIONS IN SPECIAL POPULATIONS

Women Younger Than 40

No available evidence supports screening in women younger than age 40 years who are at average risk of breast cancer. Because this subpopulation has a low breast cancer rate, a very large number of women would need to be screened to

detect a single case of breast cancer. Younger women are also more likely to have dense breast tissue, which is associated with less accurate screening performance, thus increasing the likelihood of false positives and false negatives.

Elderly Women

Defining the upper age at which breast cancer screening should no longer be recommended is challenging, and this topic is often neglected by guidelines, especially as published RCTs of mammography have not included women older than age 80. In general, a woman's overall state of health should be considered in any decision to undertake or forgo screening.

Women with Limited Life Expectancy

Among women with severe comorbidities who have limited life expectancy, it is critical to balance the potential benefits of screening against the potential harms. Such women might have severe lung disease, such as chronic obstructive pulmonary disease; end-stage renal failure; cardiovascular disease; or metastatic cancer from other organs. Early breast cancer detection and treatment are unlikely to reduce morbidity and mortality in these subpopulations.

It is often assumed that breast cancer screening should be considered for women expected to survive at least 5 more years (121). The harms associated with screening, such as false positives and the attendant anxiety, occur immediately after screening, while the potential benefits are not seen for many years, if at all. In addition, a diagnosis of breast cancer in these women would probably result in a recommendation for treatment, which could impair rather than improve their quality of life without improving their overall survival. Unfortunately, many women with limited life expectancy due to age or health status still undergo screening (122).

Women with Increased Breast Density

Women with extremely dense breast tissue have a three to five times greater lifetime risk of developing breast cancer compared to women with almost entirely fatty breasts, even after adjusting for associated risk factors such as age (21–23). Increased breast density is now regarded as an independent risk factor for breast cancer regardless of the populations studied and the influence of other known risk factors (123). As of 2013, several states including California, Connecticut, Texas, Virginia, and New York require imaging centers to report heterogeneously or extremely dense breast tissue directly to patients, informing them that they may be at increased risk for developing breast cancer. Moreover, some states also require women with dense breasts to receive notice that they may benefit from additional screening studies beyond the mammogram (25). However, there is currently little evidence that adjunct screening, such as with breast ultrasound, would have any additional mortality benefit.

Women with a Family History of Breast Cancer

While breast cancers result from multiple gene mutations, only a small subset are inherited mutations with the majority being sporadic and nonfamilial in nature. Simply having a family member with breast cancer does not play a very large role in determining a patient's lifetime risk of developing breast cancer because the majority of breast cancers are sporadic in nature and not inherited. Currently, major societies do not recommend additional or more frequent screening for women who have a relative with diagnosed breast cancer unless there is greater than 20%–25% lifetime risk for developing breast cancer based on available risk models (124).

Genetic Mutations That Increase Breast Cancer Risk

Women with the *BRCA1* or *BRCA2* mutations are at high risk for breast and ovarian cancer. According to two meta-analyses, the estimated cumulative risk of breast cancer by age 70 is 55% to 65% for carriers of *BRCA1* and 45% to 47% for carriers of *BRCA2* (125,126). Given this heightened risk, some carriers opt for prophylactic mastectomy. Mutation carriers who decide to keep their breasts are advised to consider beginning screening mammography and MRI before age 40.

Unfortunately, preliminary data suggest that mammography is less sensitive for women with *BRCA1* or *BRCA2* than for other women (127). One study found an association between the presence of "pushing margins" (histopathologic terminology for a pattern of invasion) and false negative mammograms in women with *BRCA1* or *BRCA2* (127). In addition, rapid doubling times for tumors in women who carry these mutations may mean that an apparently normal breast examination could be followed shortly afterward by a detectable malignancy (128).

In 1997, the Cancer Genetics Studies Consortium Task Force issued special recommendations for female carriers of *BRCA1* or *BRCA2*. They advised initiating annual mammography at age 25 to 35, performed at a consistent location with prior films available for comparison (129). More recently, the National Comprehensive Cancer Network has recommended annual screening beginning at age 25, while the American College of Radiology recommends annual screening beginning at age 30 (124,130). Meanwhile, the American Cancer Society recommends that initiation of screening be based on individual preferences and circumstances (29).

While *BRCA* mutation carriers may be more prone to radiation-induced breast cancer than women without mutations (131), some studies have not shown an increased risk from radiation (132,133). Any potential benefit of mammographic screening must be carefully weighed against potential risks, particularly in young women (134). However, we have insufficient evidence to suggest that mutation carriers should avoid mammography, particularly as some breast cancers are identified by mammography but missed by MRI.

Several studies have described the outcome of using MRI to screen women at high risk of breast cancer (31,33,35,135–140). These studies are variable in terms of the underlying population studied, the equipment and protocols used, and the calculation and reporting of results. Also, the number of screening rounds is limited, and the distinction between prevalent (first round of screening) and incident cancer detection rates is often unclear.

Despite these caveats, studies consistently demonstrate that breast MRI is more sensitive than either mammography or ultrasound in detecting hereditary breast cancer, although concerns have been raised about the reduced specificity of MRI compared with other screening modalities (31,33,35,138,141,142). Nevertheless, annual MRI screening of *BRCA*1 gene mutation carriers in addition to annual screening mammography has been shown to be cost-effective (143). Alternating MRI and mammography screening at 6-month intervals beginning at age 30 years has been identified as one approach to applying current guidelines in *BRCA1* gene mutation carriers (144).

Women Who Received Thoracic Radiation at an Early Age

Screening has been recommended for women who were exposed to therapeutic thoracic radiation, especially if their exposure occurred before age 30. These women have a much higher incidence of breast cancer (145).

Men

Breast cancer screening is not recommended for men. Even though they may develop breast cancer, such cases are uncommon; only about 1% of all breast cancers occur in men (146). Given this low incidence, no studies to date have addressed breast cancer screening for men.

THE U.S. MAMMOGRAPHY QUALITY STANDARDS ACT

The Mammography Quality Standards Act (MQSA), passed by the U.S. Congress in 1992, requires mammography facilities to meet uniform quality standards (147). The Act sets standards for personnel involved in performing and interpreting mammograms, effective quality control programs for each facility, and medical audit systems for following up abnormal mammograms and obtaining biopsy results. A 1997 report by the U.S. General Accounting Office found that MQSA positively affected mammography quality by ensuring that minimum national standards were met with regard to equipment operation, film processing, image interpretation, and results reporting (148).

It should be noted that MQSA applies only to mammography; mandatory minimum quality standards do not yet exist in the United States for other breast imaging modalities such as MRI and ultrasound (25). Accreditation and certification for operating and maintaining other modalities (e.g., breast ultrasound) remain mostly voluntary and optional. Nevertheless, the American College of Radiology, which is the only organization nationally approved to accredit MQSA, offers nonmandatory accreditation and certification programs for ultrasound, ultrasound-guided biopsy, and stereotactic-guided biopsy (149).

GUIDELINES AND INFORMED MEDICAL DECISION-MAKING

Numerous guidelines on breast cancer screening have been developed, with frequent changes as more evidence appears. The National Guideline Clearinghouse (http://www.guideline.gov) provides free, online access to summaries of evidence-based guidelines for clinical practice (150). This Web-based resource, supported by the U.S. Department of Health and Human Services and the Agency for Healthcare Research and Quality, is updated regularly, enabling comparisons of current recommendations by different groups. Most groups generally recommend mammographic screening for women aged 50 and older and recommend against both CBE and BSE. Nevertheless, recommendations often stress that women should understand and feel comfortable with the contour of their own breasts. Although recommendations for women in their 40s vary, it is clear that initiating screening at age 40 presents more challenges in terms of balancing risks against benefits than does deferring regular screening until age 50. In addition, guidelines over the years have increasingly encouraged clinicians to engage women in informed decision-making so that they can determine which approach to screening is right for them.

CONCLUSION

A breast cancer screening program asks healthy, asymptomatic women to undergo a screening examination in order to detect clinically occult, early-stage breast cancer. While data supports a mortality benefit from screening mammography examinations, the potential harms to individual patients cannot be ignored. Most medical groups currently recommend regular breast cancer screening with mammography for women of average risk, while the available imaging modalities for breast cancer screening and diagnosis continue to expand for women of higher risk. All women should be more fully informed of the balance between the benefits and risks associated with screening mammography, and should take a more active role in making the screening choices that are right for them.

MANAGEMENT SUMMARY

- Regular mammographic screening is widely recommended for asymptomatic women aged 50 years and older.
- Clinicians should engage women in informed decision-making about mammographic screening, weighing the associated benefits and harms, especially among women aged 40 to 50 years.
- Digital mammography is favored over screen-film mammography given its improved accuracy among certain subpopulations of women and in light of workflow and digital data management efficiencies.
- There is currently no evidence to recommend adjunct ultrasound screening in asymptomatic women with dense breasts who are at average risk of developing breast cancer. Adjunct screening breast MRI is recommended for women with *BRCA1* and *BRCA2* gene mutations, as well as women whose lifetime risk of breast cancer is higher than 20% to 25% according to available risk models.

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CHAPTER 11

Imaging Analysis: Mammography

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CHAPTER CONTENTS

Mammography is widely practiced in the United States and internationally for screening and diagnostic indications. High-quality examinations and interpretations are necessary for successful practice. Mammography refers to the process of obtaining images of the breast utilizing low energy x-rays. *Breast imaging* is a more general term that encompasses mammography, breast sonography, breast MRI, breast PET scanning, and other emerging technologies. Although it is convenient to discuss mammography independent of other breast imaging modalities, modern practice stresses an integrated approach of various imaging modalities, in particular, mammography, sonography, and more recently MRI.

This chapter will describe the basics of mammographic interpretation and usage in screening and common diagnostic situations. Efficacy of screening mammography, breast sonography, and MRI are covered in Chapters 11, 13, and 14.

Radiography of the breast has been performed for over 95 years. Although palpable breast cancer was often found to have characteristic mammographic findings, the application of mammography into practice was slow. The potential of mammography to detect clinically occult cancer led to international efforts to refine mammographic technique and eventually led to screening trials, primarily in northern European countries and North America. These showed mortality reduction in screened women which formed the basis for the current recommendation for mammographic screening (1). While some controversy exists regarding frequency and age to begin screening, most organizations recommend regular screening mammography. The explosive increase in mammographic screening in the United States in the 1980s and 1990s was associated with extensive public scrutiny and regulation. Breast imaging was first among imaging specialties to develop a standard lexicon and assessment categories to improve quality and communication between radiologist, referring physicians, and patients. Federal law (the Mammography Quality Standards Act [MQSA]) regulates mammographic equipment, quality operations, technologists, and interpreting physicians (2). Direct communication of mammographic results via written reports to patients is required. The Food and Drug Administration (FDA) performs annual on-site regulatory inspections. All sites, equipment, technologists, and reading physicians in the United States require FDA approval to perform and interpret mammograms. Individual states may have additional regulations.

TECHNIQUE

Basic understanding of radiologic physics is necessary for mammographic interpretation. A typical mammographic machine generates low energy (25–32 kVp) x-rays utilizing a small (0.3-mm) focal spot source, such as molybdenum, rhodium, or tungsten. The breast is compressed between an image receptor (film or digital detector) and a transparent plastic compression plate. Compression is used to minimize thickness and motion and is necessary to limit the radiation dose and improve image quality. X-rays are differentially absorbed by different types breast tissue. X-rays that are not absorbed pass through the breast and are detected by an image receptor. There are now two types of FDA approved receptors, film/screen and digital. In film/screen systems, the energy is eventually received by film, which is developed to produce a mammographic image similar to a photographic negative. In contrast, a digital detector receives the x-rays and electronically converts the energy into an electronic data set, which can be projected on a video monitor or printed as a film or stored and manipulated electronically similar to digital photography. Since 2005, there has been a marked trend toward digital mammography. Currently, over 85% of mammography units in the United States are digital. The mammographic appearance of cancer such as calcifications or masses is not different, although each system may offer some theoretical advantages at displaying these findings (3). Dark areas on a mammogram represent areas with minimal absorption (fat) while white areas represent moderate absorption by fibroglandular tissue or extensive absorption by calcium.

Image quality is affected by a host of factors including breast tissue "density," compressed thickness, positioning, motion, focal spot size, detector performance, and radiation dose. Manufacturers attempt to maximize multiple factors to achieve optimum image quality at the lowest possible radiation dose. The FDA limits dose to 3 mGy (300 mrad) for an average thickness breast per exposure. Mammographic technical requirements are mandated by the MQSA. Passing a yearly facility on site inspection by an FDA-approved agent is necessary to maintain operational accreditation. The mammographic technologists play a critical role in insuring quality screening program by optimizing mammographic positioning. The radiologist can interpret only the parts of the breast that have been included in the imaged field, so the skill of the technologist in maximizing positioning is essential for a quality mammogram. The American College of Radiology (ACR) reviews facility mammograms to assess positioning and technique prior to required certification.

SCREENING VERSUS DIAGNOSTIC MAMMOGRAPHY

Screening mammography refers to obtaining routine mammographic images of asymptomatic women in order to detect cancer at a preclinical stage. This is the primary role of mammography. The goal of screening is high sensitivity for early cancer detection. *Diagnostic* mammography refers to mammography used to evaluate abnormal clinical findings such as a breast mass, thickening, or nipple discharge. Diagnostic mammography also refers to obtaining incremental mammographic images (such as magnification views or spot views) for characterization of possible abnormalities detected by screening mammography at time of recall or call back. "Magnification" views employ smaller focal spots (0.1 mm) and larger subject to receptor distances and produce a 2× magnified image. "Spot" compression utilizes smaller compression paddles that focally decrease breast thickness in an area of concern. Unfortunately, the distinctions between screening and diagnostic mammography have been confused by definitions utilized for insurance billing purposes. An insurer may consider a woman with a prior biopsy of "fibrocystic disease" as "diagnostic" mammography for billing even though that individual may have no current abnormal palpable findings. For our purposes, screening mammography refers to the mammographic evaluation of an asymptomatic individual. In the United States, a screening study consists of two views of each breast, craniocaudal (CC) and mediolateral oblique (MLO). Usually screening mammography is performed without the presence of the physician with mammographic interpretation occurring later in a batch reading situation, which improves efficiency and allows for low-cost screening.

Not infrequently, findings noted on screening mammography require additional diagnostic imaging to resolve. Only a small portion of women recalled for diagnostic imaging will have cancer. A simplified U.S. screening pyramid (Fig. 11-1) provides an overview of the screening process. Assuming a cancer incidence of 3 per 1,000 of annually screened women and a recall rate of 8%, the following outcome is expected for 1,000 normal risk women undergoing annual screening mammography: 920 per 1,000 (92%) will be normal and 80 per 1,000 (8%) will be recalled for diagnostic mammography or ultrasound. Of the 80 women who are recalled, 70 per 1,000 (7%) will be normal or probably benign at diagnostic imaging and returned to mammographic screening and 10 per 1,000 (1%) will require tissue diagnosis for a mammographic abnormality. Of the 10 undergoing biopsy, 3 per 1,000 (0.3%) will be found to have cancer (4). These numbers are illustrative but will vary with incidence, screening frequency, recall rate, and biopsy rate.

Digital Breast Tomosynthesis

The major weakness of mammography is the detection of cancer in women with radiographic dense breasts. While nearly all cancers will be apparent in fatty breasts, many fewer will be visible in extremely dense breast. This is due to masking of noncalcified cancers by surrounding dense tissue. Digital breast tomosynthesis (DBT) mammography is a new technology derived from digital mammography that was approved by the FDA in 2011 to improve detection and

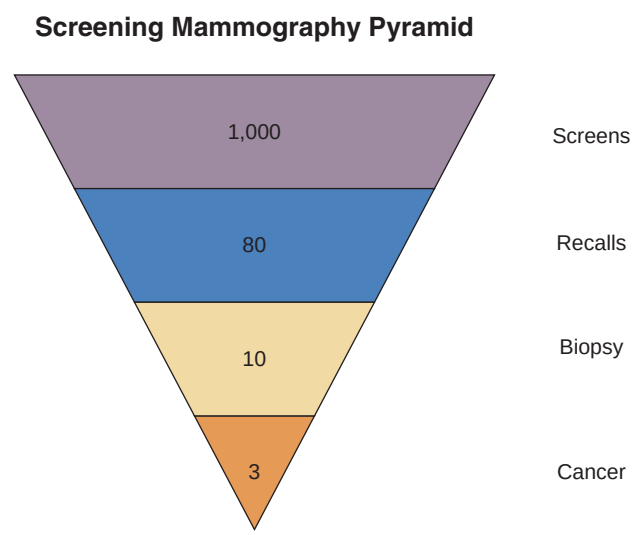

FIGURE 11-1 Simplified screening pyramid showing typical outcomes of 1,000 annually screened women of normal risk.

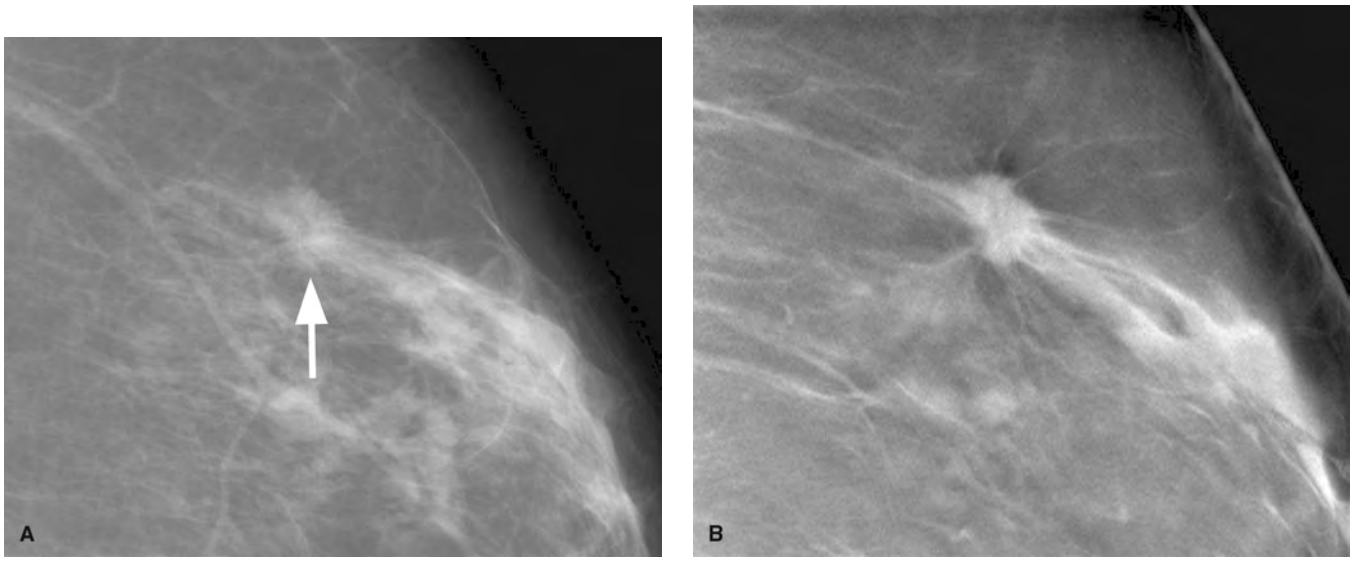

FIGURE 11-2 **(A)** Film screen mediolateral oblique mammography view of a patient with invasive ductal carcinoma *(arrow)*. **(B)** The cancer is better visualized on the 1-mm-thick tomosynthesis image.

characterization of breast lesions especially in women with nonfatty breasts (5). In DBT, the source x-ray tube is moved through a limited arc angle while the breast is compressed and a series of exposures are obtained (6). To a patient, DBT will be very similar to conventional digital mammography except there will be some movement of the x-ray tube head during exposures. These individual exposures are only a fraction of the total dose used during conventional digital mammography. The image data sets are reconstructed and the clinical reader is presented with a series of images (slices) through the entire breast that are read at a workstation analogous to CT or MRI study. Because each reconstructed slice may be as thin as 0.5 mm, masses and mass margins that may otherwise be superimposed with out-of-plane structures may be more visible in the reconstructed slice (Fig. 11-2). This should allow better visualization and characterization of noncalcified lesions. While the basic image interpretation will be similar to conventional mammography, new recall thresholds and probably benign thresholds will be established for DBT specific findings. In early studies, DBT has shown the ability to increase both sensitivity and specificity and has the potential to dramatically change not only how routine "mammography" is performed but also improve the clinical outcome of mammographic screening (5).

MAMMOGRAPHIC INTERPRETATION

Mammographic interpretation is a difficult task that can be dichotomized into two basic processes: detection (perception, visualization) of a possible abnormality and characterization (classification, analysis) of a potential abnormality. The goal of image interpretation by screening is high-detection sensitivity which requires the generation of false positives due to the nonspecific appearance of most small cancers. High sensitivity involves the ability to perceive potential abnormalities, only a fraction of which will prove to be cancer. Careful analysis of recalled patients by additional diagnostic imaging is necessary to evaluate a suspected lesion. With additional diagnostic mammography and ultrasound, a group of abnormalities of sufficient probability for malignancy will be recommended for biopsy. The commonly used U.S. threshold for biopsy is a probability of malignancy greater than or equal to 2% which corresponds to a BI-RADS classification of "suspicious finding" or BI-RADS 4 (7). Experienced readers can assign a reasonable probability of malignancy to a finding recommended for biopsy, but tissue diagnosis is necessary to confirm diagnosis even for lesions of very high probability. Mammographic appearances are seldom tissue specific.

Radiologists' Performance

Interpretation of mammographic images involves the art and science of medicine. While the recognition and characterization of classic large tumors is often straightforward, the detection of the small, subtle lesions can challenge the most expert reader. Interpretive variability exists for screening and diagnostic mammography. Key factors that influence overall performance include physician expertise, recall rates, observation time, biopsy rates, double reading, and CAD. The relationships among these parameters are complex.

Similar to other areas of human endeavor and medicine, differences have been found among radiologists interpreting mammograms (8–14). Beam et al., using an experimental model, found variation among practicing American radiologists with overall sensitivity ranging from 59% to 100% and specificity 35% to 98% (11). Sickles and colleagues reported higher cancer detection rates for specialists than generalists (6.0 per 1,000 vs. 3.4 per 1,000) within a single academic center in a retrospective clinical study (10). Specialists had higher volumes, more frequently participated in CME programs and fellowship training, and more often participated in radiologic–pathologic correlation conferences than generalists. The influence of reading volume on performance has not been consistent. Beam et al. tested 100 radiologists with an enriched study set of 148 mammograms with a 43% cancer incidence (11). They found reading volume not to be tightly associated with improved sensitivity. Rather complex multifactorial processes were found to be associated with expertise. Miglioretti and colleagues reported better performance for readers of diagnostic mammography at academic centers, those concentrating their time in breast imaging, and those performing breast biopsies (14). Volume was not

associated with performance. To date, no definite set of parameters completely predict reader expertise. Common associations with favorable interpretive skills and expertise include concentration in breast imaging, academic practice, continuing education, association with a multidisciplinary breast center, and practice audits (10,12,14). Reading a minimum of 480 mammographic cases per year is required by the FDA to maintain certification.

Sensitivity and specificity are inversely related for any particular reader due to nonspecific appearance of early breast cancer. Sensitivity increases with recall rate over a range of recall rates. High sensitivity can be achieved only when a sufficient number of women are recalled from screening for additional diagnostic mammography and ultrasonography (9,13,15,17). The ideal balance between sensitivity and recall rate is controversial and reflects philosophy, cost, cultural issues, and medical–legal issues. Yankaskas and colleagues demonstrated sensitivity increased from 65% at recall rates of 1.9% to 4.4% and to 80% sensitivity at recall rates of 8.9% to 13.4% in a study of practicing North Carolina radiologists (15). Karssemeijer et al., in an enriched study population, found sensitivity for masses improved from approximately 35% at a 3% callback rate to 59% at a 20% callback rate (9). Gur and colleagues noted improvements in sensitivity with increasing recall over a wide range (7.7% to 17.2%, $p < .05$) at a large clinical practice (17). On average, a 0.22 per 1,000 cancer detection rate improvement occurred for every 1% absolute increase in recall rate. Otten et al., in an experimental situation, found 47% sensitivity improvement when FP rate increased from 1% to 4% (16). In the United States, callback rates of 5% to 15% are common. Rosenberg et al. reported the middle 50% recall rate for practicing U.S. radiologists to be 6.4% to 13.3% (mean 9.8%) for 2.5 million screening studies (13). European callback rates are frequently lower. Dutch breast cancer screening program has reported callback rates as low as 1.1% (9,16). Emphasis on specificity and low cost will limit recall rate. Emphasis on high sensitivity will increase callback rates.

Mammographic sensitivity increases with reader observation time. Nodine and colleagues noted experienced mammographers made 71% of detections in the first 25 seconds but had continued true positive detections for approximately 80 seconds, albeit at a slower rate (18). Krupinski observed the detection of subtle findings occurred later in observation cycle than obvious masses which required longer visual dwell times (19). The threshold to initiate biopsy will influence cancer detection similar to recall rate thresholds. Higher thresholds for biopsy may be associated with higher false-negative (FN) rates and lower sensitivity (14).

Double Reading

Double reading (DR) has been advocated as a method to detect abnormalities overlooked by a single reader. Most independent DR studies have demonstrated improvement in sensitivity at a cost of lowered specificity. A review of clinical independent DR studies shows detection rate improvements of 4% to 15% (20). However, recall rates (FP) increased by 11% to 45%. These divergent trends for DR between sensitivity and specificity tend to balance accuracy. Taplin et al. showed independent DR improved sensitivity by 8.9% and decreased specificity by 13.6% similar to clinical trials (21). Accuracy, as determined by ROC methods, did not change suggesting that independent DR acted to shift the decision threshold towards sensitivity at the expense of specificity. DR with expert or consensus readers as the second reader appears to retain most improvements in sensitivity without large declines in specificity but this outcome may reflect in part the expertise of the second reader.

Computer-Aided Detection (CAD)

CAD systems, commercially available, use artificial computer intelligence in an attempt to act as a second reader. Like DR, most clinical CAD trials have shown improvement in sensitivity but declines in specificity. A CAD system functions as a second reader by placing "marks" on a mammographic site deemed suspicious. The radiologists then characterize these CAD detections. CAD can correctly identify approximately 60% to 80% of cancers with highest performance for microcalcifications. Unfortunately, CAD systems are very nonspecific with 2 to 4 marks placed per every exam. It has been estimated that only 1 in 5,000 CAD marks will reflect a true-positive finding representing a unique cancer missed by the radiologist (20). The interactions between radiologist and CAD are complex but tend to mirror DR studies. Clinical studies with CAD show sensitivity improvements varying from 1.7% to 19.5%, with declines in specificity as noted by increased recall rate of 0.1% to 26% (20). CAD effect on accuracy has often been incompletely reported so the determination whether CAD is increasing accuracy or shifting the threshold toward sensitivity has been questioned. Fenton et al. showed reader accuracy as measured by ROC methods declined with incremental use of CAD in a retrospective clinical study of 684,956 women (22). They showed a nonsignificant 6% improved sensitivity but a 13% significant loss of specificity. Sensitivity improvement for CAD was for DCIS. The reason for this negative result is uncertain but may result from overrelying on CAD, changing radiologists reading patterns, spending less overall time in observation, and radiologists being overwhelmed with the large number of false-positive CAD marks. While CAD remains controversial, CAD is in its infancy and the future of CAD is robust for detection and characterization tasks as a second reader. More effort will be required to improve the human interaction with CAD to reap the theoretical advantages of CAD. Current CAD systems are best viewed as a second reader with moderate sensitivity and poor specificity. Overreliance on CAD should be avoided and may actually degrade overall reader performance if used incorrectly. CAD should never be used to discount a finding deemed by the radiologist to be suspicious.

CHARACTERIZATION OF MAMMOGRAPHIC FINDINGS

Characterization is the process to determine if a suspected mammographic finding represents normal tissue, a benign finding, or potentially breast cancer. The goal of characterization is to establish a probability of malignancy and threshold the finding to determine if tissue sampling is required. This assessment is based on morphologic appearance of a finding and stability or change over time.

Mammography is not tissue specific. Some very low-probability-appearing abnormalities will prove to be malignant and conversely, some high-probability findings will be benign. Distinguishing between what lesions require biopsy and which can be followed involves thresholds. Most U.S. radiologists recommend biopsy for probability of cancer greater or equal to 2% (7). Individual radiologists assess their thresholds by auditing their practice by reviewing the frequency of malignancy for lesions recommended for biopsy (positive predictive value), their false-negative rate for lesions recommended for follow-up, tumor size, and stage. The U.S. Department of Health and Human Services has suggested the following as desirable goals for screening mammography which have been attained by highly skilled

experts: Positive predictive value for biopsy 25% to 40%, recall rate 5% to 10%, incident cancer detection 2 to 4 per 1,000, minimal cancer detection >30%, stage 0, 1 >50%, sensitivity >85%, and specificity >90% (4). Different patient populations will significantly impact on the ability of a screening population to attain these goals.

FDA/BI-RADS FINAL ASSESSMENT CATEGORIES

To provide national uniformity for reporting and assessment of mammographic findings, the American College of Radiology developed a lexicon for final assessment classifications ("BI-RADS") (7). After analyzing a mammogram, radiologists classify their findings into one of five final assessment categories (2,7). MQSA requires the use of final assessment categories paralleling those of the American College of Radiology (2). This lexicon is now used internationally. The final assessment categories are presented in Table 11-1. The categories are as follows:

Category 1: negative
Category 2: benign finding
Category 3: probably benign finding
Category 4: suspicious abnormality
Category 5: highly suggestive of malignancy (risk ≥95%)

Category 4 can be subdivided by risk into 4A (low), 4B (intermediate), and 4C (moderate). Functionally, Categories 1 and 2 represent a normal screening mammogram without

TABLE 11-1

American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) Assessment Categories: Mammography

Complete Final Assessment Categories		
Category 1	Negative	There is nothing to comment on. The breasts are symmetrical and no masses, architectural disturbances, or suspicious calcifications are present.
Category 2	Benign finding	Like Category 1, this is a "normal" assessment, but here, the interpreter chooses to describe a benign finding in the mammography report. Involuting, calcified fibroadenomas, multiple secretory calcifications, fat-containing lesions such as oil cysts, lipomas, galactoceles, and mixed-density hamartomas all have characteristically benign appearances and may be labeled with confidence. The interpreter may also choose to describe intramammary lymph nodes, vascular calcifications, implants, or architectural distortion clearly related to a prior surgery while still concluding that there is no mammographic evidence of malignancy. Note that both Category 1 and Category 2 assessments indicate that there is no mammographic evidence of malignancy. Note that both Category 1 and Category 2 should be used when describing one or more specific benign mammographic findings in the report, whereas Category 1 should be used when no such findings are described.
Category 3	Probably benign finding: initial short interval follow-up suggested	A finding placed in this category should have less than a 2% risk of malignancy. It is not expected to change over the follow-up interval, but the radiologist would prefer to establish its stability. There are several prospective clinical studies demonstrating the safety and efficacy of initial short-term follow-up for specific mammographic findings. Three specific findings are described as being probably benign (the noncalcified circumscribed solid mass, the focal asymmetry, and the cluster of round (punctate) calcifications; the latter is anecdotally considered by some radiologists to be an absolutely benign feature). All the published studies emphasize the need to conduct a complete diagnostic imaging evaluation before making a probably benign (Category 3) assessment; hence it is inadvisable to render such an assessment when interpreting a screening examination. Also, all the published studies exclude palpable lesions, so the use of a probably benign assessment for a palpable lesion is not supported by scientific data. Finally, evidence from all the published studies indicates the need for biopsy rather than continued follow-up when most probably benign findings increase in size or extent. While the vast majority of findings in this category will be managed with an initial short-term follow-up (6 months) examination followed by additional examinations until longer-term (2 years or longer) stability is demonstrated, there may be occasions where biopsy is done (patient wishes or clinical concerns).

TABLE 11-1 *(Continued)*

American College of Radiology Breast Imaging Reporting and Data System (BI-RADS) Assessment Categories: Mammography

Complete Final Assessment Categories		
Category 4	Suspicious abnormality: biopsy should be considered	This category is reserved for findings that do not have the classic appearance of malignancy but have a wide range of probability of malignancy that is greater than those in Category 3. Thus, most recommendations of breast interventional procedures will be placed within this category. By subdividing Category 4 into 4A, 4B, and 4C as suggested in the guidance chapter, it is encouraged that relevant probabilities for malignancy by indicated within this category so the patient and her physician can make an informed decision on the ultimate course of action.
Category 5	Highly suggestive of malignancy: appropriate action should be taken	These lesions have a high probability (95%) of being cancer. This category contains lesions for which one-stage surgical treatment could be considered without preliminary biopsy. However, current oncologic management may require percutaneous tissue sampling as, for example, when sentinel node imaging is included in surgical treatment or when neoadjuvant chemotherapy is administered at the outset.
Category 6	Known biopsy: proven malignancy; appropriate action should be taken	This category is reserved for lesions identified on the imaging study with biopsy proof of malignancy prior to definitive therapy.
Category 0 Incomplete	Need additional imaging evaluation and/or prior mammograms for comparison	Finding for which additional imaging evaluation is needed. This is almost always used in a screening situation. Under certain circumstances this category may be used after a full mammographic workup. A recommendation for additional imaging evaluation may include, but is not limited to, the use of spot compression, magnification, special mammographic views, and ultrasound. Whenever possible, if the study is not negative and does not contain a typically benign finding, the current examination should be compared to previous studies. The radiologist should use judgment on how vigorously to attempt obtaining previous studies. Category 0 should be used only for old film comparison when such comparison is required to make a final assessment.

findings of malignancy. Category 2 may include a normal finding such as a calcified fibroadenoma, normal lymph node, or stable benign appearing calcifications. Category 3, probably benign, represents a finding of such low probability for malignancy that imaging follow-up is recommended instead of biopsy. Multiple studies have established the risk of malignancy to be less than 2% (23). The risk of malignancy expresses itself generally over the first 2 years. Recommended management consists of a follow-up mammogram at 6 months following the initial examination with subsequent follow-up at 12 and 24 months unless biopsy is elected by patient or physician. Diagnostic mammography should be performed prior to using the probably benign category. Category 4 and 5 assessments are abnormalities that require tissue biopsy for diagnosis. These categories represent a broad range (3% to 100%) of risk for cancer and experienced radiologists can render reasonable probability of malignancy estimates.

A category "incomplete" (BI-RADS 0) is used when a screening study requires additional imaging such as recall for diagnostic mammograms or comparison with older exams prior to rendering a final assessment. An incomplete assessment is just that, incomplete. An incomplete exam should not be considered "abnormal" as most will be shown to be normal. Only after diagnostic imaging or comparison with older films can a Category 1 to 5 final assessment be rendered. "Incomplete" has been used to categorize a normal mammogram in a setting of a palpable mass with assessment decision deferred to findings on ultrasonography. Although this is an acceptable use per FDA guidelines, it has led to some confusion in the performance literature based on BI-RADS codes alone. We prefer a definitive mammographic assessment as "negative" in this situation but recommend ultrasound examination of the palpable finding and report the sonographic finding independently. BI-RADS Category 6, "Known biopsy proven malignancy," can be used for cases with known malignant diagnoses.

Although BI-RADS reporting system has been favorably received, confusion can arise from patients and clinicians when a suspicious palpable or sonographic mass has a

"negative" mammogram report. In these situations, tissue biopsy is recommended when the palpable or sonographic findings are suspicious even if the mammogram is "negative." A "negative" mammogram in the presence of a suspicious clinical finding, suspicious USN, or suspicious MRI should never obviate a needed surgical biopsy. Mammography cannot "rule out" cancer.

MAMMOGRAPHIC APPEARANCE OF BREAST CANCER

There is a tendency to limit mammographic analysis to morphologic features. In practice, temporal change on serial mammograms provides a separate axis of analysis from morphologic features. A group of four calcifications that have been present for five years and unchanged may be observed while four new calcifications that were not present on a prior mammogram may be biopsied. Most mammographic cancers appear as masses, calcifications, asymmetry, distortion, or a combination of the four. Masses and calcification account for about 90% of all cancer appearances. Similar to the final assessment categories, a lexicon has been established by the ACR BI-RADS for describing and characterizing morphologic features (7). This lexicon use is not required by MQSA. The following discussion summarized the lexicon. Mammographic interpretation remains a *visual* interpretation process and not a verbal descriptive process. The figures have been chosen to show a range of appearances of breast cancer, not just obvious cases.

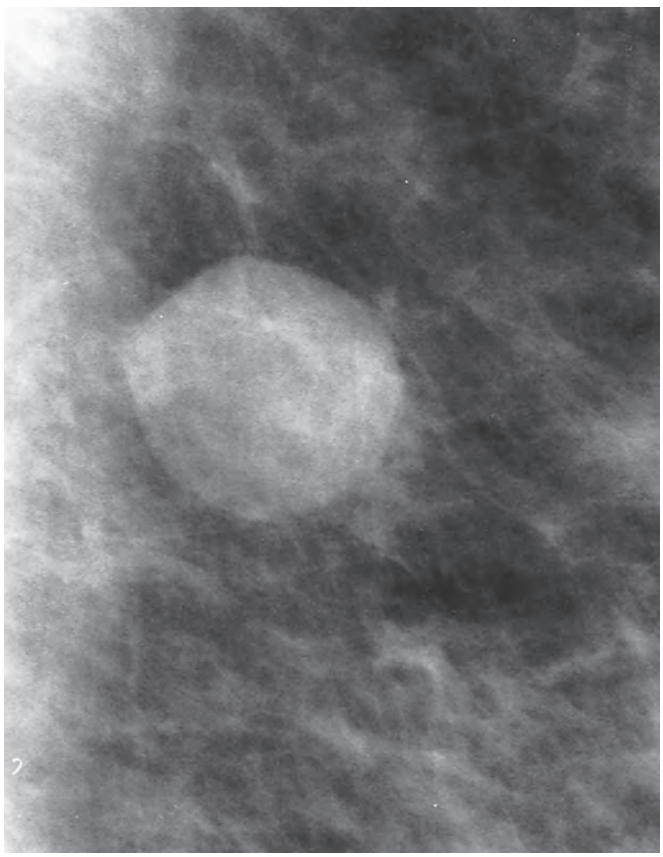

FIGURE 11-3 Smoothly marginated round 14-mm mass. Sonogram demonstrated a simple cyst.

Masses

Masses account for nearly half of all mammographic cancers. Masses refer to space occupying lesions that can be detected in two different projections. If a finding is noted only in a single view same as a CC view, it is referred to as a focal asymmetry. A focal asymmetry may or may not prove to be a "real" finding. Masses are characterized by their shape, margin, and density in order to determine a probability of malignancy.

Shape

Because of the infiltrative biologic nature of most breast cancers, irregular or lobular shaped masses are more likely associated with malignancy than round or oval masses.

Margins

The margin between a mass and the surrounding breast tissue is the key feature for analysis of masses because it relates to the infiltrating pattern of cancer. Often, margins are obscured by breast tissue rendering this evaluation impossible. Circumscribed, well-defined margins tend to represent a benign process (Figs. 11-3 and 11-4) such as cysts or fibroadenomas. Margins that are indistinct or microlobulated suggest infiltration into normal breast tissue and higher risk for malignancy. Smoothly marginated masses are usually subjected to ultrasound interrogation to assess if they represent a breast cyst for which no further intervention is required or a solid mass which often requires biopsy. Masses with indistinct margins may also be interrogated with ultrasound to assess for size, character, and visibility for potential biopsy procedure. Masses with spiculated borders forming a stellate or star-type pattern of radiating lines are associated with the highest risk of malignancy. As shown in Figures 11-3 through 11-7, there is a continuum in appearance of malignant and benign masses.

Mass Density

Lesions that are fat density (black on a mammogram) are benign and do not require tissue diagnosis. These typi-

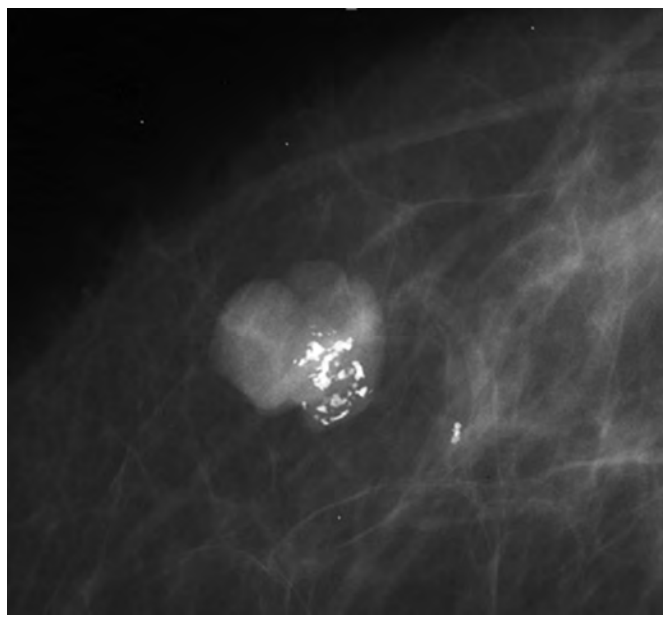

FIGURE 11-4 Spot compression view of a circumscribed mass with associated, very coarse calcifications, typical for a benign, degenerating fibroadenoma.

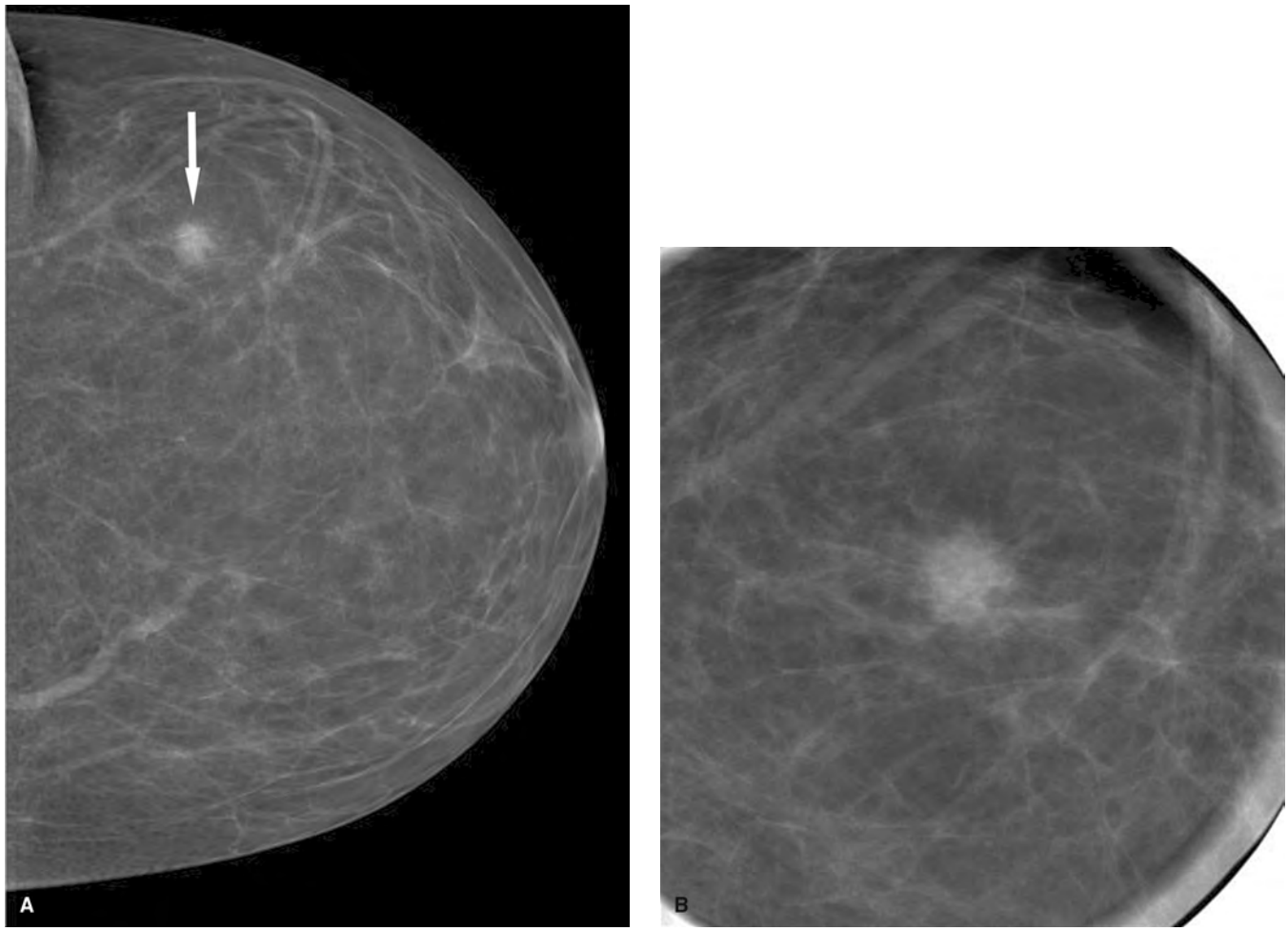

FIGURE 11-5 **(A)** Craniocaudal view shows a new small focal asymmetry in the lateral aspect of the breast *(arrow)*. **(B)** Spot compression magnification view confirms the presence of an indistinct, noncalcified mass: invasive ductal carcinoma.

cally represent lipomas or areas of traumatic fat necrosis with oil cyst formation. Certain circumscribed fat containing and fibroglandular density tissues may have appearance pathognomonic for a benign hamartoma and not require biopsy. Otherwise, density is of limited value in discriminating benign from malignant lesions, although high density is often a suspicious sign.

Calcifications

For reasons not entirely understood, calcifications are formed or are associated with breast carcinoma. Fortunately, calcifications are exquisitely detected by mammography with particles as small as 50 μm being visible. Because calcium absorbs x-rays, they produce a bright white spot on a mammogram. This inherent contrast between calcification and background tissue is a significant reason why mammography is successful in detecting small tumors, especially those associated with ductal carcinoma *in situ*. Calcifications can be seen reasonably well in dense breasts because calcium absorbs more x-ray energy than dense tissue. Unfortunately, many benign conditions such as fibrocystic change also produce breast calcifications that may mimic breast cancer calcifications. Some type of calcification is present on most mammograms. The radiologist is faced with a common problem regarding the nature and significance of calcifications. Magnification mammography is critical in characterizing calcifications. This allows better morphologic assessment of individual particles and clusters. Assessment of microcalcifications includes location, morphology, distribution, number, and biologic stability or progression. All of these factors are important in determining a risk of malignancy.

Location

Calcifications present within the skin may masquerade as parenchymal calcifications. These calcifications are typically small (less than 1 mm) with lucent centers. Radiologists can, with incremental imaging, prove with certainty that calcifications reside in the skin by tangential views. Dermal calcifications require no intervention. Other than dermal calcifications, location is of limited use in assessment.

Morphology

Artery calcifications appear as parallel lines associated with blood vessels and usually when established can be readily distinguished from linear calcifications of carcinoma. Large, coarse peripherally based "popcorn" calcifications are noted with fibroadenomas that are undergoing involution with age (Fig. 11-4). These also can be recognized as a specific benign entity and require no tissue diagnosis. Rod-like linear

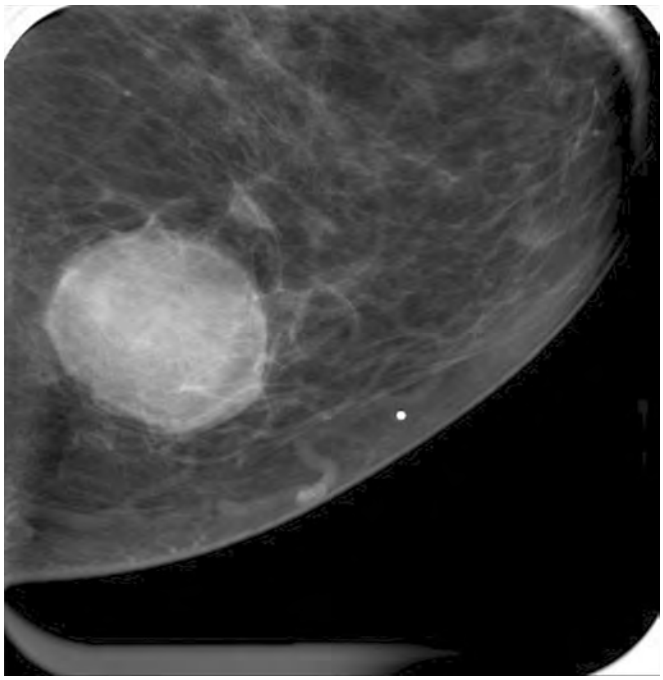

FIGURE 11-6 Spot compression view demonstrates the circumscribed margins of an invasive ductal carcinoma, medullary type.

calcifications associated with benign ductal ectasia appear to fill ectatic ducts, are bilateral, and rather homogeneous (Fig. 11-8). In established cases, these calcifications provide no diagnostic dilemma. Early ductal ectatic calcifications may appear indistinguishable from ductal carcinoma in situ. Calcifications containing lucent centers ("eggshell" or "rim" calcifications) are benign and associated with calcified fat necrosis, calcified cysts (Fig. 11-9). Dystrophic calcifications associated with fat necrosis often follow trauma such as surgery and irradiation. They are usually larger than 0.5 mm and have lucent centers. Calcifications which appear to layer with gravity are consistent with sedimenting calcifications within small cysts ("milk of calcium" or "microcystic adenosis"). They are ill defined on the craniocaudal view and are sharply defined on the lateral view with dependent linear calcifications within small cysts. Biopsy is not required.

Most calcifications associated with cancer are small (< 0.5 mm) and often require magnification views for characterization. Malignant calcifications are notable for heterogeneity in size, shape, and geographic clustering. Malignant calcifications vary in appearance from subtle to obvious (Figs. 11-10 through 11-12) and may be associated with mass. Focal areas of amorphous indistinct calcifications are nonspecific in appearance and usually require tissue diagnosis. Positive predictive value for this type of calcification is about 20%.

High probability for cancer calcifications include pleomorphic or heterogeneous calcifications which are fine

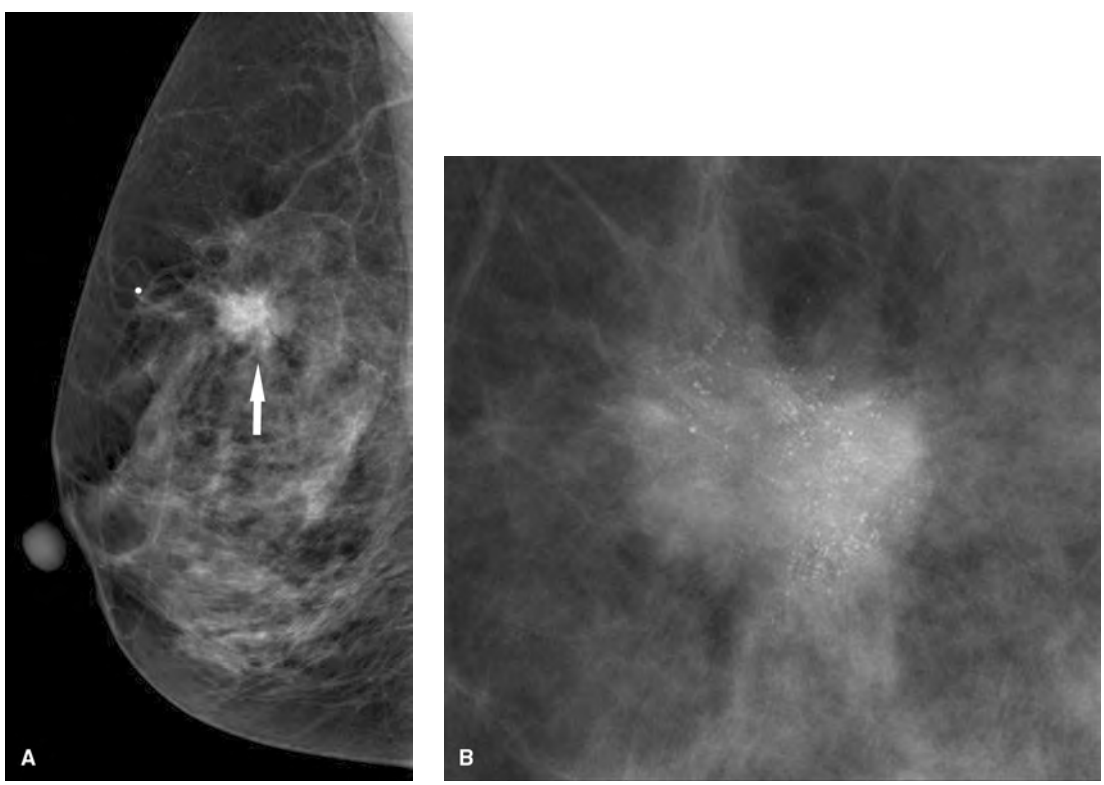

FIGURE 11-7 **(A)** Palpable, spiculated mass with associated microcalcifications *(arrow)*. **(B)** Spot magnification view confirms the presence of the spiculated mass with associated calcifications: invasive ductal carcinoma with DCIS.

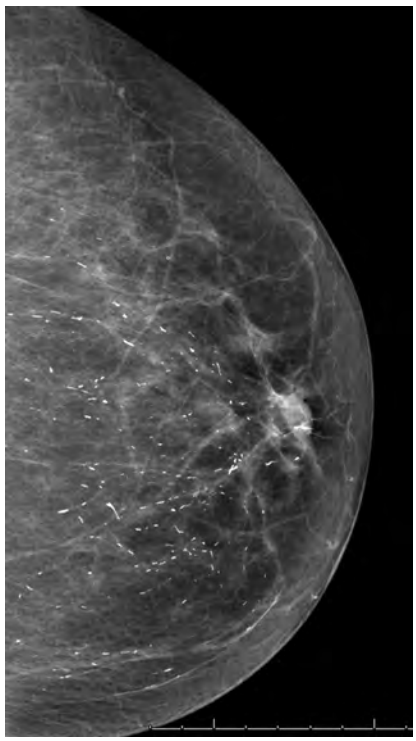

FIGURE 11-8 Benign calcifications associated with ductal ectasia. These rod-shaped calcifications are oriented toward the nipple in this postmenopausal woman.

linear or fine linear branching calcifications conforming to a casting pattern of a duct. These calcifications are often associated with high-grade ductal *in situ*, with or without invasive cancer (Fig. 11-11).

Number

Although no number absolutely distinguishes benign from malignant, attempts have been made to determine reasonable thresholds for clinical intervention based on number of calcifications in a cluster. Five or more clustered calcifications not typically benign have been a threshold advocated by some experienced readers for biopsy. Others have noted increased frequency of cancer with increasing number of calcification particles. Most radiologists incorporate number of calcifications in a cluster, morphology and change with time to form an assessment regarding need to biopsy.

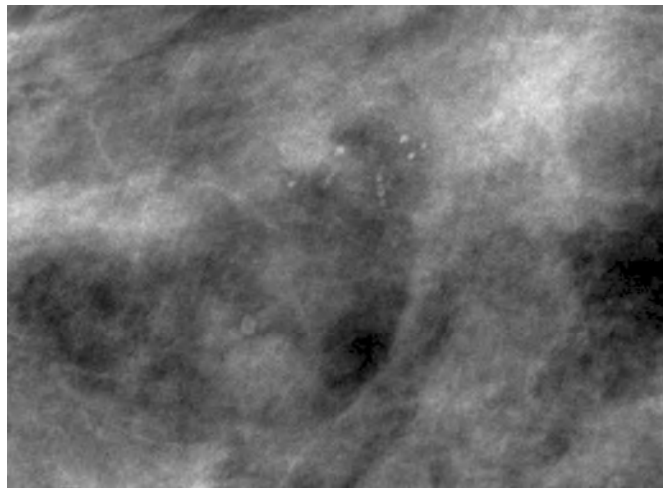

FIGURE 11-10 A 7-mm cluster of amorphous calcifications: ductal carcinoma *in situ*.

Distribution

Distribution of calcifications in addition to morphology, number, and biologic change helps establish a probability of malignancy.

- Grouped or clustered: Clustered calcifications refer to a group of calcifications in a less than 2 cm^3 volume of tissue. Although "cluster" has historically been associated with malignancy, this term can be used as a neutral designator.
- Linear: Calcifications that appear to be arranged within a line or duct imply a ductal origin. This is of moderate suspicion.

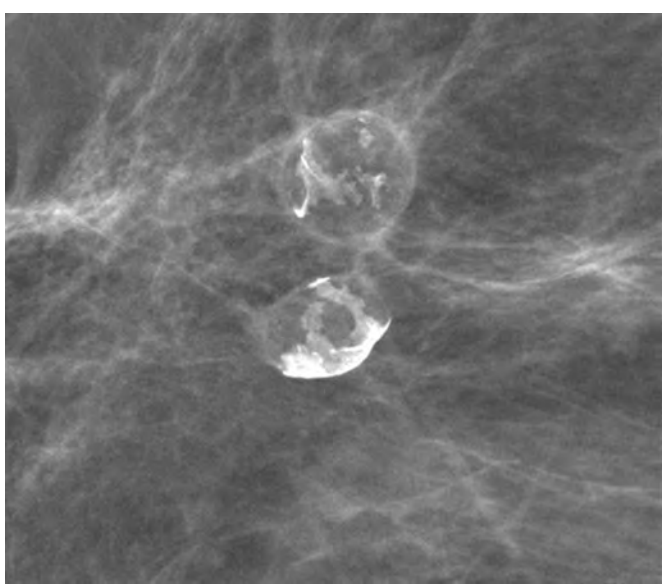

FIGURE 11-9 Benign calcifications associated with lucent masses typical for oil cysts and fat necrosis.

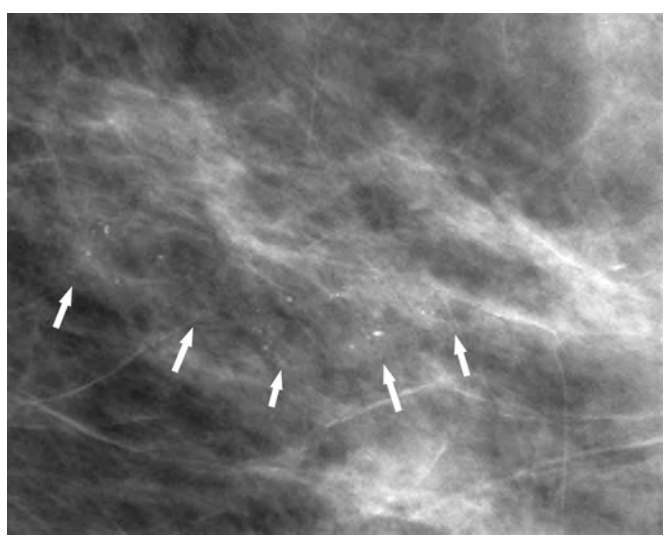

FIGURE 11-11 A 7-cm area of calcifications in a linear distribution *(arrows)*: ductal carcinoma *in situ*.

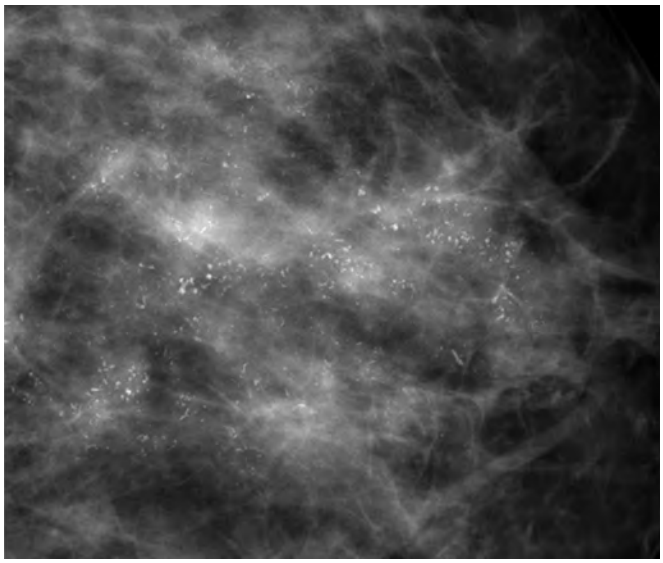

FIGURE 11-12 Magnification view of diffuse, pleomorphic microcalcifications in a heterogeneously dense breast. High-grade DCIS and invasive ductal carcinoma found at pathology.

Segmental: Calcifications restricted to a segment or wedge-shaped portion of the breast may arise within a single ductal system and its branches. This is a distribution frequently associated with malignancy.

Diffuse/scattered: Calcifications that appear to be randomly distributed throughout the breast are referred to as diffuse or scattered. Compared to linear or segmental, scattered calcifications are associated with lower risk of malignancy. By chance, randomly distributed calcification will have areas of higher concentration of calcification particles and areas of fewer not dissimilar to a shotgun pellet pattern. These more concentrated groups are viewed with less suspicion than a similar isolated group of calcification.

Architectural Distortion

Architectural distortion may be a very subjective appearance on a mammogram or a straightforward observation. Architectural distortion refers to an unusual pattern that includes spiculations and retraction (Fig. 11-13). Unless associated with an area of prior biopsy or area of prior infection, architectural distortion requires tissue diagnosis. Benign, radial sclerosing lesions may have this appearance but biopsy is necessary to establish histology. Skin retraction and nipple retraction carry significant risk of malignancy and require tissue biopsy.

Unusual Findings

Focal skin thickening may be associated with benign or malignant ideologies. Malignant causes would include inflammatory carcinoma (Fig. 11-14) and local skin thickening adjacent to a known carcinoma. Skin thickening may be present with benign conditions such as infection and venous obstruction. Clinical management assumes primary importance in these situations.

Focal asymmetry describes an area of asymmetry that lacks the appearance of a true mass. Additional imaging and ultrasound may be required for characterization (Fig. 11-5) but this may be a very subtle manifestation of early breast cancer, especially if a new finding.

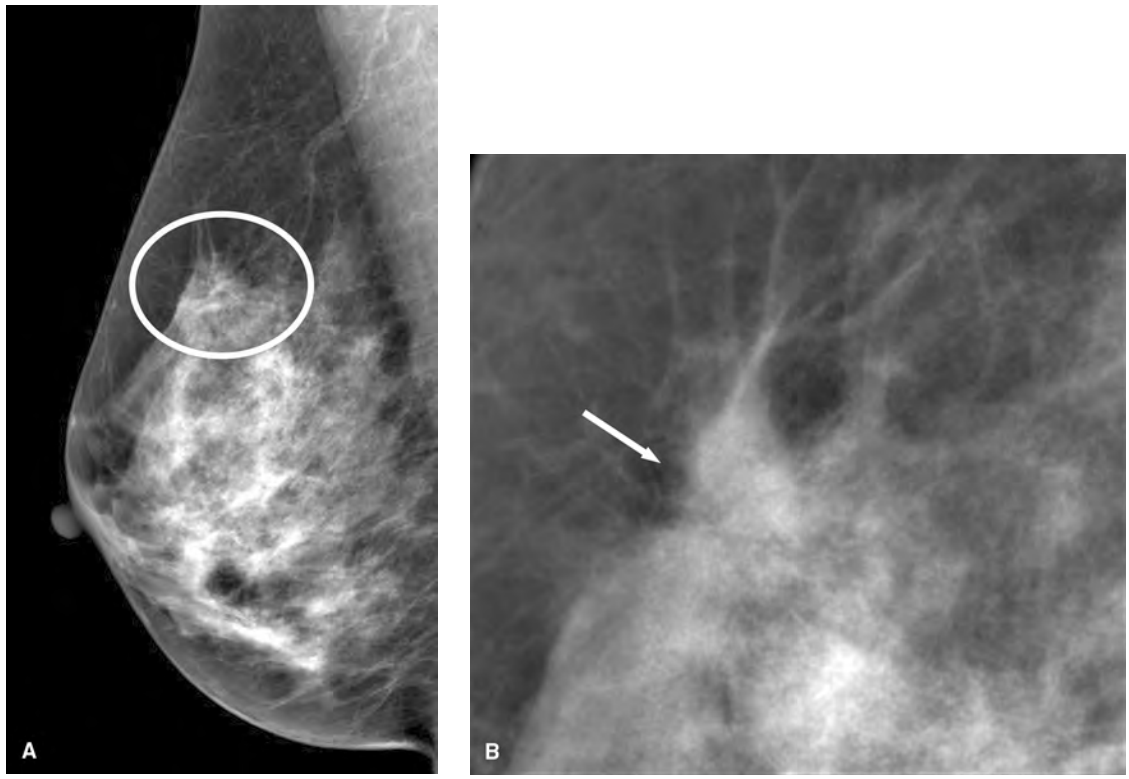

FIGURE 11-13 **(A)** Subtle area of architectural distortion *(circle)*. **(B)** Spot magnification view demonstrates distortion *(arrow)*.

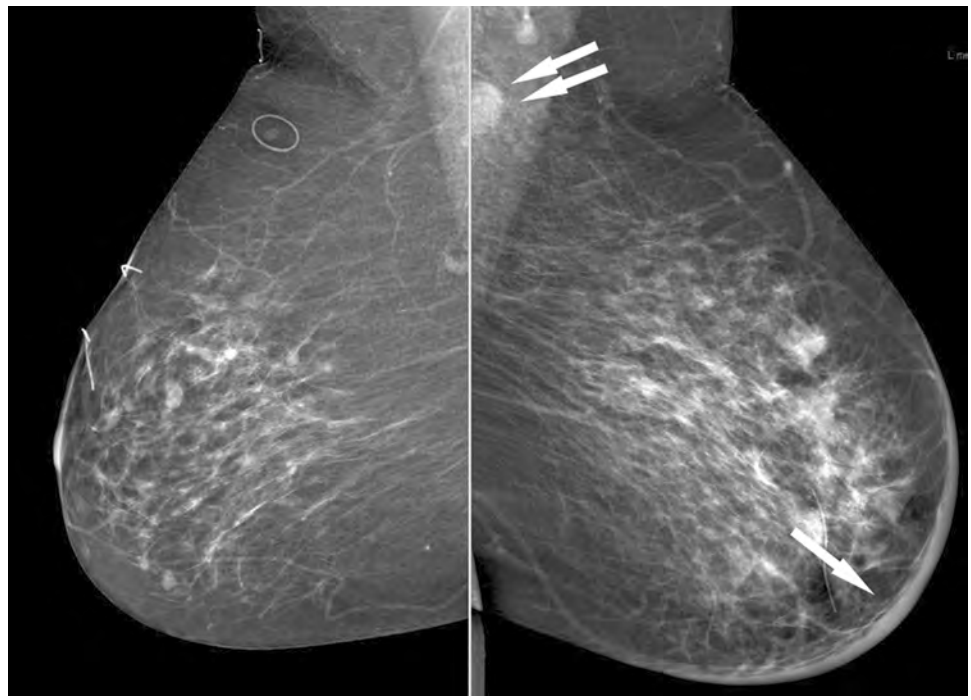

FIGURE 11-14 Bilateral mediolateral oblique views demonstrates skin thickening *(arrow)* of the breast on the right, increased density, as well as a dense axillary lymph node *(arrows)*: inflammatory carcinoma.

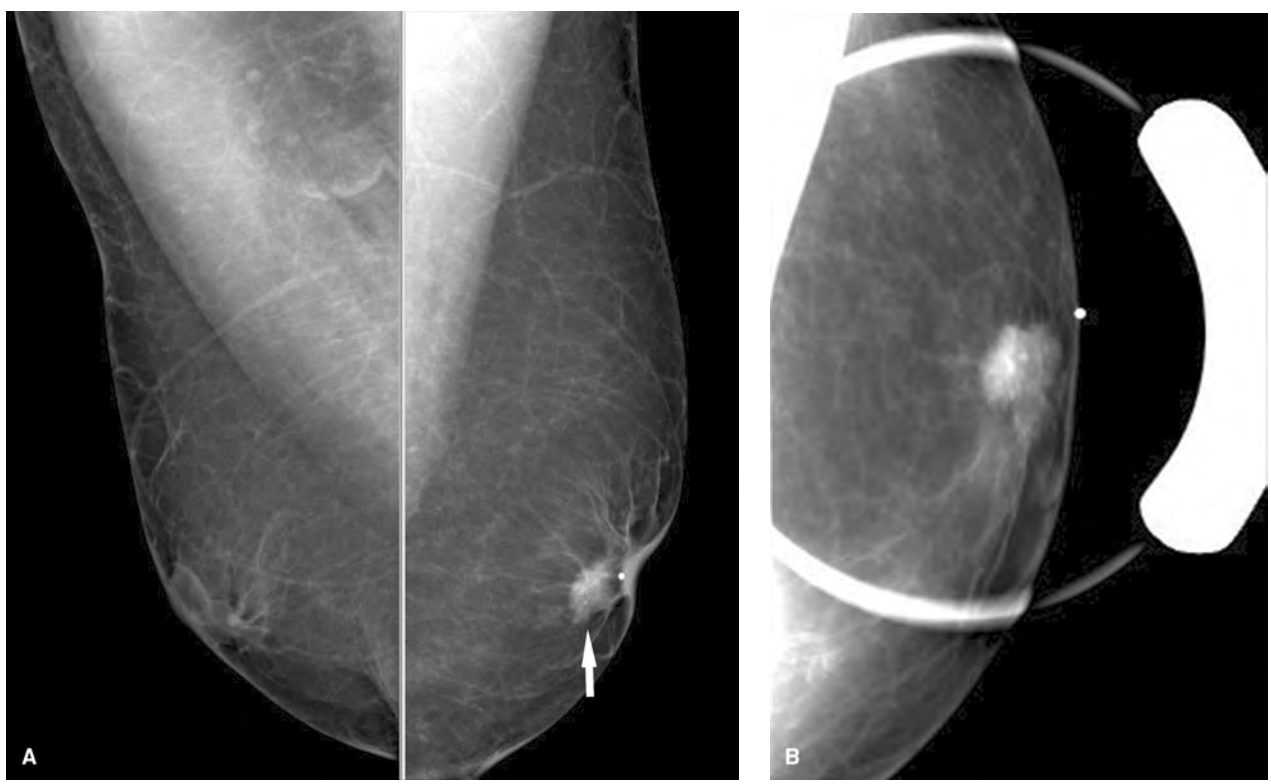

FIGURE 11-15 **(A)** Male breast cancer presenting as an irregular, retroareolar mass *(arrow)*. **(B)** Spot compression view demonstrates the irregular mass.

ROLE OF THE MAMMOGRAPHY IN EVALUATION THE SYMPTOMATIC PATIENT

The evaluation of a symptomatic patient is common. Physical examination has poor specificity with only 4% of symptomatic women found to have malignancy (14). The goal of mammography in this setting is to characterize the palpable finding and assess the balance of the breast. Breast ultrasound is used extensively in the setting of a symptomatic patient in addition to mammography. Use of standard practice guidelines is recommended for imaging and management of symptomatic women (24). A suspicious clinical finding should undergo surgical consultation even if imaging is negative.

Palpable Mass or Thickening

Individuals with a palpable breast abnormality such as a discrete mass or focal thickening or nodularity should undergo diagnostic imaging prior to biopsy since biopsy can alter mammographic and sonographic appearances. Women 30 years and older are recommended for mammography and sonography; women younger than 30 are initially evaluated with sonography, although mammography may be necessary in certain circumstances (24). Spot compression views of the palpable area increases sensitivity. Approximately 5% to 15% of patients with a palpable cancer will have a false-negative mammogram. This number is higher for women with extremely dense breasts and lower for women with extremely fatty breasts. An individual clinician may overestimate mammography performance due to the low incidence of cancer in the symptomatic population. Of a typical group of 250 diagnostic patients referred for mammography, there will be 10 cancers. Only 1 of the 250 will have cancer and a false-negative mammogram (assumes a 4 per 100 cancer incidence and a 10% false-negative rate) but this low number is due primarily to the low incidence of cancer rather than the superb mammographic performance. If the mammogram is negative, ultrasound is performed of the palpable area since most cancers with false-negative mammography will be identified as abnormal by sonography. A patient with a negative mammogram and negative ultrasound in the setting of a palpable finding is at very low risk of malignancy. The false-negative rate of combined ultrasound and mammograms at experienced breast centers is 0% to 3% (25–28). The management of patients with palpable findings with negative mammogram and ultrasound depends on the clinical assessment. Suspicious palpatory findings should be biopsied even if imaging is negative. If biopsy is not elected for a very low clinical suspicion palpable findings with negative imaging, short-term clinical follow-up and imaging are recommended to assess for change (24).

Bloody or Serous Discharge

Mammographic sensitivity may be as low as 10% for intraductal cancer presenting as nipple discharge (29). If the mammogram is negative, retroareolar breast ultrasound can be performed to assess for intraductal masses or other findings. If mammogram and ultrasound are negative in the setting of a suspicious discharge, one may proceed with ductography, MRI, or excisional biopsy. Abnormalities on ductography include filling defects, obstructions, and cysts. Characterization of benign and malignant intraductal masses is not sufficient to distinguish benign papilloma from ductal carcinoma *in situ*. Filling defects or stenoses require surgical excision to determine histologic cause. An MR may show areas of abnormal enhancement and possibly intraductal masses. MR size resolution is less than ductogram. Rarely, a ductogram or MR may demonstrate a distal intraductal mass, which may not be reached during routine retroareolar duct surgery. In this situation, the mass can be localized for the surgeon to ensure proper excision. A negative ductogram, mammogram, ultrasound, or MR in a setting of a clinically suspicious nipple discharge should not dissuade surgical excision (24).

Skin Changes or Inflammatory Breast Findings

Women presenting with inflammatory breast findings are referred for diagnostic mammography and often sonography. The distinction between inflammatory cancer and infection is frequently not possible by imaging alone as both may show skin changes, interstitial edema, and abnormal axillary lymph nodes (Fig. 11-14). Unless a suspicious mass or calcifications are found which would direct biopsy, urgent clinical evaluation is recommended. Sonography may detect a fluid collection consistent with abscess which can be confirmed with aspiration. For those women initially treated with antibiotics for suspected mastitis, very short-term clinical reevaluation to ensure resolution is imperative. Early surgical consultation is recommended for nonresponders (24).

Axillary Lymph Node Presentation of Breast Cancer

Less than 1% of women with breast cancer will present with an axillary mass found to represent metastatic breast cancer in axillary lymph nodes with normal breast physical examination. Diagnostic mammography should be performed of both breasts to assess for occult breast cancer. If mammography is negative, breast MR has been advocated. Buchanan et al. found occult cancer by MR in about half of the cases (30).

Symptomatic Pregnant and Lactating Women

Sonography is the initial imaging evaluation of pregnant and lactating women, many whom have never been screened due to young age although mammography may be also useful in some cases to assess for calcifications (31). Due to the extremely low fetal radiation dose, mammography is not contradicted when sonography or physical findings are suspicious for cancer. The radiation dose of a two-view mammogram to the uterus or fetus is less than 1 per 10,000 the breast dose (0.03 μGy or 0.003 mrad) which is further reduced by a factor of 2 to 7 with shielding (32).

NEWLY DIAGNOSED BREAST CANCER

Diagnostic mammography has an important and critical role in evaluating the patient's eligibility for breast conservation therapy. Morrow showed that diagnostic mammography, physical exam, and pathologic analysis could correctly determine 97% of patients' eligibility for breast conservation versus mastectomy (33). Extensive calcifications associated with ductal carcinoma *in situ* by mammography are generally a contraindication to breast-conservation therapy. Multicentric disease by mammography is also a contraindication to breast-conservation therapy. Review of patients' mammograms after histologic diagnosis of breast cancer may change surgical management. Newman et al. reported 10.7% patients had change in management after mammographic review at a multidisciplinary academic center and 7% incremental detection of cancer (34). The impact on

survival is unknown. Magnification mammography is routinely used in the setting of breast cancer manifested as microcalcifications to assess extent. Following lumpectomy with negative pathologic margins, mammography is recommended in cases with malignant calcifications to ensure excision. Suspicious residual calcifications should be subject to reexcision prior to radiation therapy. The use of "staging" MR is controversial and covered in Chapter 14.

BREAST-CONSERVATION-TREATED (BCT) PATIENT SURVEILLANCE

Mammographic surveillance following breast-conservation therapy is typically performed at 6 months, 12 months, and then yearly, although variations exist and the optimal intervals have not been established. Because normal post-BCT changes may mimic cancer by mammography, the first mammogram can serve as a baseline for future evaluations. Typical findings such as mass, edema, and skin thickening are observed. Since these mammographic findings can be signs of malignancy, specificity of mammography is low so aggressive mammographic interpretation at the first post-BCT exam in women with a margin negative cancer is not appropriate. The reported sensitivity of mammography for detection of in-breast recurrence is variable (35). Vapiwala et al. reported 68% of local recurrences (including skin) were positive by mammography (36). The biopsy PPV was higher for mammography than physical exam (65% vs. 40%) and was highest when both mammography and physical exam were abnormal (79%), showing the complementary role of imaging and physical exam. Mammographic surveillance following BCT for ductal carcinoma *in situ* appears reasonable at detection of recurrences, although data are limited. Pinsky and colleagues found 97% of recurrences after BCT for DCIS were apparent by mammography and 91% were minimal cancer at detection (37).

Symptomatic Males

Men presenting with palpable findings may undergo breast imaging, although some clinicians proceed directly to biopsy when the clinical findings are suspicious. The normal male breast is entirely fatty. Gynecomastia presents as retroareolar mammographic density without calcification which may be asymmetric. This often has a characteristic flame-like pattern of distribution and does not appear mass-like. Enlarged breast due to excessive adipose tissue ("pseudogynecomastia") appears as fat on mammography and requires no further evaluation. The mammographic findings of male carcinoma are similar to female cancer but microcalcifications are unusual (Fig. 11-15). Mammography is very sensitive for breast cancer detection due to the lack of breast tissue in most men with negative predictive values of 99% to 100% reported (38). Because some unusual forms of gynecomastia may appear mass-like by mammography, biopsy is required in these cases to establish the diagnosis. Similar to women, a suspicious palpatory finding in the setting of a negative mammogram should not deter biopsy.

SCREENING: SPECIAL SITUATIONS

Screening mammography of high-risk women is performed in a manner similar to routine screening but at an earlier age. Early screening (prior to age 40) has been advocated for women treated with chest mantle radiation during youth, genetic carriers of breast cancer genes such as *BRCA1* and *BRCA2,* other genetic risks, and women with strong premenopausal family history with both annual mammography and MR (24,39). This screening may start as early as ages 25 to 30. There are no randomized control trials to show survival benefit as exists for women aged 40-and older. Mammographic appearance of cancer in some high-risk groups may be similar to the population in general. However, because these are young women, mammography may be less sensitive due to higher frequency of dense breasts and possible aggressive tumor biology. The use of digital mammography in young women with dense breasts may improve sensitivity (3).

MAMMOGRAPHIC ASSESSMENT OF BREAST DENSITY AS A RISK FACTOR

Mammographic breast density is an independent risk factor for breast carcinoma. Fibroglandular tissue attenuates x-rays and produces a white ("dense") area on a mammogram. Fatty areas of the breast do not attenuate x-rays as much and produce a dark (nondense) area on the mammogram. Mammography cannot discriminate between density attributed to fibrotic tissue and that attributed to glandular tissue. Estimation of breast density can be made qualitatively using the four-category BI-RADS classification:

1. Entirely fat
2. Scattered fibroglandular densities
3. Heterogeneously dense
4. Extremely dense (7) (Fig. 11-16)

Approximately 80% of women will have scattered or heterogeneously dense breasts. Only 10% will have extremely dense or fatty breasts (40). This subjective density classification scheme was developed to address the issue of mammographic sensitivity rather than the estimation of risk. More quantitative measurements can be made with computer software programs. Thresholds between the white and nonwhite tissue are not absolute and will influence reproducibility and accuracy. While these classifications have merit, there is variability among readers (41). Although breast density is correlated with risk, changes in breast density may or may not be associated with changing risk. Breast density has not been shown to be a causative factor for breast cancer. Several states have now passed legislation regulating breast density reporting to patients and recommendations for supplemental screening with ultrasound or MR for women with dense breasts. The impact of these laws is unknown, although no randomized control trial exists for supplemental screening of women with dense breasts.

FACTORS AFFECTING MAMMOGRAPHIC SENSITIVITY

The ability of mammography to detect cancer varies greatly among patients. Factors affecting sensitivity and specificity include breast density, age, hormone replacement therapy, biologic subtypes of cancer, and breast thickness.

Breast Density

Breast cancer attenuates x-rays and appears as a white density. A white density against a black (fatty) background is easy to detect (high signal-to-noise ratio). A white density cancer against a white background of fibroglandular tissue is difficult and, in many situations, impossible to detect. The normal dense tissue camouflages the cancer. Extensive breast density has been associated with higher frequency of false-negative mammograms. Whether these

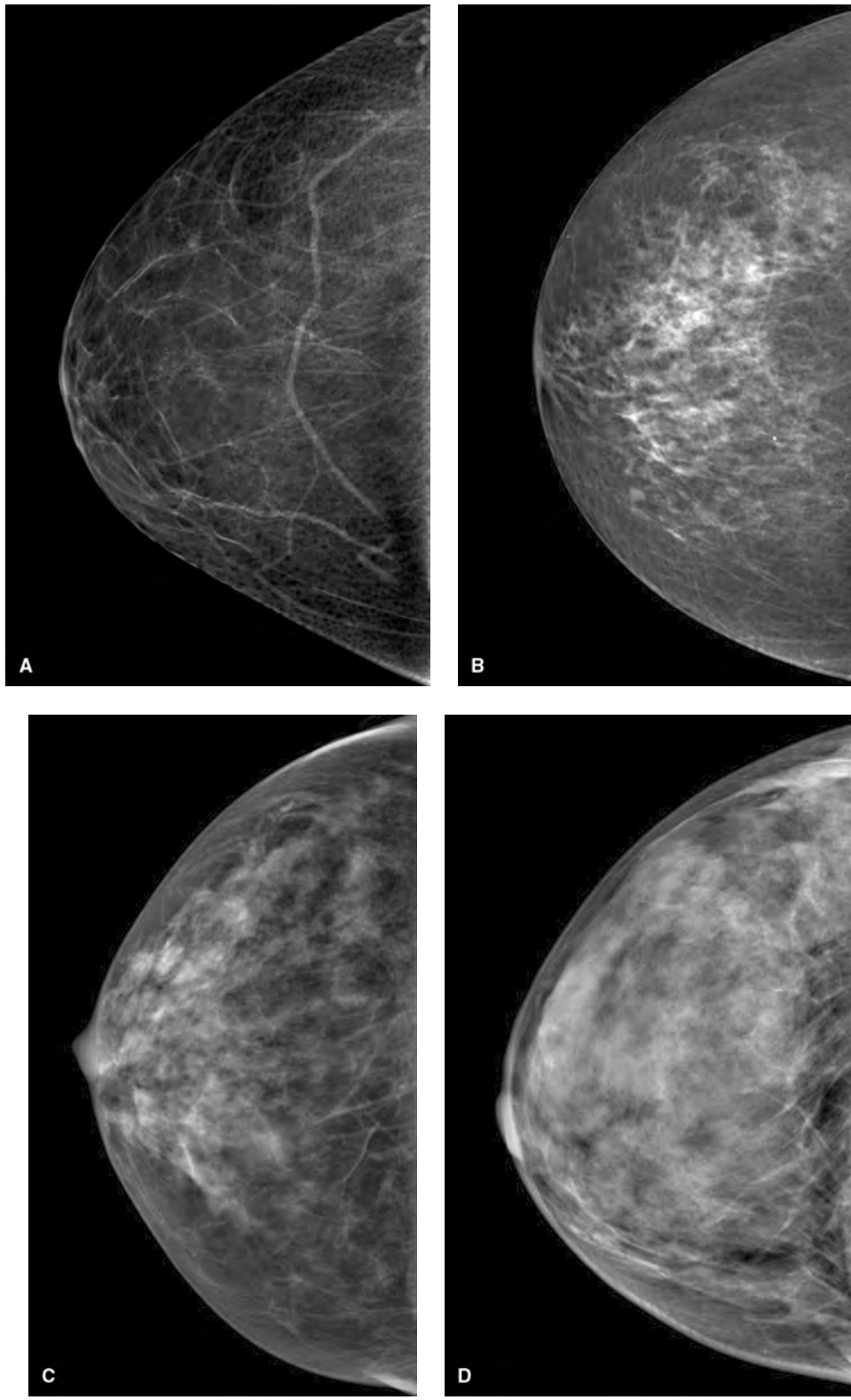

FIGURE 11-16 Spectrum of breast density showing **(A)** fatty; (**B)** scattered fibroglandular; **(C)** heterogeneously dense; and (**D)** extremely dense.

differences relate entirely to imaging by the masking of cancers by dense tissue or to more aggressive tumor biology occurring in women with dense breasts is unknown. The relative insensitivity of mammography in women with dense breasts is a significant limitation of the technique. Alternative methods of imaging these individuals with ultrasound, MRI, tomosynthesis, and digital mammography are ongoing investigations.

Age

Breast density generally declines slowly with age without abrupt change at menopause. Variations exist to defy this trend and postmenopausal hormone replacement therapy can reverse this trend so that age alone rarely is a useful factor in assessing mammographic density. Benign processes that mimic cancers such as fibrocystic changes are less common in older women. For these reasons the accuracy of mammography is highest in that age group compared to younger women (14).

Hormone Therapy

Hormone therapy is associated with increases in breast density in some women, especially those products containing estrogen and progestin. This may mask cancers and limit detection of developing asymmetries. Some drugs such as tamoxifen used for chemosuppression have been associated with a decrease in breast density. Theoretically, this should allow easier detection of malignancy.

Biologic Subtypes

Invasive lobular cancer (ILC) is difficult to detect by mammography prior to clinical presentation. The infiltrative pattern of ILC often does not produce a recognizable mass by mammography when small. Additionally, only 5% of ILC is associated with microcalcifications. Invasive lobular cancer is detected at a larger size than invasive ductal carcinoma and represents a disproportionate number of false-negative mammograms. Invasive mucinous or medullary cancers and some anaplastic cancers may appear as a circumscribed mass mimicking benign conditions such as cysts or fibroadenomas and can produce mischaracterization. Detection is not affected. Sonographic evaluation demonstrates solid masses and biopsy establishes the diagnosis. Triple-negative cancers are more often rounded masses with irregular borders and contain less calcification than other ductal cancers (42).

Patient Factors

Achieving optimal mammographic position requires full patient cooperation. Portions of the breast may not be imaged, especially areas adjacent to the chest wall which become a silent area for mammography. Mammographic image quality declines as breast thickness increases. The decline is due to loss of geometric sharpness, contrast, and increased motion. Breast thickness generally increases with body mass index. Breast implants, especially those placed anterior to the pectoral muscle, may limit mammographic sensitivity even when implant displaced views are performed. The implant absorbs x-rays which precludes mammographic display of portions of the breast.

SUMMARY

High-quality mammography has dramatically changed the evaluation of women for breast cancer in the last 25 years. Age-appropriate routine screening mammography is recommended. Diagnostic breast imaging of symptomatic individuals can assist characterization of palpable findings. However, clinically suspicious abnormalities should be surgically evaluated even when breast imaging examinations are normal.

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CHAPTER 12

Imaging Analysis: Ultrasonography

Emily L. Sedgwick

CHAPTER CONTENTS

The use of breast ultrasound for the characterization of breast masses was described as early as 1966 in a Russian journal (1). For many years, the primary indication for sonography was to assess if a breast mass was cystic or solid; however, technological advancements in the resolution and speed of breast ultrasound, in addition to its comparatively low cost, have made breast ultrasound a valuable tool in the evaluation of several breast conditions.

TECHNICAL CONSIDERATIONS

The utility of breast ultrasound depends upon two key factors: equipment and who is performing the ultrasound. Breast ultrasound should be performed with a high-frequency linear transducer, 10 MHz or higher. At a minimum, gray-scale ultrasound (also known as "B mode") is performed, and Doppler ultrasound (either color or Power Doppler) should be used to interrogate for vascularity associated with any lesion. In an effort to better characterize a lesion, such as differentiating a simple from a complicated cyst, harmonic imaging is used. Harmonic imaging takes advantage of the different ultrasound frequencies created by different tissues to create an image (2). Compound imaging is helpful to reduce image graininess and to produce better characterization of a lesion's margins. Compound imaging constructs an image by combining ultrasound waves from different angles (2).

Elastography is another ultrasound tool to help to characterize a lesion. Elastography is the measurement of mass stiffness. In general, a benign mass is stiffer than the adjacent normal breast tissue, and a malignant mass is stiffer than a benign mass. A variety of elastography methods have been proposed. A simple demonstration of elastography is merely applying gentle pressure to the lesion and watching it change in shape or asking the patient to hum during the examination to assess its effect on ultrasound sound waves as they move through the lesion (also known as fremitus). Recently, technological advances have been developed in an effort to standardize elastography performance and interpretation. Formal elastography is not commonly used in most clinical practices, but its use may become more frequent since the new edition of the American College of Radiology (ACR) ultrasound Breast Imaging Reporting and Data System (BI-RADS) is expected in 2014 and may address elastography in image analysis.

IMAGE DOCUMENTATION

The ACR recommends that at least two images be performed of a lesion to document its appearance in orthogonal planes (3). The ACR Practice Guidelines also recommend image labeling to include clock face position, transducer orientation, and distance from the nipple (3). Documenting the presence of any internal vascularity associated with the finding is also recommended.

The person who holds the ultrasound transducer is just as important as the technical parameters of ultrasound. The sonographer identifies a lesion and takes representative images. If the operator is inexperienced or inattentive, the opportunity for early detection and appropriate characterization is lost. In many practices, the primary operator is a technologist who may or may not have advanced training in breast imaging; however, it is recommended that the responsible physician checks the relevant ultrasound findings at the time of ultrasound performance or actually performs the ultrasound (3). Few studies have assessed the accuracy of the different operators; however, interobserver variation exists, especially for lesions smaller than 5 mm (4).

TABLE 12-1

Typical Ultrasound Features of Common Breast Masses

Suspected Diagnosis Based on US features	*Shape*	*Orientation to skin*	*Internal Echotexture*	*Margin*	*Vascularity*	*Posterior acoustic features*
Simple cyst	Oval/Round	Variable	Anechoic	Circumscribed	None	Enhancement
Complicated cyst	Oval/Round	Variable	Hypoechoic (mobile debris)	Circumscribed	None	Variable
Fibroadenoma	Oval	Parallel	Hypoechoic	Circumscribed	Variable	Variable
Lactating adenoma	Oval	Parallel	Hypoechoic	Circumscribed	Variable	Variable
Galactocele	Oval/Round	Variable	Mixed	Circumscribed	None	Variable
Lymph Node	Oval/Round	Variable	Hypoechoic	Circumscribed	Present	Variable
Phyllodes	Oval	Parallel	Hypoechoic	Circumscribed	Present	Variable
Abscess	Round/Irregular	Anti-parallel	Mixed	Noncircumscribed	Present	Variable
Fat Necrosis	Irregular	Anti-parallel	Mixed	Noncircumscribed	Variable	Variable
Invasive Ductal Carcinoma	Irregular	Anti-parallel	Hypoechoic	Noncircumscribed	Present	Shadowing
Invasive Lobular Carcinoma	Irregular	Anti-parallel	Hypoechoic	Noncircumscribed	Present	Shadowing

INTERPRETATION (SEE TABLE 12-1)

Once a lesion has been identified and imaged, the radiologist uses the BI-RADS lexicon to characterize the lesion and form a final impression to guide management. The first edition of the ultrasound BI-RADS lexicon was released by the American College of Radiology in 2003. It was modeled after the mammography lexicon mandated by the Mammography Quality and Standards Act of 1992. The lexicon is organized into major categories: mass, calcifications, special cases, vascularity, and final assessment (5).

The first, and most common, category in the lexicon is "mass." Once a finding has been confirmed in orthogonal planes, it is further characterized by the descriptors of shape, orientation, margin, lesion boundary, echo pattern, posterior acoustic features, and surrounding tissue. Shape is further subdivided into oval, round, or irregular. Each of these has its own positive predictive value (PPV) for malignancy: oval (16%), round (100%), and irregular (62%) (6).

Mass orientation relative to the skin is the second descriptor. A mass that is parallel to the skin is more likely to be benign. A mass with an antiparallel orientation to the skin (common described as "taller than wide") has a PPV for malignancy of 69% (6).

As with mammography and breast MRI, the margin of a mass is most strongly predictive of malignancy. The margin can be described as circumscribed or noncircumscribed. Noncircumscribed margin descriptors include indistinct, angular, microlobulated, and spiculated. Of the four noncircumscribed descriptors, a spiculated margin has the highest PPV for malignancy (PPV = 86%) (6).

The last three descriptors are lesion boundary, internal echogenicity, and posterior acoustic features. These descriptors are important but are not the major criteria in the characterization of a mass found by ultrasound. Occasionally, there may be an echogenic border at the mass lesion boundary; this has been associated with malignancy (7). The internal echogenicity of the mass may be isoechoic, hypoechoic, or hyperechoic relative to the patient's fat. Although other patterns have been reported, the internal echogenicity of cancers is most commonly hypoechoic (6). The final mass descriptor relates to the posterior acoustic features of a mass. Increased through transmission is a fundamental feature of a benign simple cyst; however, the classically described posterior acoustic shadowing has been shown to be a weak predictor for malignancy (6).

The BI-RADS final assessment categories are intended to guide management. If a finding is judged to be BI-RADS 1 (negative) or BI-RADS 2 (benign), routine follow-up is recommended. If a finding is probably benign (BI-RADS 3), short-term follow-up is recommended in 6 months, because the incidence of malignancy in this population is 2% or less (5). If a finding is suspicious for malignancy, the finding is assessed as a BI-RADS 4, where the expected incidence of malignancy is 3% to 94% (5). Subcategories of BI-RADS 4 have been created to stratify malignancy risk; however, more study is needed to further define the subcategories. BI-RADS 5 is used when findings are highly suspicious for malignancy. If the needle-guided biopsy is benign, surgical excision is usually recommended to ensure that malignancy was not missed, because the incidence of malignancy in this group is 95% or greater (5).

CLINICAL INDICATIONS (SEE TABLE 12-2)

Lump in Pregnant or Lactating Woman

The prevalence of breast cancer in this population is relatively low: breast cancer occurs in 1 out of 3,000 pregnancies (8). Although the amount of ionizing radiation from mammography is small, sonography is the first line in the evaluation of breast problems for pregnant women. Common findings in pregnant and lactating women include benign breast tissue (such as axillary breast tissue), simple cysts, fibroadenomas, lactating adenomas, and galactoceles. If the sonographic findings are suspicious for malignancy, a mammogram could be performed after the ultrasound to assess for associated mammographic findings that may support the suspicion for malignancy or help to define the extent of disease (e.g., calcifications associated with ductal carcinoma in situ). Ultrasound resolution is currently insufficient

TABLE 12-2

Assessment and Management Recommendations for Common Breast Masses Seen on Ultrasound

Suspected Diagnosis Based on US features	*BI-RADS Assessment*	*Management*
Lymph Node	2	Annual screening mammogram
Simple cyst	2	Annual screening mammogram
Complicated cyst	3	6-mo, then 12-mo ultrasound for 2 y
Abscess	3	US aspiration, clinical or ultrasound follow-up at 1–2 wk until resolved
Fibroadenoma (<3 cm)	3	6-mo, then 12-mo ultrasound for 2 y
Lactating adenoma	3	6-mo ultrasound
Galactocele	3	6-mo ultrasound
Fat Necrosis	3	6-mo mammogram and ultrasound
Phyllodes	4	Ultrasound guided biopsy
Invasive Ductal Carcinoma	4 or 5	Ultrasound guided biopsy
Invasive Lobular Carcinoma	4 or 5	Ultrasound guided biopsy

to reliably assess for breast calcifications due to ultrasound speckle artifact.

Lump in a Patient Younger than 30 Years of Age

The percentage of breast cancer diagnosed in women in their 20s is less than 1% (9). The vast majority of palpable breast complaints are due to normal breast tissue, simple cysts, or fibroadenomas—lesions that are well characterized by ultrasound alone. For this reason, the ACR and National Comprehensive Cancer Network (NCCN) Practice Guidelines recommend proceeding with a breast ultrasound before mammography in patients under 30 years of age (3,10). If the ultrasound finding is highly suspicious for malignancy, a mammogram can be performed to assess for other sites of disease and suspicious calcifications, as is done with pregnant women.

Recent media attention has created some discussion around the diagnosis of breast cancer in children and teens. The incidence of malignancy in this population is exceedingly low (<1% of all pediatric breast masses) and can be associated with other risk factors (e.g., TP53 genetic mutation) (11). For girls with a breast lump, sonography is the initial imaging modality of choice. Common findings include normal breast tissue, cysts, and fibroadenomas. Fibroadenomas are the most common solid mass in children (11). Large fibroadenomas (greater than 5 cm in any axis) are called giant juvenile fibroadenomas. These masses are usually removed because they are indistinguishable by imaging from phyllodes tumor (the most common breast primary malignancy in children) and because the size of the mass can affect normal breast development. Phyllodes tumors comprise approximately 1% of primary malignant masses in the pediatric population, but most malignant breast masses are due to metastases (11).

An important sonographic finding in the pediatric population is the breast bud. Imaging features of the normal breast bud (irregular shape, irregular margins, posterior acoustic shadowing) may tempt an inexperienced sonographer to recommend biopsy. Biopsy of the breast bud should be avoided, however, because the biopsy may affect breast development. The breast bud can be seen in either girls or boys complaining of a breast lump. Most boys have some breast bud development (gynecomastia) during puberty that resolves spontaneously over a 2-year period (11).

Lump in a Patient Older than 30 Years of Age

For patients older than 30 years of age with a lump, the ACR and NCCN Practice Guidelines recommend mammography prior to ultrasound based on expert opinion (3,10). There is, however, a paucity of data regarding the use of mammography and/or sonography in women aged 30 to 39 years. A recent publication by Lehman et al. found that the sensitivities of mammography and sonography in this age group were 60.6% and 95.7%, respectively (12). The negative predictive value of mammography and sonography were 99.2% and 99.9%, with mammography finding only one malignancy missed by sonography in 1,208 cases (12). They concluded that sonography should be performed before mammography in women aged 30 to 39 years (12).

For women older than 40 years of age, the incidence of breast malignancy increases, and mammography is the first step in imaging a palpable complaint. Mammography can provide important information that may obviate the ultrasound or improve the characterization of an ultrasound finding. For example, fat necrosis can be palpable and is characteristically benign by mammography but may appear malignant by sonography (Fig. 12-1). A second important reason is that it is not uncommon to find a contralateral malignancy when a patient comes in for a lump. If mammography and sonography are negative, the likelihood that the lump represents a cancer is less than 10% (13).

If the palpable abnormality is detected by the physician, it is helpful to show the patient the location of the lump so she may show the radiologist performing the ultrasound. If the ultrasound is to be performed on the same day or next day, it is recommended that the referring physician indicate the palpable area of concern on the patient's skin with a marker so the palpable area can be directly interrogated with ultrasound. It is not infrequent for an ultrasound technologist to image a nearby finding (e.g., a cyst) and assume it corresponds to the palpable complaint. For this reason, it is incumbent upon the radiologist to ensure that the palpable complaint is accurately assessed.

Mammographic Mass

One of the classic indications for a breast ultrasound is for characterization of a mammographic mass. Using the nipple as a landmark on two mammographic views, the radiologist can confidently localize a mass for characterization

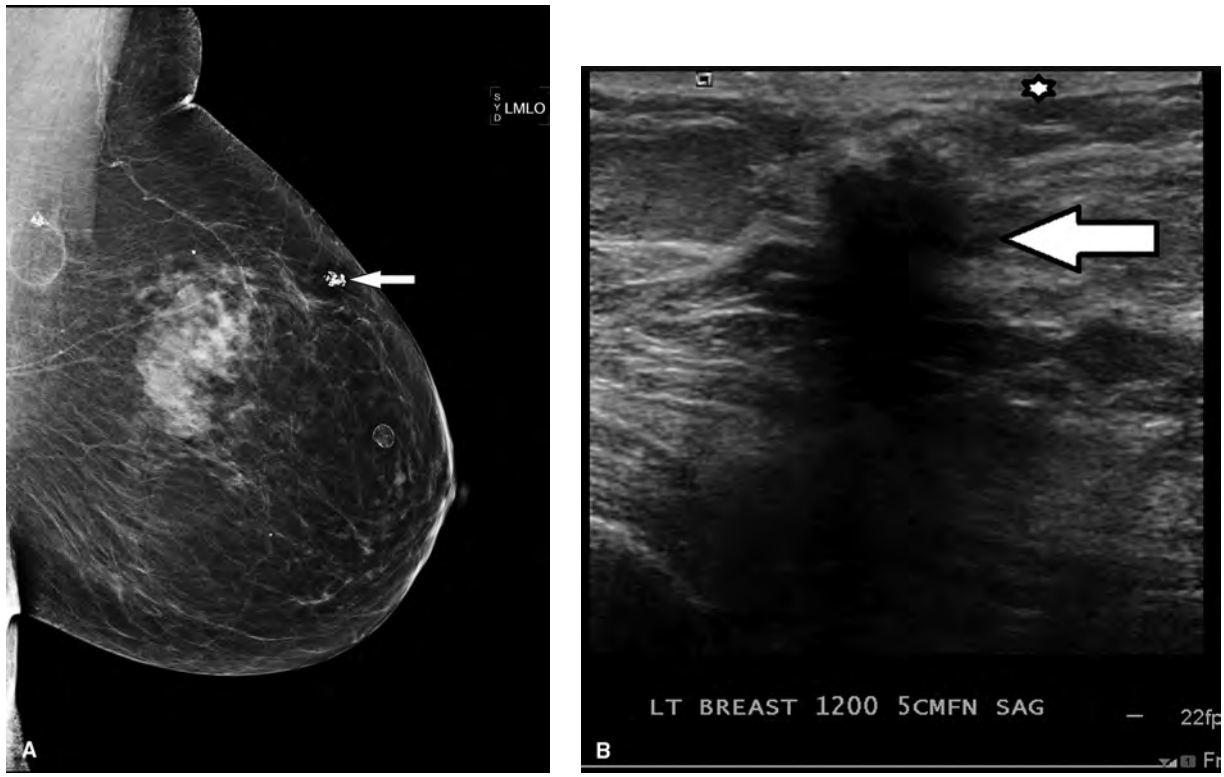

FIGURE 12-1 **(A)** Characteristic calcifications of fat necrosis on MLO mammogram (*arrow*). **(B)** Ultrasound image of corresponding fat necrosis (*arrow*). (Star indicates skin.).

by ultrasound. Once the mass is identified, the radiologist assesses its shape, orientation, internal characteristics (including vascularity), and margin. Commonly encountered masses include simple cysts, complicated cysts, fibroadenomas, lymph nodes, and cancers. A simple cyst is round or oval in shape, usually with parallel orientation, imperceptible wall, increased through transmission, and no internal vascularity (Fig. 12- 2). A complicated cyst is round or oval in shape, usually with parallel orientation, thin wall, and no internal vascularity. Its posterior acoustic features are variable. It has internal echoes, which differentiate it from a simple cyst (Fig. 12-3). A fibroadenoma is oval in shape, with parallel orientation, variable posterior features, and a circumscribed margin with fewer than four gentle lobulations. It may or may not have internal vascularity (Fig. 12-4). It can

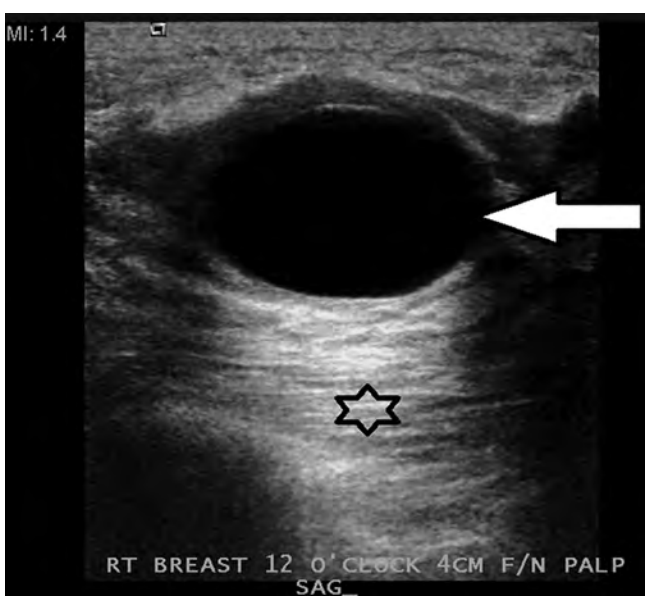

FIGURE 12-2 Simple cyst. Note increased through transmission (*star*). Note imperceptible wall (*arrow*).

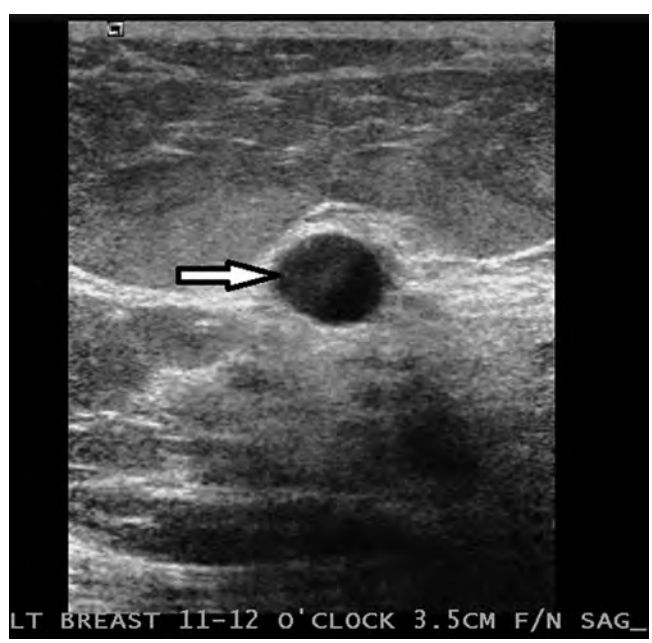

FIGURE 12-3 Complicated cyst. Note internal echoes (*arrow*).

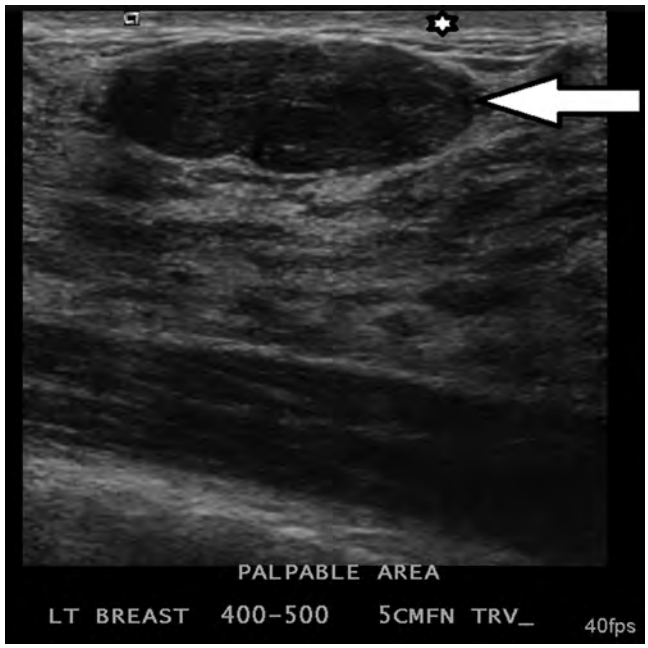

FIGURE 12-4 Fibroadenoma. Note circumscribed margin (*arrow*). It is parallel to skin surface (*star*).

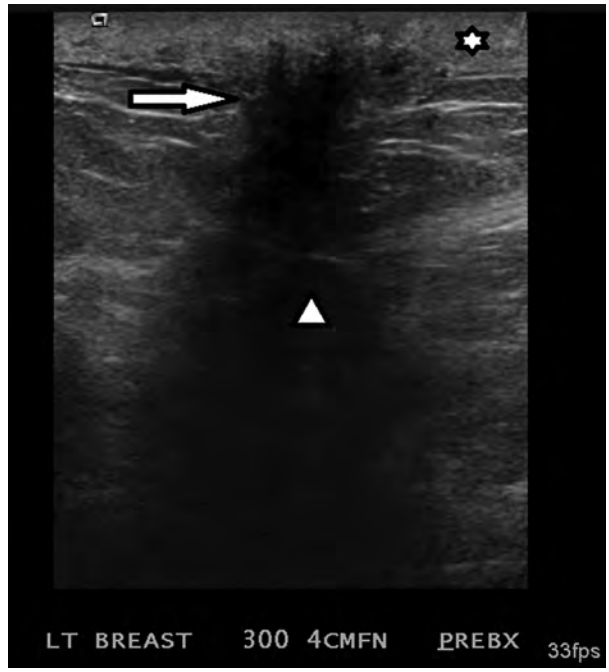

FIGURE 12-5 Invasive ductal carcinoma. Note irregular shape, angulated margin (*arrow*), posterior acoustic shadowing (*triangle*), and anti-parallel orientation to skin surface (*star*).

sometimes be difficult to differentiate a complicated cyst from a fibroadenoma. Since the likelihood for malignancy in both is similarly low, it is reasonable that management for both is the same—6-month follow-up ultrasound (14,15). A lymph node is round or oval in shape, with parallel orientation, echogenic hilum, circumscribed margin; a blood vessel can be seen entering the hilum.

Cancers typically are irregular in shape, with anti-parallel orientation, heterogeneous internal echotexture and vascularity, and a spiculated margin (Fig. 12-5). Although the clinical suspicion for malignancy is high based upon the mammographic features, an ultrasound is recommended for several reasons. First, if there is a sonographic correlate, sonography is better able to identify the area of invasive cancer (16). If a patient has a needle biopsy demonstrating invasive cancer, she will undergo fewer surgical procedures (17). Finally, ultrasound guided biopsy is less expensive and more comfortable for the patient than stereotactic core needle biopsy or wire localization for surgical excision (18).

Cancers may not have all of the classic features as described above. Since approximately 90% of all breast cancers are invasive ductal cancer (IDC), a cancer lacking the typical features is still likely to be an IDC. Lobular cancer may be difficult to perceive on mammography; however, it may be well seen with sonography (Fig. 12-6). Other histologies can have atypical sonographic features but should still be suspicious for cancer because they do not satisfy all of the criteria for benignity. For example, mucinous cancers are round or oval in shape, with lobulated margins; they may have posterior acoustic enhancement (19). Upon close inspection, the margin has multiple lobulations, and the internal architecture is heterogeneous. The latter findings should lead to biopsy (Fig. 12-7).

Suspicious Mammographic Findings without Mammographic Mass

Findings such as pleomorphic calcifications or architectural distortion have a high positive predictive value for malignancy but may have no associated mammographic mass (Fig. 12-8). Ultrasound can be helpful to assess for the presence of an associated mass that may represent an area of invasive cancer and aid in biopsy planning. Finding a sonographic correlate can be especially helpful in the setting of dense tissue on mammography.

Complementary Modality to Breast MRI

In addition to mammography, sonography can be a useful complementary tool to breast MRI. Occasionally, targeted sonography may be beneficial for further characterization of a MRI finding: specifically, an intramammary lymph node. Small enhancing lymph nodes can have suspicious enhancement, and the characteristic fatty hilum may not be resolved on MR imaging. Targeted sonography can often elucidate the characteristic fatty hilum, obviating biopsy.

Sonography can also be helpful if there is a suspicious enhancing mass on MRI for which a biopsy has been recommended. MRI guided breast biopsy has a high cost and relatively low accessibility; consequently, targeted sonography is usually recommended to assess for a sonographic correlate to the MRI finding. LaTrenta et al. found that 43% of lesions with a sonographic correlate were cancer, and 14% of lesions without a sonographic correlate were cancer (20). MRI guided biopsy is therefore recommended if no sonographic correlate is found. If there is a question about whether a sonographic finding correlates to the MRI target, ultrasound guided biopsy with marker placement with an abbreviated follow-up MRI has been reported (21).

Breast Pain

Breast cancer is usually painless (22). Breast pain, however, is one of the most common complaints in the breast imaging department. There is not usually an easily identified anatomic source for the pain unless it is related to fibrocystic changes or infection (abscess). If there is focal pain, an ultrasound can be performed. The sonographic appearance

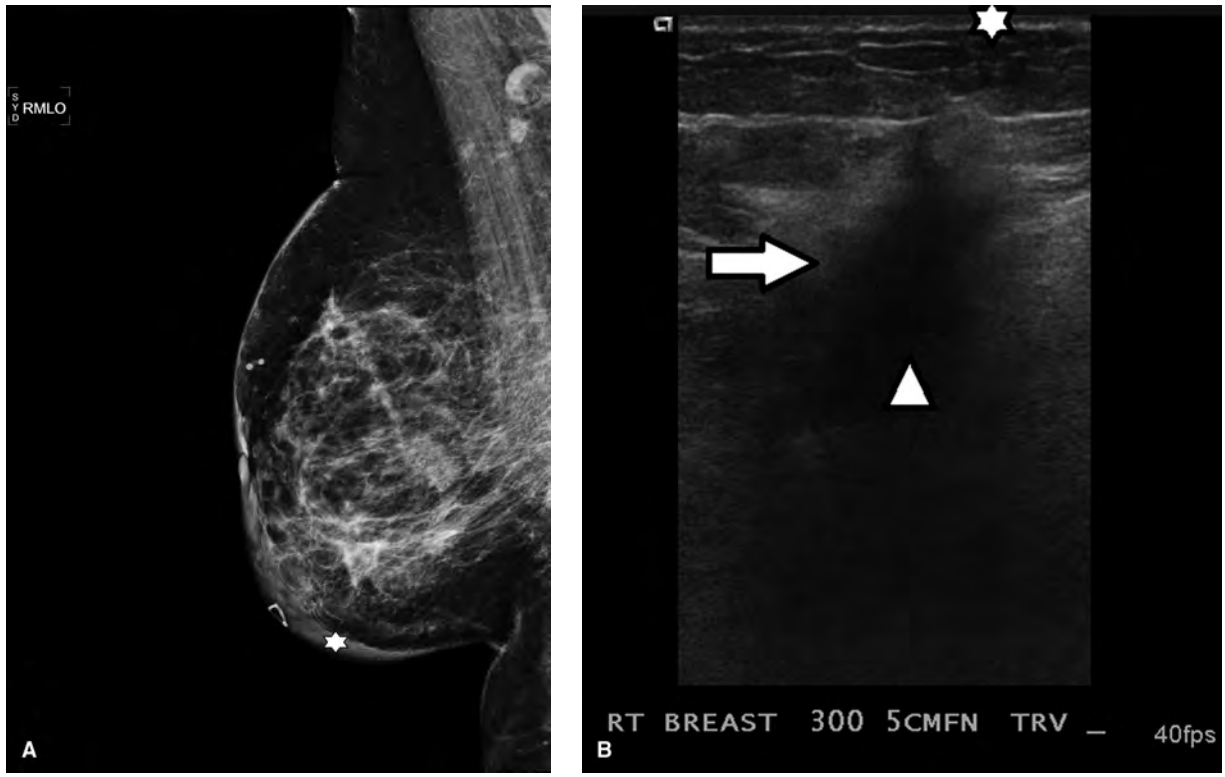

FIGURE 12-6 **(A)** Invasive lobular carcinoma mammogram. No discrete mass is seen. Note skin thickening (*star*). **(B)** Invasive lobular ultrasound. Note irregular shape (*arrow*), posterior acoustic shadowing (*triangle*), and anti-parallel orientation to skin surface (*star*).

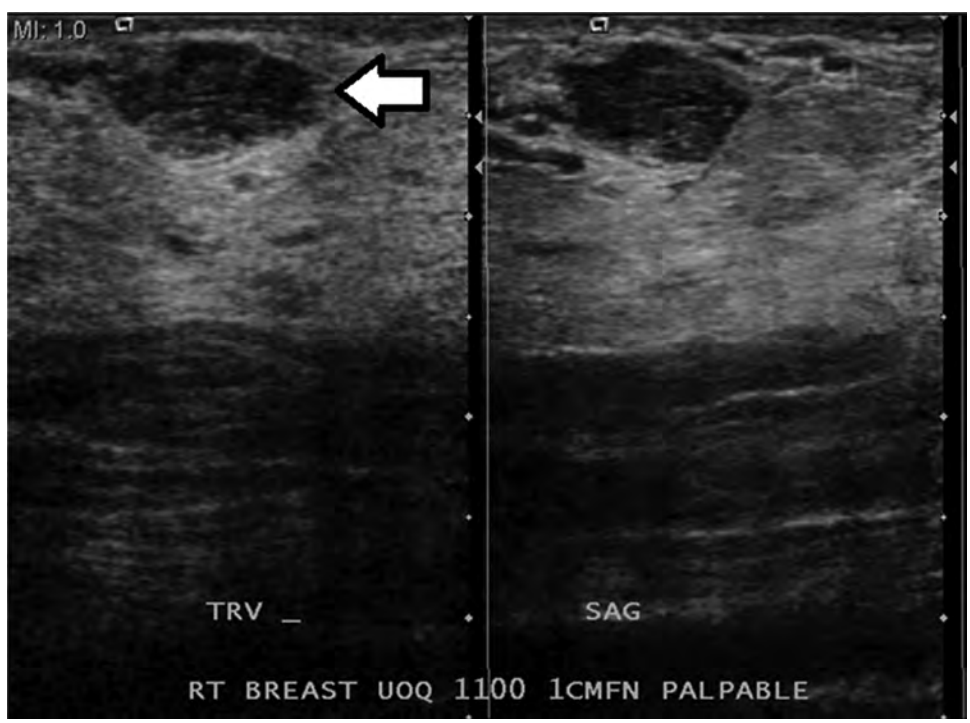

FIGURE 12-7 Mucinous carcinoma. Note the multi-lobulated margin (*arrow*) and heterogeneous internal echotexture, which should prompt a biopsy.

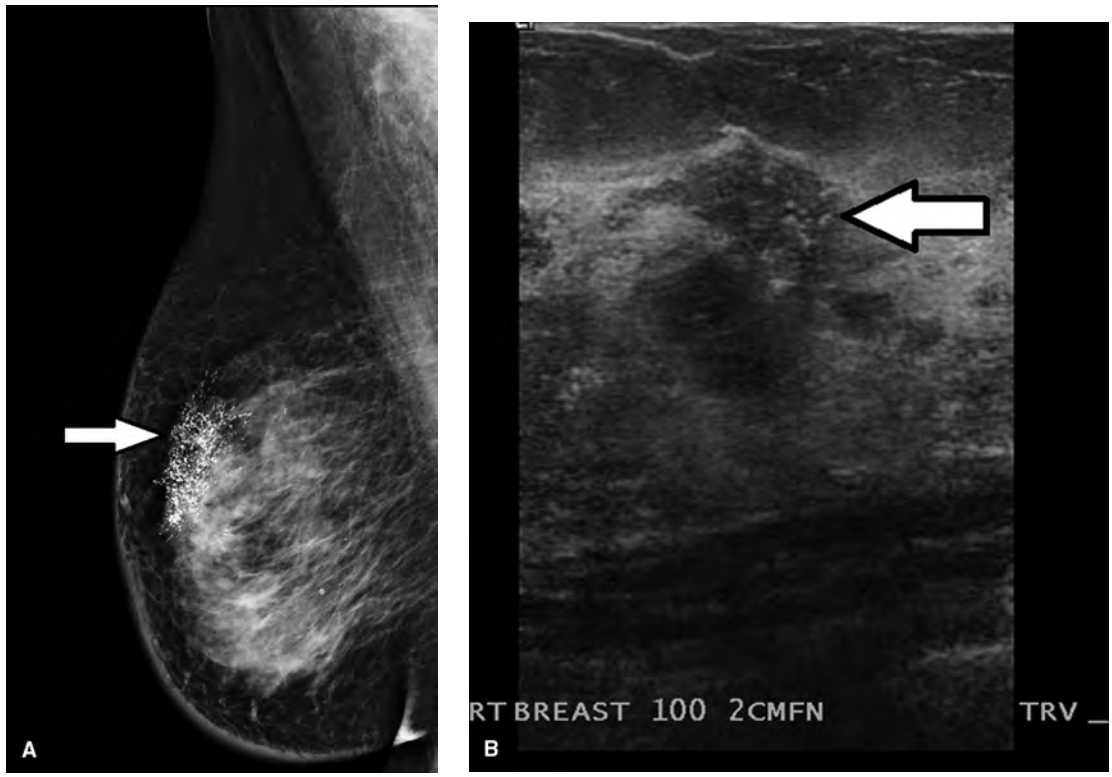

FIGURE 12-8 **(A)** Pleomorphic calcifications on mammography in upper inner right breast without associated mammographic mass (*arrow*). **(B)** Irregular corresponding mass on sonography. Note calcifications (*arrow*).

of fibrocystic changes includes dense tissue and small cysts, often in the upper outer quadrant of the breast. If fibrocystic changes are found, patient reassurance usually resolves the patient complaint. If the patient demonstrates signs or symptoms of infection (e.g., skin redness, painful lump, or fever), she may have an abscess or infected cyst. An abscess is round or irregular in shape with indistinct margins and increased vascularity (Fig. 12-9). Aspiration can be both diagnostic and therapeutic if all or most of the fluid can be withdrawn (23). Aspiration of frank pus prompts immediate treatment with antibiotics. Although the infection is likely due to skin flora, a culture may be helpful in case the patient does not respond appropriately to antibiotic therapy (23).

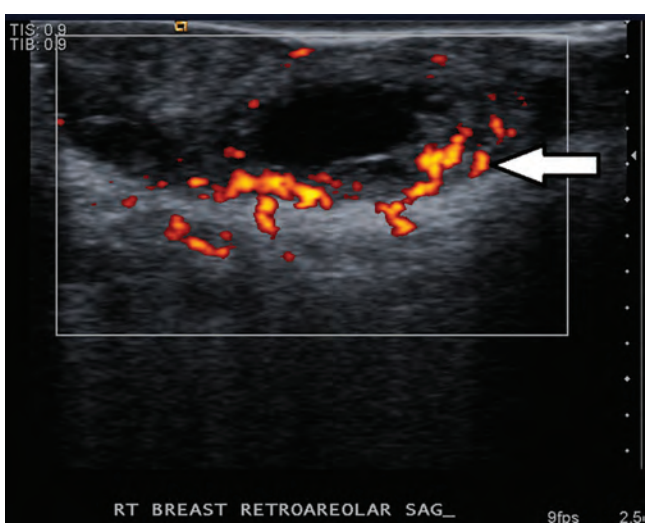

FIGURE 12-9 Abscess. Note thickened vascular rim (*arrow*).

Nipple Discharge

Nipple discharge is a frequent complaint in the breast imaging department. Nonspontaneous bilateral nipple discharge is of no concern unless it is milky. (Milky discharge may indicate a prolactinoma.) Spontaneous clear or bloody discharge from a single duct may cause clinical concern. Ultrasound has been used in conjunction with mammography to assess for an intraductal mass that may be the cause of discharge from a single duct, such as a papilloma. Ultrasound can also be helpful immediately following a galactogram to assess for an intraductal mass. The patient is transferred to the ultrasound suite with the galactogram cannula in place, so the offending duct can be persistently filled with contrast that may outline the intraductal mass. If the mass can be identified with ultrasound, it can then be biopsied using ultrasound guidance, thereby avoiding blind surgical excision.

Implant Rupture

Saline implant rupture is clinically evident. Silicone implant rupture can be identified by sonography. The "stepladder sign" is where the native wall of the implant can be seen floating in the silicone, which has been confined by the implant capsule (Fig. 12-10A). A stepladder sign is analogous to the "linguini sign," demonstrating intracapsular rupture on breast MRI (Fig. 12-10B). Extracapsular rupture, where silicone is seen outside the confines of the implant capsule, is described as an echogenic mass with echogenic shadowing, known as a "snowstorm" appearance in either the breast tissue or in axillary lymph nodes (Fig. 12-11).

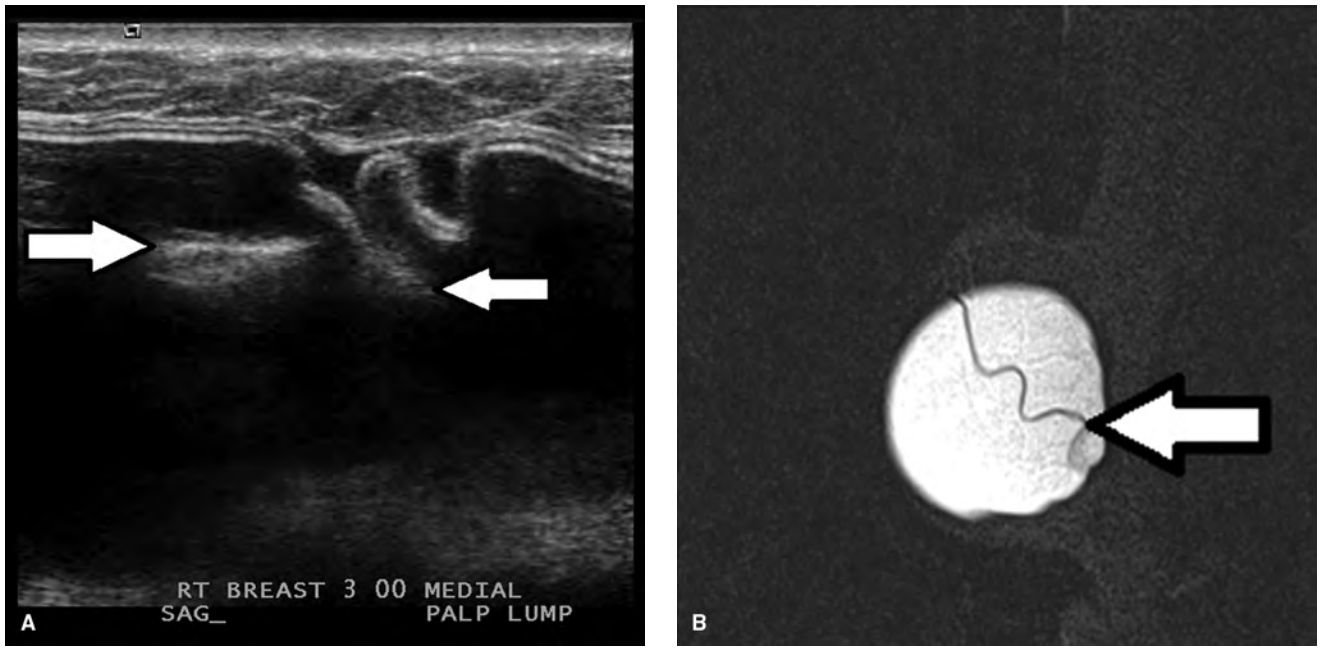

FIGURE 12-10 **(A)** "Stepladder sign" of intracapsular silicone implant rupture (*arrows*). **(B)** Corresponding "linguini sign" seen on breast MRI (*arrow*).

Occasionally, a patient with saline breast implants may complain of a lump that is related to the port. Careful sonography over the area of palpable concern confirms the presence of the valve, and the patient can return to screening mammography (Fig. 12-12).

Extent of Disease

Ultrasound can be useful to define the extent of disease when a patient has a suspected or known breast cancer. Identifying multicentric disease, skin involvement, or adenopathy can help with surgical management and staging. Many practices perform targeted sonography; however, the ultrasound can be expanded to the entire breast and axilla if a suspicious mass is found. Although breast MRI is better than sonography at assessing the extent of disease, MRI is not always paid for by insurance and access to MRI may be limited.

Most of the lymphatic drainage of the breast is to the axilla. Evaluation of the axilla at the time a suspicious breast mass is found is helpful to assess for the presence of locally advanced disease (19). Recently, ultrasound-guided fine needle aspiration (FNA) or core needle biopsy has become more commonly used to stage the axilla. With the recent release of the American College of Surgeons Oncology Group (ACOSOG) Z-0011 trial, the utility of sampling a suspicious axillary lymph node before breast conservation surgery has come into question in patients with early stage breast cancer. The ACOSOG Z-0011 trial found similar local or regional recurrence for patients with one or two positive lymph nodes who had only sentinel lymph node biopsy versus patients who had full axillary dissection (24). Lymph node involvement continues to be an important prognostic

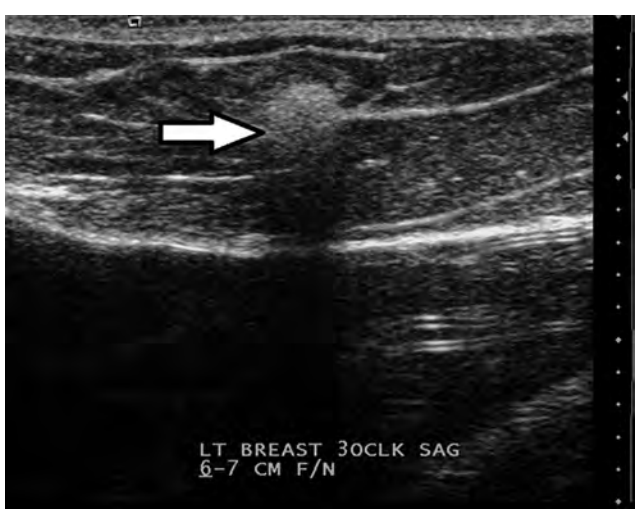

FIGURE 12-11 "Snowstorm" appearance of extraluminal silicone (*arrow*).

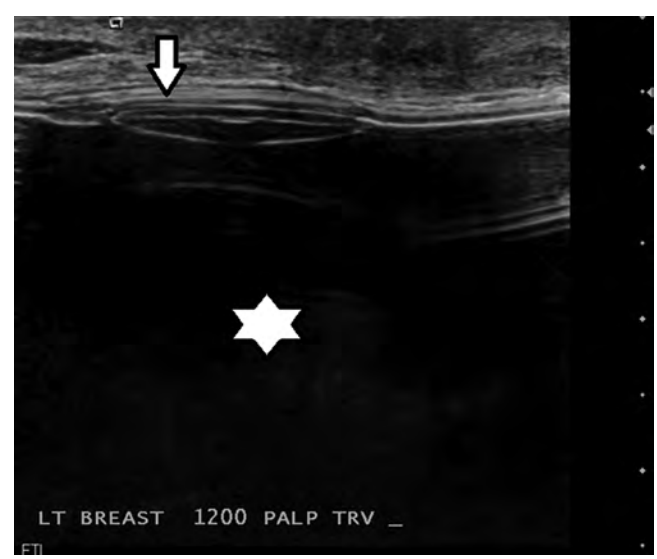

FIGURE 12-12 Saline implant valve presenting as palpable complaint (*arrow*). Intact saline implant (*star*).

indicator. The knowledge of axillary lymph node involvement prior to surgery, however, may no longer be necessary since a sentinel lymph node biopsy will be performed at the time of breast conservation surgery.

A few facilities evaluate the supra- and infraclavicular lymph node basins at the time of discovery of a suspicious breast mass (25). Newman et al. found that 29% of 142 patients had suspicious-appearing (but not biopsy-proven) infraclavicular lymph nodes that correlated with lower disease-free and overall survival. They concluded that suspicious infra- or supraclavicular lymph nodes were a useful adverse prognostic factor and advocated routine sonography of these nodal basins in patients with locally advanced breast cancer. Others have advocated evaluation and, if possible, fine needle aspiration of internal mammary lymph nodes, arguing that known internal mammary lymph node involvement would change radiation therapy (26). However, evaluation of nodal basins other than the axilla to define the extent of disease is not a common practice. The reasons for this may be multifactorial: the low likelihood of involved lymph nodes, inexperienced sonographers, uncertain clinical management significance, and lack of reliable cytology for fine needle aspiration of suspicious lymph nodes.

Follow-up of Prior Ultrasound Findings

An increasingly common use of breast ultrasound is in the management of fibroadenomas, one of the most common benign solid masses in women. First published by Stavros et al. in 1995, an oval mass with parallel orientation, circumscribed margin, and fewer than four gentle lobulations may be reliably followed by ultrasound, because the sensitivity for malignancy was 98.4% (27). It was reported that 1.6% of malignant masses were misclassified as benign (27). Harvey et al. demonstrated that palpable lesions that satisfy the above criteria can also be followed with ultrasound, similar to those patients with nonpalpable probable fibroadenomas (14). Since these studies showed a <2% malignancy rate (but not 0%), these authors recommended imaging follow-up. Based on these studies, many radiologists recommend follow-up ultrasounds (at 6 months and 12 months) for 2 years, in line with BI-RADS 3 mammography recommendations developed by Sickles (28). Meticulous attention to technique and management based upon the most suspicious imaging characteristic is fundamental to replicate those results. Although conservative imaging follow-up is not yet the standard of care, this management recommendation is gaining greater traction.

Assessment of Response to Neoadjuvant Chemotherapy

The correlation of the size of an ultrasound mass with the pathology specimen is best for masses 2 cm or smaller (29). The agreement of ultrasound with the pathology specimen falls after neoadjuvant therapy. Ultrasound is still better than clinical exam and mammography with a 35% agreement (30). The agreement of clinical exam and mammography following neoadjuvant chemotherapy are 19% and 26%, respectively (30). Ultrasound is inexpensive, reliable, and contains no ionizing radiation. Although MRI has demonstrated its superiority in assessment of neoadjuvant treatment response with a pathology agreement of 71%, its cost and inaccessibility precludes its widespread use (30).

Ultrasound as a Screening Tool

Screening ultrasound will be addressed in the chapter about screening.

SUMMARY

Breast ultrasound is an important tool in evaluation of breast complaints due to its lack of ionizing radiation and low cost. Its indications include evaluation of clinical complaints (e.g., lump, pain, nipple discharge), further characterization of mammographic and MRI findings, determining extent of disease, and as a guide for breast biopsies. Breast ultrasound is most effective when performed by an experienced operator and used in conjunction with mammography. Further refinements in ultrasound resolution and techniques (e.g., elastography) may expand its utility in the future.

MANAGEMENT SUMMARY

- Ultrasound is often indicated for characterization of a mammographic or palpable finding. For example, ultrasound can further characterize a mammographic mass as a benign cyst or a solid mass.
- Ultrasound is important for biopsy planning. It can identify the invasive component of the cancer.
- Ultrasound guided biopsy can minimize patient expense and discomfort.
- Ultrasound is the first imaging modality for a pregnant woman or a woman less than 30 years of age.

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CHAPTER 13

Imaging Analysis: Magnetic Resonance Imaging

Susan P. Weinstein and Susan Orel Roth

CHAPTER CONTENTS

Major advances have been made in the field of MR imaging of the breast since the first report of the use of gadolinium in 1989 to detect breast cancer (1). Technology has kept pace resulting in faster scanning times with greater spatial resolution. The use of gadolinium remains the cornerstone of cancer detection in breast MRI. The formation of neovascularity by malignant lesions results in more rapid uptake and washout of contrast than the surrounding parenchyma. Unlike mammography, which evaluates lesions based on morphology alone, MRI evaluates lesions using both morphologic as well as functional kinetic information with the sensitivity of MRI for invasive breast cancer approaching 100%. Similar to mammography, uniformity in image quality is being promulgated by the American College of Radiology (ACR). Technical requirements for optimal breast imaging including the requirement for a breast MRI biopsy system are now being defined as part of a ACR breast MRI accreditation program. Also, similar to mammography, the ACR BI-RADS (Breast Imaging Reporting and Data System) lexicon for breast MRI has brought uniformity to the interpretation and reporting of breast MRI examinations. With advances in imaging technique, interpretation guidelines, and increasing availability of MRI breast biopsy systems, MR imaging of the breast is now an integral component of breast imaging in clinical practice in both the diagnostic and the screening settings. The clinical indications for MR imaging of the breast have evolved over time, and although controversy exists, MR imaging is currently performed in the clinical settings of high-risk breast cancer screening, response to neoadjuvant chemotherapy, evaluation of equivocal mammographic findings, clinically concerning nipple discharge, and recently diagnosed breast cancer for staging of the ipsilateral breast and screening of the contralateral breast. The roles of breast MRI will continue to evolve as more data become available.

TECHNICAL CONSIDERATIONS

In contrast to mammography, where the techniques for optimal imaging have been well defined for years under the regulation of the Mammography Quality Standards Act (MQSA), overseen by the Food and Drug Administration (FDA) (2), the image quality of breast MRI studies has varied widely until recently. There are many variables that can affect image quality. In an effort to bring uniformity to the quality of breast MRI studies in the United States, the American College of Radiology currently runs a Breast MRI Accreditation program providing guidelines for quality assurance and control, equipment and image quality, as well as staff and radiologist qualifications (3). Initially, this accreditation program was voluntary. Starting in 2012, the MRI accreditation program became mandatory for non-hospital-based imaging centers receiving Medicare reimbursement. This hopefully will bring greater uniformity to breast MRI quality.

MRI Field Strength

Breast MRI studies should be performed on 1.5T magnets or higher. The high field strength allows for rapid acquisition with high-resolution imaging. There is a linear relationship between magnetic field strength and signal-to-noise ratio (SNR). With greater field strength, the SNR is higher, and higher spatial resolution images can be obtained with shorter acquisition times. The high field strength also makes homogeneous fat suppression possible enabling detection of subtle enhancing lesions. Although 1.5T magnets remain the standard in breast MRI imaging, 3T magnets are commercially available. The higher field strength allows for higher SNR, with more rapid imaging speed and resolution. However, there is no definitive evidence that 3T magnets are superior to 1.5T for clinical breast imaging.

Dedicated Breast Coils

A dedicated breast surface coil must be used when performing breast MRI. Many different types of surface coils are commercially available. The coils contain depressions where the breasts lie during the examination. Within each depression, there are receiver coils that detect signal from the breast and transmit information to generate the images. Coils with greater number of receiver coils will have higher SNR. At the Hospital of the University of Pennsylvania, we utilize a bilateral breast multicoil. This type of coil allows for parallel imaging techniques, which can halve the image acquisition time through imaging both breasts simultaneously. The patient is examined in the prone position, which decreases the effects of respiration as well as reducing artifacts from respiration and cardiac motion. The breasts are gently compressed between two plates, which are placed along the medial and lateral sides of the breast. The compression further minimizes patient motion and reduces the number of sagittal slices required to image the breasts and, thereby, reducing imaging time. This configuration also ensures that all of the breast tissue is close to one of the elements of the array, resulting in enhanced SNR. The compression should be applied gently, as firm compression can delay contrast uptake.

Intravenous Contrast

The cornerstone of breast MRI is imaging following the intravenous injection of a paramagnetic contrast agent (gadolinium chelate). Gadolinium is a T1-shortening agent and was first used in breast MR imaging to detect cancer in 1989 (1). Following intravenous injection, accumulation of gadolinium in tissue reflects alterations in vascular density and/or vascular permeability. The neovascularity recruited by cancer cells results in rapid uptake of contrast followed by rapid washout of contrast, and this is the basic premise of MRI cancer detection. Breast cancers will enhance more rapidly and avidly than the normal surrounding tissues, hence the importance of rapid scanning times. The contrast is injected intravenously as a bolus at the dose of 0.1 mmol/kg, followed by a saline flush.

To minimize patient movement during the exam, the IV should be placed and connected prior to positioning the patient in the magnet. Images should be acquired 1 to 2 minutes after administration of contrast with sequential images acquired immediately after. To gather information about lesion kinetics, at least three postcontrast sequences should be acquired. The pre- and postcontrast images are often obtained with fat suppression to increase the conspicuity of the enhancing lesions.

In addition to dynamic gadolinium-enhanced sequences, T2-weighted images and nonfat saturated T1-weighted images should be obtained. Both of these sequences help characterize lesions that may enhance with gadolinium. The images may be acquired in the sagittal or the axial planes, based on preference. At our institution, the images are acquired in the sagittal plane. Subsequently, delayed postcontrast sequences are obtained to better visualize the lateral tissue and the axilla.

The current maximum recommended dose of gadolinium is 0.1 mmol/kg. It was felt for a long time that gadolinium was a very safe contrast agent with fewer contrast reactions than iodinated contrast agents. While gadolinium is still considered a safe intravenous contrast agent, in 2007 the FDA issued a warning regarding the use of gadolinium contrast agents in people with decreased glomerular filtration rate (GFR) due to reported cases of nephrogenic fibrosing sclerosis (NSF) (4). The association with decreased GFR, gadolinium, and NSF was first reported in 1997. Patients with impaired renal function are at increased risk for NSF, a condition that leads to fibrosis of the skin and internal organs (4). Although the condition is rare, to avoid this potential complication it is recommended that patients with GFR ≤30mL/min/1.73m2 not be administered gadolinium.

Fat Suppression

In contrast to mammography where lesion detectabilility is increased in a fatty background, on MRI an enhancing lesion maybe difficult to detect in a background of fat. Therefore, fat suppression will improve the conspicuity of small enhancing lesions. This can be accomplished with either active or passive fat suppression. We prefer using "active" fat suppression where the signal from fat is removed prior to the injection of intravenous contrast. There are a variety of available fat suppression techniques (5). Alternatively, passive fat suppression can be accomplishing with postprocessing image subtraction (subtracting the precontrast from the postcontrast image). This requires that there be no patient motion between the pre- and the postcontrast sequences. Both methods of fat suppression (chemical fat suppression and image postprocessing image subtraction) can be used together, and in our experience does aid in the detection of small enhancing lesions.

High Spatial and Temporal Resolution

Historically, investigators studying the differentiation of malignant from benign breast lesions were divided into two "camps," the first being the "high temporal resolution camp" where lesion characterization was based on contrast enhancement kinetics which required high temporal resolution, and the "high spatial resolution camp," where lesion morphology was critical and required high spatial resolution. Unfortunately, high temporal and high spatial resolution are competing strategies, and choosing one was at the sacrifice of the other. Sensitivity for the detection of small enhancing foci improves with increasing spatial resolution, but this requires longer imaging times. On the other hand, the high temporal resolution needed for dynamic contrast enhancement is obtained at the cost of a loss of spatial resolution, signal to noise, and/or volume of the breast imaged. For optimal spatial resolution, a pixel size of less than 1.0 mm in each in-plane direction is necessary with 3-mm or less slice thickness. For optimal temporal resolution, the first postcontrast images should be obtained in less than 2 minutes following contrast injection, with subsequent scans obtained over the following 5 to 7 minutes to evaluate the shape of the enhancement curve. Different methods may be utilized to optimize these two competing factors. One is using a higher field strength magnet. 3T magnets are available for commercial use. Theoretically, compared to 1.5T magnet, a 3T magnet should provide double the SNR and therefore allowing for faster image acquisition. However, there is no conclusive clinical evidence that 3T is superior to 1.5T in terms of diagnostic performance. Image acquisition time may also be reduced while preserving spatial resolution by using parallel imaging. Parallel imaging allows for simultaneous acquisition of spatial information from both coils, thus reducing the time to acquire the spatial information. Combination of imaging methods may be used as well. Parallel imaging techniques may be further optimized on a 3T magnet.

Diffusion-Weighted Imaging

In addition to evaluating lesion morphology and kinetic information, diffusion-weighted imaging (DWI) may be used to increase the specificity of MRI. Although DWI should not

be the primary method used for lesion analysis, it can be helpful when the other imaging parameters such as lesion morphology and kinetic information are equivocal. The concept of diffusion is based on random and thermal motion of water in tissue, also known as Brownian motion. Tissues with high cellularity restrict the motion of water whereas tissues with low cellularity allow for more free movement of the water molecules. Tumors tend to have higher cellularity and hence have restricted motion. On DWI, the restricted motion results in a higher signal intensity (Fig. 13-1). The technique that is most commonly used to generate DWI imaging is T2-weighted echo planar imaging. Due to the higher cellularity of carcinomas, there is restricted diffusion in invasive cancers relative to benign lesions and normal parenchyma, resulting in relatively brightness of malignant lesions compared to benign lesions. Different diffusion gradients, b, are applied. The signal loss from the different gradients is exponentially proportional to the amount of diffusion of the water molecules. The apparent diffusion coefficient (ADC) can be calculated from at least two diffusion weighted image sets at different b values. Restricted diffusion and high cellularity results in lower ADC values.

Various studies have shown that using an ADC cutoff value can aid in discriminating between benign and malignant lesions (6,7). However, there is no standardization of diffusion techniques. Different ADC cutoff values and diffusion gradients are used from institution to institution. In addition, although most carcinomas have high cellularity and low ADC values, some benign lesions can exhibit these characteristics. Likewise, some malignant lesions can

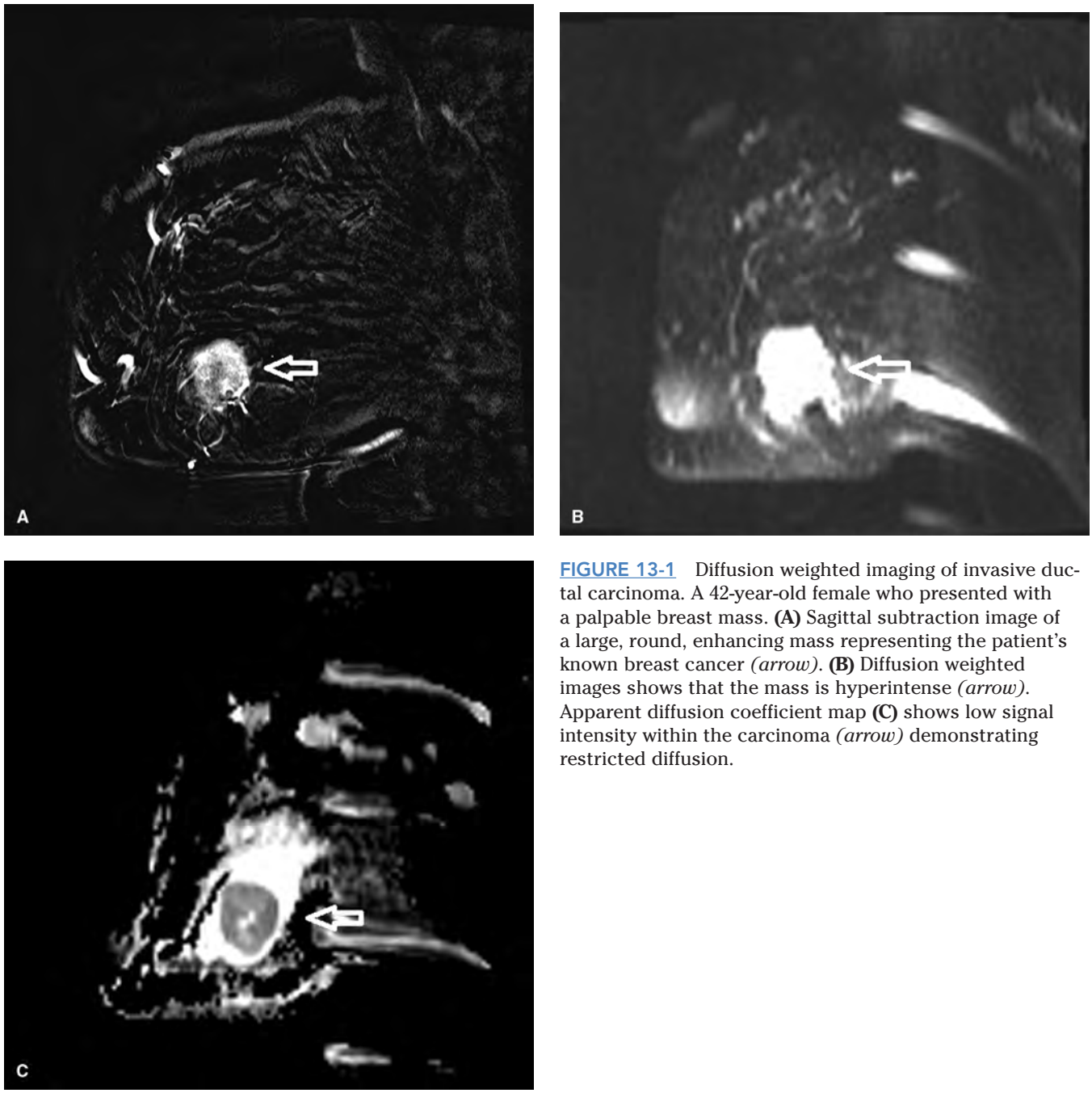

FIGURE 13-1 Diffusion weighted imaging of invasive ductal carcinoma. A 42-year-old female who presented with a palpable breast mass. **(A)** Sagittal subtraction image of a large, round, enhancing mass representing the patient's known breast cancer *(arrow)*. **(B)** Diffusion weighted images shows that the mass is hyperintense *(arrow)*. Apparent diffusion coefficient map **(C)** shows low signal intensity within the carcinoma *(arrow)* demonstrating restricted diffusion.

also demonstrate benign features on DWI such as necrotic tumors, tumors with cystic components, and mucinous tumors. At this time, given these limitations and overlap with benign and malignant features, one cannot reliably use DWI alone to differentiate benign from malignant lesions but rather use this information in combination with morphologic features and kinetic information.

MRI-Guided Localization or Biopsy Capability

The ability to perform MRI-guided interventional procedures is an integral part of MRI imaging. A requirement of the ACR breast MRI accreditation program, the facility performing breast MRI must either have the capacity to perform MRI-guided breast interventional procedures or to create a referral arrangement with a cooperating facility that will provide these services (3). There will be malignant lesions detected on MRI that will be occult on mammography, sonography, and clinical examination, hence the need to perform MRI-guided biopsies. With a technique that is highly sensitive but not highly specific, a needle localization or core needle biopsy system is needed to differentiate true positive enhancing malignant lesions from false positive benign enhancing lesions. The two available options are MRI-guided core needle biopsy and MRI-guided needle localization.

Historically, MRI-guided intervention was limited to needle localization followed by excisional biopsy. Currently, many different MRI-compatible core biopsy systems are commercially available. MRI-guided core needle biopsy is a safe and accurate way to biopsy MRI detected lesions (Fig. 13-2). Similar to ultrasound-guided core needle biopsy, the advantages of MRI-guided core biopsy over excisional biopsy are the less invasive nature of the procedure, minimizing the number of surgical procedures in patients diagnosed with breast cancer, and reduced costs.

A major limitation of MRI-guided needle localization and core biopsy remains the inability to verify successful lesion removal or lesion sampling. In the case of needle localization,

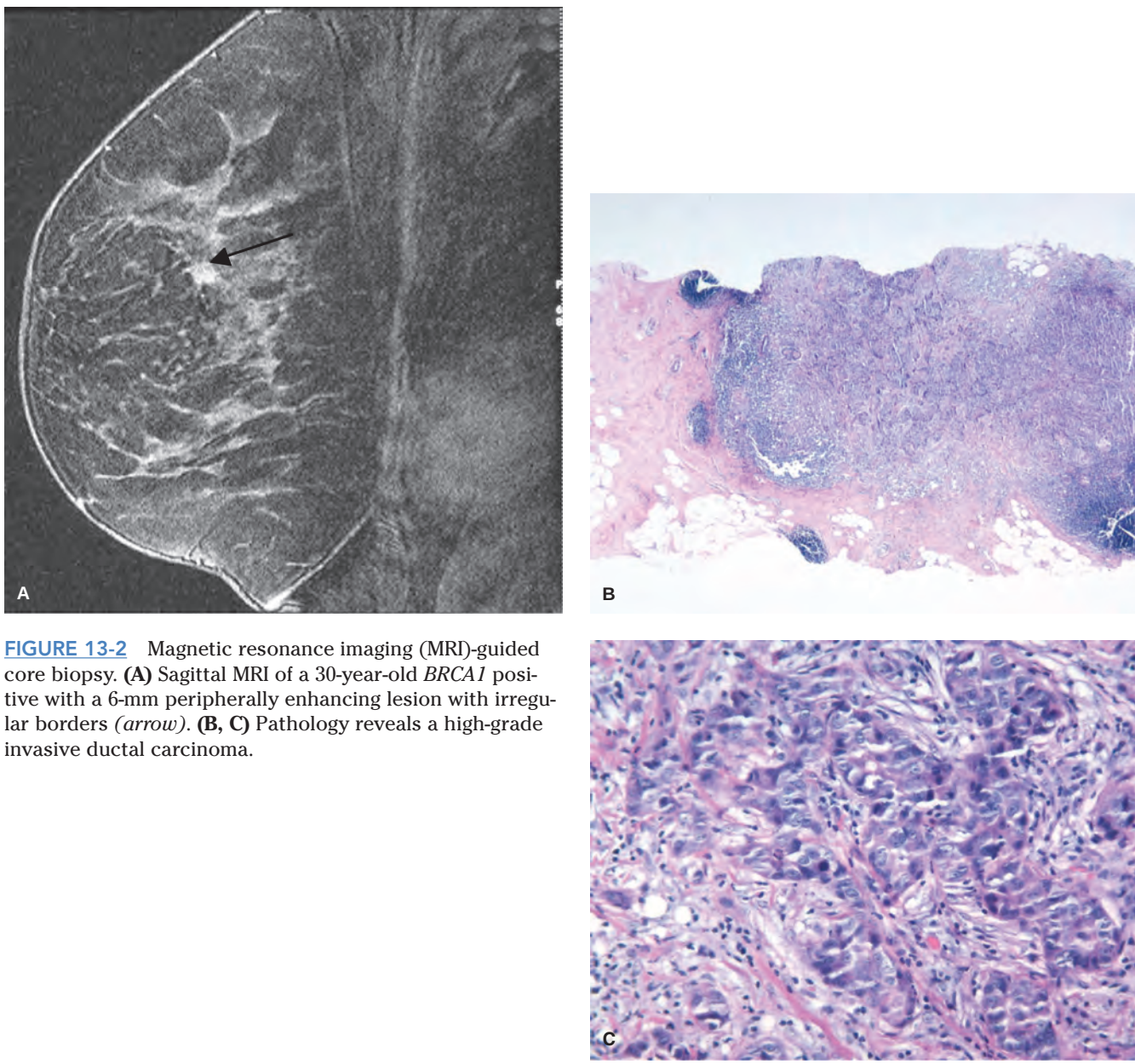

FIGURE 13-2 Magnetic resonance imaging (MRI)-guided core biopsy. **(A)** Sagittal MRI of a 30-year-old *BRCA1* positive with a 6-mm peripherally enhancing lesion with irregular borders *(arrow)*. **(B, C)** Pathology reveals a high-grade invasive ductal carcinoma.

the lesion localized with MRI guidance is usually not visible with mammographic specimen radiography. In the case of core biopsy, the ability to document successful sampling can be impossible due to the washout of contrast during the procedure. While a clip is placed following most MRI core biopsies, documentation of accurate clip placement can be difficult if the lesion is not visible at the end of the procedure. In such situations where there is washout of contrast, correlation with anatomic landmarks is recommended to confirm appropriate biopsy site and clip placement. Careful radiologic–pathologic correlation is needed to determine if the pathology findings are concordant with the imaging findings. In any case where the MRI finding is highly suspicious but the pathology is benign, immediate repeat MRI is required. Repeat MRI shortly after the biopsy is needed to confirm that the lesion has been adequately been sampled. If the targeted lesion is still present on the follow-up MRI, repeat MRI percutaneous biopsy or excisional biopsy would be necessary. However, when there is concordant benign histology, the management can vary from routine follow-up to a 6-month follow-up MRI. Whether short interval MRI follow-up should be performed in all cases with a nonspecific benign pathology result (i.e., fibrocystic changes or benign breast tissue) remains to be defined.

For a MRI-detected lesion, a targeted ultrasound examination or second-look ultrasound may be done in correlation with the MRI findings. The likelihood of visualizing the MRI-detected lesion on sonography is dependent on lesion morphology, size, and pathology (8,9). Greater success will be had with enhancing masses than nonmass enhancement. In addition, malignant lesions were more likely to be visible than benign lesions. Also, the larger the lesion size, the more likely it will be visible on targeted sonography. The success rate of targeted second-look ultrasound has been reported to be 23% to 89%.

If the MRI-detected lesion is sonographically visible, ultrasound-guided biopsy is the preferred method of biopsy. It is cheaper, faster, and more readily available when compared to MRI, with greater patient comfort. However, intermodality correlation is essential to confirm the sonographic lesion correlates with the MRI lesion. This involves correlation of the lesion size, depth in the breast, and location relative to other anatomic structures. Due to differences in patient positioning, supine for breast ultrasound and prone for breast MRI, occasionally this can be challenging. Meissnitzer et al. found on follow-up of 80 histologically benign cases that were biopsied under ultrasound and felt to be concordant to the MRI lesions, the sonographic mass did not correlate with the MRI lesion 12% of the time (10). Careful correlation is needed and follow-up imaging should be considered.

Image Interpretation

MRI has emerged as an important imaging technique for the detection, diagnosis, and staging of breast cancer. The value of MRI in this setting is derived primarily due to high sensitivity for the detection of breast cancer, with reported sensitivities ranging from 88% to 95% (11). However, high reported sensitivities have been tempered by relative low specificity, with reported specificities reports rates widely ranging from 37% to 97% (12). The low specificity is due to the overlap in morphologic appearances and enhancement behavior of benign and malignant lesions. Contrast enhancement has been seen not only in cancer, but also in fibroadenoma, fibrocystic changes including sclerosing adenosis, fat necrosis, radial scar, mastitis, atypical ductal hyperplasia, and lobular neoplasia (Fig. 13-3). In addition, presumably normal breast tissue may enhance following contrast enhancement. This enhancement has been shown to vary with different phases of the menstrual cycle, being greatest in weeks 1 and 4, lowest in week 2 (13) (Fig. 13-4). When using enhancement kinetics alone, it was shown in one study that up to three-fourths of enhancing lesions with suspicious enhancement kinetics were no longer visible when the study was repeated at a more optimum time in the menstrual cycle (13).

The characterization of enhancement as normal, benign, or concerning for malignancy remains a challenge. Historically, image interpretation was complicated by two fundamentally different methods for performing breast MRI; one utilizing three-dimensional high spatial resolution scans to assess lesion morphology, and the other utilizing rapid, dynamic imaging to assess enhancement kinetics. As discussed earlier, advances in both software and hardware now permit imaging with high spatial resolution and high temporal resolution so that both morphology and enhancement kinetics can be evaluated in the same study. While it has become increasing apparent that both architectural features and enhancement characteristics may yield greater accuracy than using either alone, characterization of morphologic features appears to be more predictive of malignancy than is characterization of the enhancement kinetic cure (14–16).

Numerous morphologic and dynamic enhancement curve criteria for classifying an enhancing lesion as benign or suspicious for malignancy have been described in the literature. In an effort to bring uniformity to breast MRI reports, an MRI breast imaging lexicon (BI-RADS) has been created through the efforts of the Susan Komen Foundation, the Public Health Service Office on Women's Health, and the American College of Radiology (ACR) (17). The first version of the MRI breast lexicon was published by the ACR in 2003, with the second edition due out in 2013. Results from many studies that evaluated the positive predictive value of morphologic and kinetic feature were incorporated into the first edition of the lexicon, and findings from more recent studies will be added to the second edition. One addition to the second BI-RADS MR imaging lexicon will be the description of background parenchymal enhancement (BPE), which refers to the presumably normal enhancement of the fibroglandular tissue identified on the first contrast-enhanced series. BPE is thought to be related to endogenous hormone status and fluctuates with the menstrual cycle, highest during weeks 1 and 4 and lowest during week 2 as noted above. It has been found to increase in postmenopausal women undergoing hormone replacement therapy, and to decrease in women treated with tamoxifen or aromatase inhibitors (18). Currently the degree of BPE is subjective, and is reported as minimal (less than 25%); mild (26% to 50%); moderate (51% to 75%); and marked (greater than 75%) (Fig. 13-5). It has been postulated that the degree of BPE may decrease the sensitivity of breast MRI by obscuring enhancing malignancies. Investigators evaluating BPE and impact of the diagnostic performance of MRI have reported that increasing background enhancement is associated with younger patient and age and higher abnormal interpretation rate (BI-RADS Category 3, 4, or 5), but found no significant difference in positive biopsy rate or cancer detection rate among the BPE categories (19,20).

Following the description of BPE, an area (or areas) of abnormal enhancement is then described using lesion descriptors (morphology and enhancement kinetics). Enhancing lesions are divided into three main categories: focus or foci, mass, and nonmasslike enhancement (NMLE) (Fig. 13-6). A focus (foci) is defined as enhancement measuring less than or equal to 5 mm that cannot be otherwise characterized due to size. A mass is a 3-D lesion that occupies a

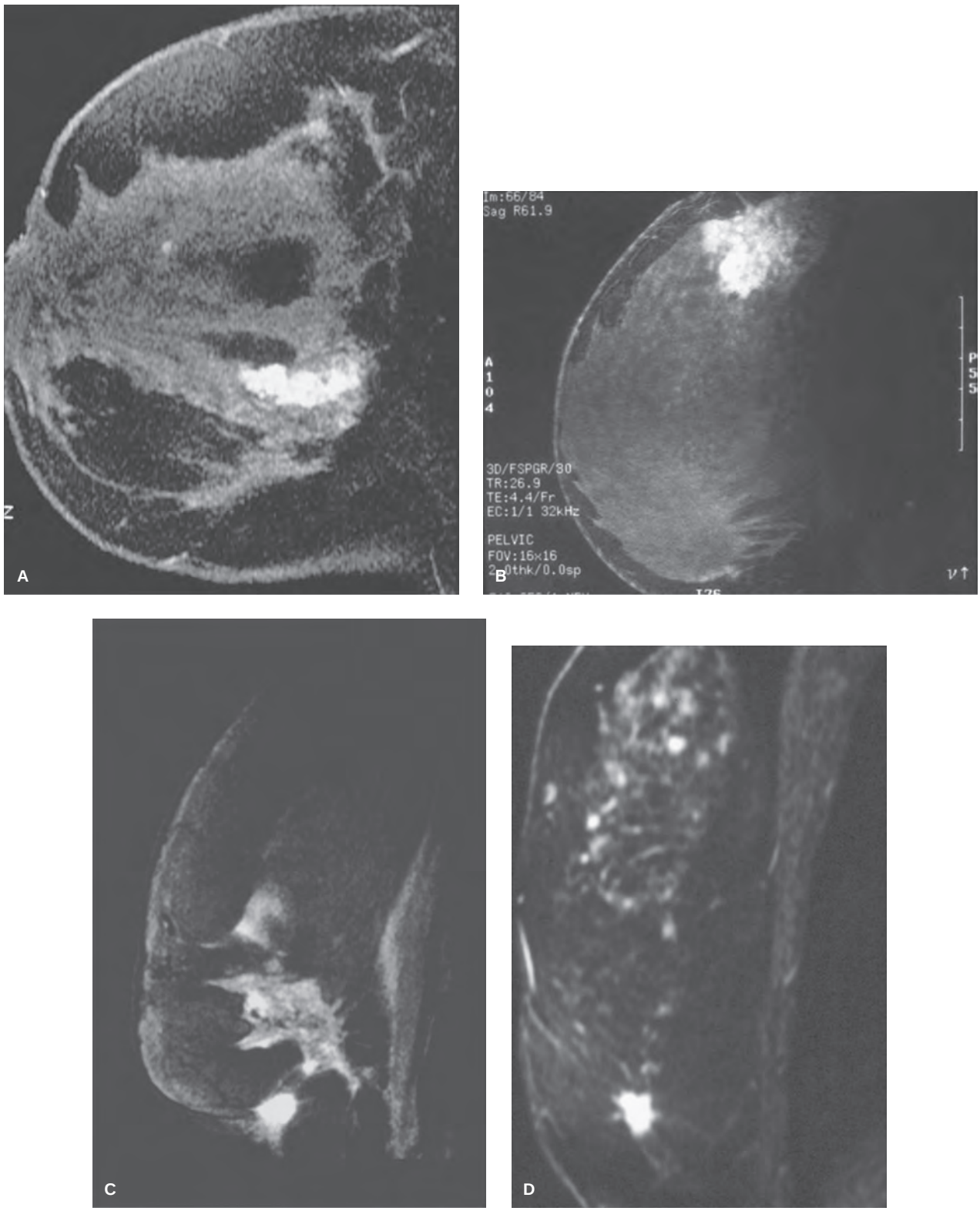

FIGURE 13-3 False-positive enhancing lesions. Contrast enhancement is demonstrated in **(A)** sclerosing adenosis, **(B)** chronic mastitis, **(C)** fat necrosis, and **(D)** radial scar.

space in the breast, and is described in terms of shape, margin, and internal enhancement. NMLE is an area of enhancement without an associated mass (space occupying lesion) and is characterized by distribution, internal enhancement, and symmetry. Enhancement curve assessment includes the initial enhancement phase in first 2 minutes (slow, medium, or rapid), and the delayed phase (persistent increasing, plateau, or washout) (Fig. 13-7).

Architectural features reported to be highly predictive of benign disease include masses with smooth or lobulated

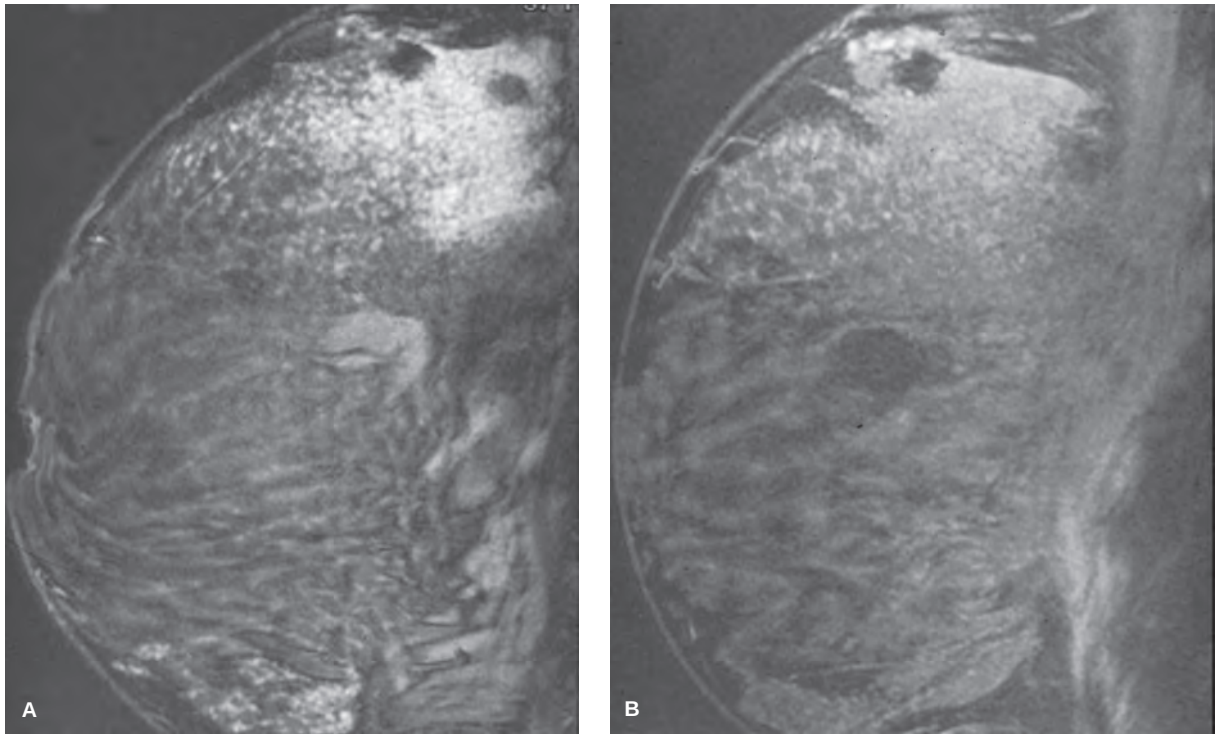

FIGURE 13-4 Hormonal variability of contrast enhancement. Sagittal magnetic resonance image of a patient with a family history of breast cancer reveals an area of regional enhancement in the superior breast, which was no longer present when the patient was imaged at a different time in her menstrual cycle.

borders, the absence of mass enhancement, and a circumscribed mass with nonenhancing internal septations, which in some reports was specific for the diagnosis of a fibroadenoma (14,21). While circumscribed borders on mammography are associated with a 2% likelihood of cancers (22), it has been suggested that this morphologic feature may not be a reliable indicator of benignity on MRI for several reasons including the circumscribed borders of some cancers in high-risk patients, and the perception of margin smoothness which is dependent on spatial resolution and window and level settings (16,23,24). This can be especially problematic in masses smaller than 1 cm in size. In a study of positive predictive value of various morphologic and kinetic features, Liberman et al. reported that 17% of smoothly marinated masses in their series were malignant (16). In contrast, Gutierrez et al. reported that masses of 1 cm or greater with smooth margins and homogeneous enhancement in their series had the lowest predicted probability of malignancy of 3% (24). However, this was not the case with smaller masses, where the likelihood of malignancy for small masses (less than 1 cm in size) with smooth margins and homogeneous enhancement was 16%. Histologic subtypes that may have smooth margins include mucinous cancer, intracystic papillary cancer, and some high-grade tumors, such as triple-negative cancer (25). Despite smooth margins, these malignant lesions often display other concerning morphologic features including heterogeneous enhancement, rim enhancement, and/or an enhancement kinetic curve showing contrast washout over time.

Architectural features with highest PPV for malignancy include a mass with spiculated or irregular margins, irregular shape, marked internal enhancement, and/or rim enhancement (11,12,14–16). These findings suggest the presence of an invasive cancer. For NMLE, the features with highest PPV for malignancy include segmental or clumped linear enhancement (11,12,14–16,24) and suggest the diagnosis of DCIS. The enhancement kinetics with the highest PPV is rapid initial enhancement with delayed phase showing plateau or washout (11,12,14–16). However, as noted previously, kinetic information is less predictive of malignancy than is morphologic characterization. This is especially true with NMLE, where DCIS not uncommonly displays suspicious ductal or segmental morphology, but with benign kinetic curves (24).

The overall impression and final recommendation categories are virtually identical to the BI-RADS mammography lexicon. A BI-RADS Category 0 study is incomplete, where comparison with a previous MRI study or correlation with mammography and/or ultrasound is needed. A BI-RADS Category 1 study is negative. A BI-RADS Category 2 study demonstrates benign findings such as postsurgical/postradiation changes, cysts, or an enhancing lesion(s) with benign MRI characteristics. Reported NPV for BI-RADS Category 1 examination (no abnormal enhancement was cancer found) have ranged from 88% to 99% (11,15). Mahoney at el. reported an NPV of 100% in their BI-RADS Category 2 cases (15). A BI-RADS Category 3 study demonstrates an enhancing lesion (or lesions), which is deemed to be probably benign, and short-term interval follow-up, usually at 6 months, is recommended. At the present time, approaches for what type of enhancing lesion should be placed into the probably benign category are intuitive. The type of enhancement that should be classified as probably benign as opposed to normal, benign, or suspicious remains unclear. In mammography, findings that should be placed into the probably benign category have been well studied. In clinical investigation, it has been demonstrated that the likelihood of a lesion classified as probably benign, BI-RADS Category 3 on mammography, but ultimately prove to be malignant should be less

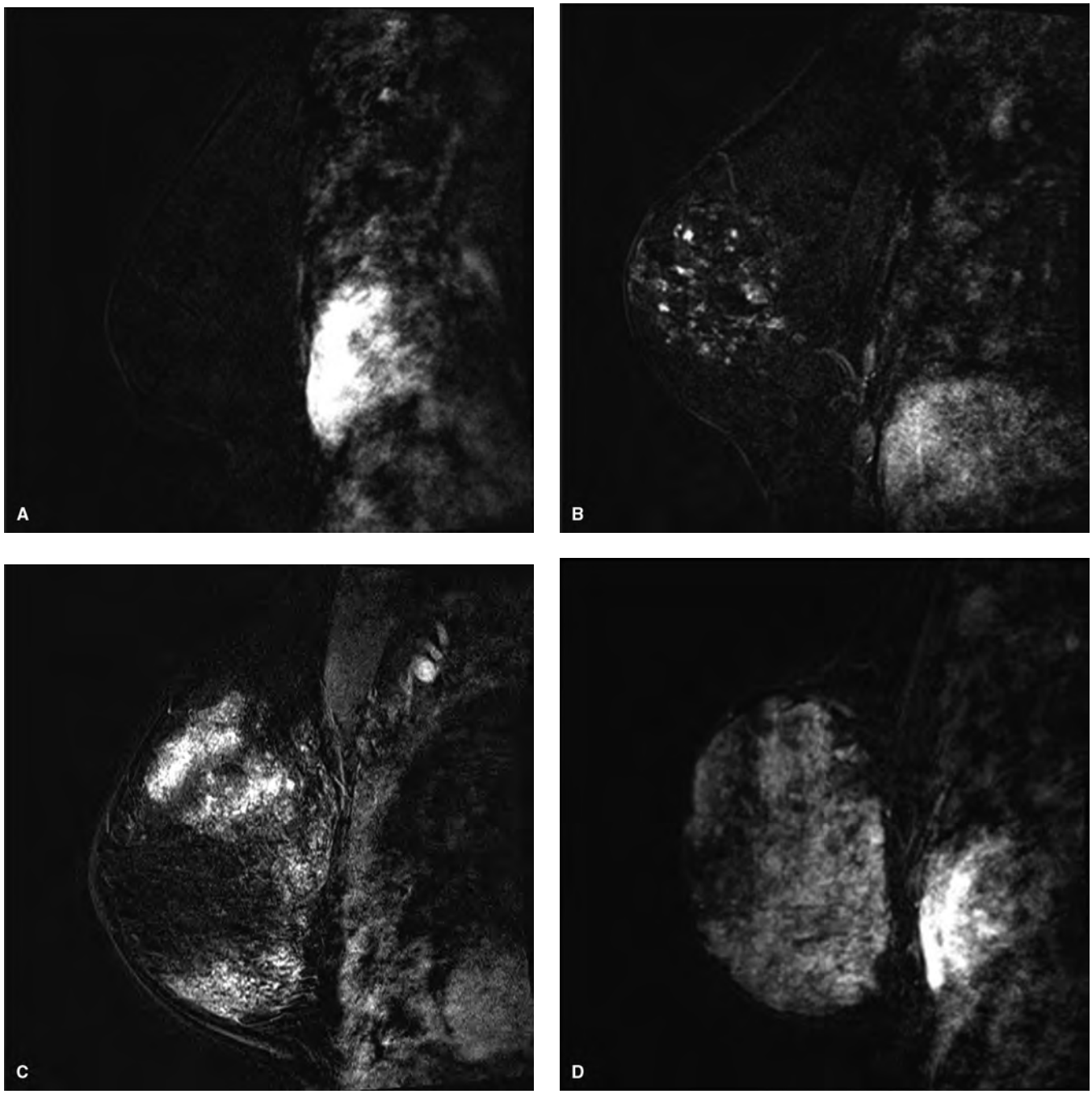

FIGURE 13-5 Background enhancement. Sagittal contrast-enhanced subtraction images showing different levels of background parenchymal enhancement. **(A)** Minimal background enhancement, **(B)** mild background enhancement, **(C)** moderate background enhancement, and **(D)** marked background enhancement.

than 1% to 2% (22). In contrast to mammography, there has been very little published on the outcome of lesions placed into the BI-RADS Category 3 (23). There is a wide variation in the use of probably benign assessment, which has been applied in 6.6% to 25% of examination (23). The cancer yield in cases placed into BI-RADS 3 has also been widely variable, ranging from 0% to 10%. The wide discrepancy in reported results is likely due to differences in inclusion criteria for patient population: screening high-risk women only, screening and diagnostic MRI, and BI-RADS 0 mammographic and sonographic workup. Further investigation is needed to determine if there are distinct morphologic and/or kinetic characteristics that can be deemed appropriate for short interval follow-up with an acceptable cancer yield and maintain favorable prognosis. In addition, overall cost must be considered when interpreting a breast MRI as probably benign. In contrast to mammography, where placing a patient into short interval follow-up was a relatively fast and inexpensive alternative to surgical excision, one or more 6-month follow-up MRI examinations are very expensive. The cost–benefit of short interval follow-up MRI (how often and for how long) relative to how readily available MRI-guided

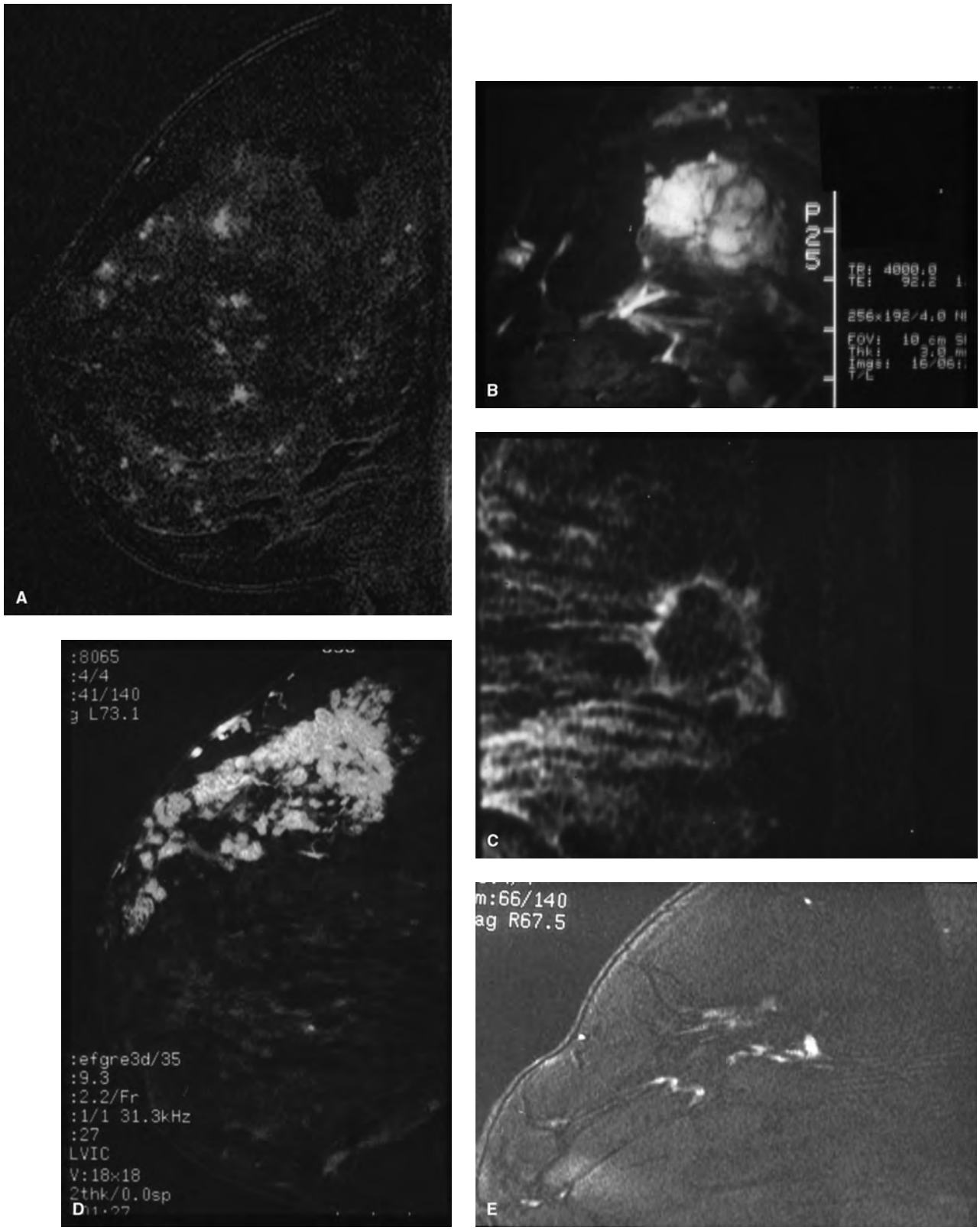

FIGURE 13-6 Architectural features: **(A)** scattered foci (less than 5 mm) of enhancement, **(B)** lobulated enhancing mass with nonenhancing internal septations in fibroademoma, **(C)** peripheral enhancement and spiculated borders in invasive ductal carcinoma, **(D)** clumped segmental nonmass enhancement in DCIS, and **(E)** linear nonmass enhancement in DCIS.

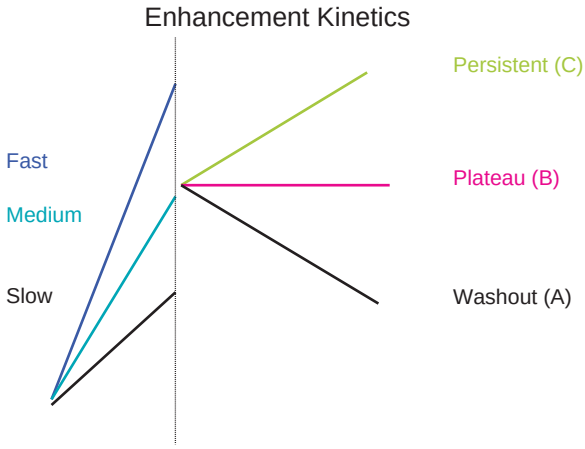

FIGURE 13-7 Enhancement kinetics. Enhancement measured over time shows three enhancement curves: **(A)** washout of contrast commonly seen in cancer, **(B)** plateau enhancement seen in both malignant and benign lesions, and **(C)** persistent increasing enhancement common in benign lesions.

core needle biopsy is needs to be studied. Finally, BI-RADS Category 4 (suspicious) and 5 (highly suspicious) studies demonstrate an enhancing lesion (or lesions) for which a biopsy is recommended. The biopsy can be performed with MRI guidance if seen only on MRI, or with ultrasound guidance in those cases where the MRI finding can be identified on a directed ultrasound study. In those cases where targeted ultrasound is recommended for possible guidance for biopsy, these should be categorized as BI-RADS 4, biopsy recommended (MRI-guided biopsy if ultrasound is negative), not BI-RADS Category 0. Reported PPV for BI-RADS Category 5 lesions have ranged from 67% to 71% while reported PPV for BI-RADS Category 4 lesions have ranged from 19% to 21% (15,16).

CLINICAL INDICATIONS

Problem Solving: The Equivocal Mammogram, Ultrasound, or Physical Examination Finding

Breast MR imaging can be used as a problem-solving tool in the setting of equivocal imaging (mammography and/or ultrasound) findings (26–28). MR imaging can be a very useful clinical tool when breast cancer is suspected but the diagnosis cannot be established by means of conventional methods. MRI, however, should never be used in place of a full mammographic and sonographic evaluation. A thorough conventional imaging evaluation should be completed prior to recommending a MRI. In one study, the most common mammographic findings that led to the recommendation for MRI were architectural distortion and asymmetries, findings seen only on one view (29). No suspicious enhancement was seen in the region of the mammographic abnormality in 87% of the cases. However, correlative enhancing masses were seen in 13% (15 per 115) cases with biopsy of all 15 cases yielding 6 cancers (6 per 115, 0.5%) (29). Based on results of several studies demonstrating sensitivity of MRI for the detection of invasive cancer approaching 100%, it has been suggested that a negative MRI examination image in the setting of equivocal imaging or physical examination findings virtually excludes the presence of invasive cancer. However, there have been multiple reports (30–33) documenting false-negative MRI cases, not only of noninvasive cancer but of invasive ductal cancer as well, including invasive lobular cancer and invasive ductal cancer. The reported false-negative rates of MRI range from 4% to 12% (30–33), although up to 47% of the cases may be attributed to differences in image perception and interpretation rather than true false negatives (34). Regardless, as is true with a negative mammogram or a negative ultrasound study, in a patient with a suspicious palpable abnormality, a negative MRI study should not preclude biopsy.

Another potential problem-solving tool that was FDA approved in 2011 and rapidly gaining clinical acceptance is tomosynthesis imaging. Tomosynthesis is 3-D imaging of the breast based on the digital platform. One of the main advantages of tomosynthesis is that, similar to breast MR, the 3-D imaging decreases the superimposition of fibroglandular tissue that may obscure lesions. The 3-D imaging also allows for improved triangulation, or localization of mammographic findings seen in one view, and lesion analysis and thus can be used as problem-solving tool (35). In addition, there is current ongoing research to add contrast to tomosynthesis imaging. It is feasible that tomosynthesis may decrease the role of MRI in the evaluation of inconclusive mammographic findings in the future. This remains to be seen.

Axillary Node Malignancy and Unknown Site of Primary Tumor

Occult primary breast cancer presenting as malignant axillary adenopathy represents less than 1% of breast cancers. Traditionally, treatment offered to these women was mastectomy and axillary node dissection. Pathologic evaluation of the mastectomy specimen in such situations has demonstrated the primary cancer in only one-third of the time. The ability of mammography to identify a primary breast cancer in this clinical setting has been disappointing, with reported rates ranging from 0% to 56%. In contrast, MRI has demonstrated very high sensitivity for the detection of an ipsilateral breast cancer primary (36,37) in these patients. In a review of six studies, the overall sensitivity of MRI was 94% with a specificity of 94% to 100% and estimated PPV was 90% (37). The results of these studies support the clinical use of MRI as the imaging study of choice in the clinical setting of malignant axillary adenopathy and unknown site of primary tumor. In this patient population, MRI offers the potential for breast cancer detection as well as staging, which can then be used to guide treatment planning. The identification of localized disease may offer some patients the option of breast conservation therapy as an alternative to mastectomy. If MR does not demonstrate the primary breast cancer, options include mastectomy or whole breast radiation followed by systemic therapy.

Monitoring Response to Chemotherapy

In patients presenting with locally advanced cancers, preoperative chemotherapy is necessary prior to surgical therapy. Decreasing the size of the tumor also can allow for less radical surgery, converting a clinically indicated mastectomy to potential breast-conserving therapy. However, monitoring clinical response can be challenging. The resulting fibrotic response from chemotherapy may sometimes make clinical breast evaluation difficult. There are also limitations to mammography as overlying glandular tissue can make assessment difficult. Studies have shown that MRI is superior to mammography and clinical breast examination in establishing a baseline tumor extent and in monitoring these patients (38,39). In addition, it has been shown that MRI can

provide evidence of response to therapy as early as after one cycle of chemotherapy with tumor volumetric measurement being the superior method to monitor change than tumor diameter measurement (38). Given that MRI can detect early response, it is equally important to identify patients who do not respond to therapy so appropriate chemotherapy regimen changes may be made. However, it has been shown that MRI may over- and underestimate tumor response. In some cases, MRI following treatment demonstrates no residual enhancing tumor, yet residual tumor nests, which may be extensive, are found at excision. The absence of enhancement even in the presence of residual invasive tumor is likely secondary to chemotherapy-induced decreased tumor vascularization and/or decreased vascular permeability. It has also been demonstrated that the underestimation of residual tumor burden on MRI may vary with the chemotherapeutic agent. Tumors treated with a taxane-containing regimen are often underestimated (40). It is postulated that the underestimation of tumor volume by MRI is secondary to the numerous nests of tumor left following the taxane regimen compared with a more concentric tumor shrinkage with other chemotherapeutic agents. As there can be "complete imaging response," placement of a clip at the original tumor site is recommended prior to neoadjuvant treatment so the tumor site can be identified and localized at the time of surgery. If there is no residual enhancement at completion of therapy, the clip can be localized at the time of surgery.

The imaging pattern of response may depend on the original appearance of the tumor. In cases of focal disease, there is concentric shrinkage of the tumor in responders, which can be easy to follow. However, when tumor presents as multifocal or multicentric disease, response to therapy can result in residual small foci of tumor scattered in the breast, some of which may be below the threshold of imaging.

In addition to contrast-enhanced MRI, studies have shown the diffusion-weighted imaging may have a role in monitoring response to chemotherapy (41). As diffusion-weighted imaging measures movement of water molecules at the cellular level, these studies have reported increases in ADC reflect damage at the cellular level in response to the chemotherapy prior to morphologic changes became detectable. Pickles et al. found increase in ADC values to be statistically significant after one cycle of chemotherapy but comparison was made to lesion diameter rather than volume (41), whereas Hylton and colleagues found tumor volume measurement to be a more sensitive measure than diameter (38). The role of diffusion-weighted imaging in monitoring response to chemotherapy remains to be seen, but it may have a valuable role in patients with renal dysfunction or gadolinium allergy as intravenous contrast is not needed.

Despite its limitations, MRI does appear, at the current time, to be the most accurate imaging methods for evaluating response to chemotherapy. While it is superior to mammography and clinical breast examination, potential over- and underestimation of tumor burden should be taken into account when incorporating MRI in this clinical setting.

Breast Cancer Screening in Women at High Risk

In the 1990s, the first prospective, nonrandomized studies were initiated in The Netherlands, the United Kingdom, Canada, Germany, the United States, and Italy to determine the benefit of adding annual MRI to mammography for women at increased risk for developing breast cancer including women with *BRCA1* or *BRCA2* mutations or women with at least a 20% to 25% lifetime risk of developing breast cancer (42–47). In a review of 8 of these trials, Lehman et al. reported that 144 cancers were detected in 4,271 women for a cancer yield of 3% (48). Despite substantial differences in patient population (i.e., age, risk) and MRI technique, all reported significantly higher sensitivity for MRI compared with film mammography (or any of the other modalities). Overall, the studies reported a high sensitivity for MRI, ranging from 71% to 100% versus 0% to 40% for mammography in high-risk populations (48).

In August 2006, the American Cancer Society convened an expert panel to review the literature on MRI high-risk screening published between 2002 and 2006 with the intent to develop guidelines for adding MRI to mammography for screening of women at elevated risk for developing breast cancer. Based on evidence (reported results of prospective, nonrandomized studies), the panel concluded that annual screening MRI should be added to annual screening mammography in *BRCA1* or *BRCA2* mutation carriers, for first-degree relatives of *BRCA1* or *BRCA2* mutation carriers but were not themselves tested, or based on risk assessment had a lifetime risk of 20% to 25% or greater for developing breast cancer (49) (Fig. 13-3). Based on expert consensus, given limited published experience, the panel recommended annual screening MRI in patients who received radiation to the chest between ages 10 and 30, patients with Li-Fruameni syndrome and first-degree relatives, and those with Cowden and Bannayan-Riley-Ruvalcaba syndromes and first-degree relatives (49).

When screening with MRI should begin, how often it should be performed, and when it should be stopped remain unclear. In a statement published in 2010, The Society of Breast Imaging and the American College of Radiology recommend that screening MRI be performed annually, beginning by age 30, but not before age 25 in *BRCA1* or *BRCA2* mutation carriers or first-degree relatives (50). For women with 20% or greater lifetime risk, annual MRI is recommended to begin by age 30 (not before 25) or 10 years before the age of the youngest affected first-degree relatives. For those with a history of chest irradiation (ages 10 to 30 years), annual MRI beginning 8 years after treatment, but not before age 25 is recommended. The age to stop MRI screening in the United States has yet to be defined. In the United Kingdom, the National Institute for Health and Clinical Excellence (NICE) guidelines for MRI screening of women at increased risk are as follows: Annual MRI should be offered to women who are *BRCA1* and *BRCA2* mutation carriers aged 30 to 39; TP 53 carrier greater beginning at age 20; women aged 30 to 39 with greater than 8% 10-year risk; women aged 40 to 49 years with greater than 20% 10-year risk or greater than 12% 10-year risk with dense breasts on mammography; MRI should not be offered to women older than age 50 (51).

The ACS panel found insufficient evidence to recommend annual screening MRI in patients with lifetime risk of 15% to 20%; a history of biopsy proven LCIS, ALH, or ADH; those with a personal history of breast cancer; or those with heterogeneously or extremely dense breasts on mammography. However, single-institution, retrospective studies published after the ACS guidelines were defined have reported cancer detection rates on screening MRI in patients with a history of LCIS or a personal history of breast cancer similar to detection rates in women with a *BRCA1* or *BRCA2* mutation or those with greater than 20% lifetime risk, suggesting that screening MRI may be of value in these patients as well (52,53). The Society of Breast Imaging (SBI) and the American College of Radiology (ACR) suggest that MRI screening be considered in women with between 15% and 20% lifetime risk of breast cancer on the basis of personal history of breast or ovarian cancer or biopsy-proven

neoplasia or ADH (50). The ACS guidelines (and the SBI and ACR) recommend against MRI screening in women at less than 15% lifetime risk.

While it has become increasing clear that MRI is a highly sensitive imaging technique to detect mammographic and clinically occult cancer in selected high-risk populations, there are two major interrelated limitations that need to be addressed, the first being limited specificity of MRI resulting in false-positive findings and the second being potential high costs related to the actual screening MRI costs and the potential downstream costs when an abnormality is detected. In terms of specificity, reported callback rates for additional imaging following screening MRI have ranged from 8% to 17% (average 10%), and biopsy rates ranged from 3% to 15% (average 5%) (48,49). However, it has been reported that recall rates decreased in subsequent rounds of screening, where the prevalence screens had the highest false-positive rates, which subsequently dropped to less than 10% (44,48,49). While the callback and biopsy rates of MRI were higher than for mammography in high-risk populations, the proportion of biopsies yielding a malignant diagnosis (positive predictive value) in these studies was also higher for MRI, ranging from 20% to 40% (44,48,49).

The potential for heightened patient anxiety following a false-positive MRI examination remains of concern. Results of relatively small studies have demonstrated variable degrees of elevated anxiety in women following a false-positive MRI examination. In a study looking at the psychological impact and acceptability of MRI and mammography in the United Kingdom national study for MRI screening of women at familial high risk of breast cancer (MARIBS), women were assessed psychologically 4 weeks before mammography and MRI, immediately after, and then 6 weeks after (54). Women reported that both mammography and MRI were acceptable with high levels of satisfaction and low psychological morbidity, but women reported that MRI was more distressing, they had higher anticipatory anxiety before MRI, the anxiety persisted at 6 weeks, and they stated they were more likely to return for mammography than MRI. In the Canadian screening trials, the authors reported that MRI did not have a detrimental psychological impact on women with a *BRCA* mutation, and that recalling these women for further imaging after a false-positive MRI temporarily increased global anxiety (55).

There has been anecdotal evidence that a false-positive MRI screening examination in a woman at high risk for the development of breast cancer may result in the request for prophylactic mastectomy. The actual frequency of prophylactic mastectomy secondary to a false-positive MRI study remains to be determined. Hoogerbrugge et al. reported their experience in a study of 196 *BRCA* mutation carries that underwent screening with MRI (56). In this study, 41% (81 per 196) of women had at least one positive MRI or mammogram. The probability that a positive MRI result was a false positive was 83%. In patients with a prior preference for mastectomy, prophylactic mastectomy was performed in 89% in those with a false-positive MRI versus 66% with a negative MRI ($p = .06$). No significant difference was found in women with prior preference for surveillance (63).

High cost, in large part related to false-positive findings, remains perhaps the greatest barrier to the implementation of widespread screening MRI of women at high risk. The costs associated with MRI include the initial MRI cost, but additional "downstream" costs when the MRI examinations yield false-positive results leading to immediate recall MRI studies, short interval follow-up MRI studies, additional mammogram and ultrasound studies, and benign breast biopsies. Several cost-effectiveness studies have been published. Each study has used a different computer model taking into account breast cancer risk, sensitivity, and specificity of MRI; cost of MRI; and cost per quality-adjusted life-year (QALY) gained with MRI. Using QALY in the range of $50,000 to $100,000, several studies have demonstrated that MRI does appear to be cost-effective. Plevritis et al. concluded that the cost per QALY saved for annual MRI plus film mammography, compared with annual film mammography alone, varied by age and was more favorable in carriers of a mutation in *BRCA1* than *BRCA2* because *BRCA1* mutations confer higher cancer risk, and higher risk of more aggressive cancers, than *BRCA2* mutations (57). Estimated cost per QALY for women aged 35 to 54 years was $55,420 for women with a *BRCA1* mutation and $130,695 for women with a *BRCA2* mutation. The most important determinants of cost-effectiveness were breast cancer risk, sensitivity of mammography, cost of MRI, and quality of life gains from MRI. An evaluation of the cost-effectiveness in the United Kingdom (based on MARIBS study) showed that the incremental cost per cancer detected for women at approximately 50% risk of carrying a *BRCA* gene mutation was $50,911 for MRI combined with mammography over mammography alone (58). For known mutation carriers, the incremental cost per cancer detected decreased to $27,544 for MRI combined with mammography, compared with mammography alone. Taneja et al. also reported that MRI appeared cost-effective in *BRCA1* or *BRCA2* mutation carries (QALY $25,277) and might be cost-effective in other high-risk groups depending on expected prevalence of disease (QALY $45,566 [300 cases], $310,616 [50 cases]) (59). In a cost-effectiveness study of MRI and mammography for screening *BRCA1* mutation carriers, Lee et al. concluded that combined annual screening with mammography and MRI provided the greatest life expectancy and was likely to be cost-effective when the value placed on gaining an additional QALY was in the range of $50,000 to $100,000 (60). In contrast to these reports, Moore et al., in a cost-effectiveness analysis of MRI compared to mammography for breast cancer screening in young women at high risk, found that although MRI may provide health benefits when compared to mammographic screening for some high-risk women, it did not appear to be cost-effective even at a willingness to pay thresholds above $120,000 (61).

Nipple Discharge

Nipple discharge is a relatively common complaint, with a reported incidence of 2% to 5%. Although most nipple discharge is caused by benign processes such as papillomas and duct ectasia, the risk of cancer among patients presenting with nipple discharge has been reported to be 5% to 21%. There have been a few reports, with relative small numbers of patients, demonstrating the potential of MR imaging to identify both malignant and benign lesions in this clinical setting. One of the earliest studies to evaluate the role of MRI for patients with nipple discharge described 22 patients with nipple discharge and negative mammography of whom 14 underwent excisional biopsy following the MRI (62). The authors reported that the MRI findings correlated with histologic findings in 10 of 14 (71%) cases that underwent surgical excision, including the identification of 5 of 6 underlying malignancies. More recent experience also supports the potential of MRI in the setting of clinically concerning nipple discharge. In a retrospective study of 306 patients with negative mammography who underwent ductography (DG) ($n = 163$) and /or MRI ($n = 52$), the overall incidence of malignancy was 10% (63). DG had a PPV of 19% and NPV of 63% while MRI had a PPV of 56% and NPV of 87%. The authors concluded that ductography is a poor indicator of underlying

pathology and cannot exclude underlying malignancy while MRI offered higher predictive values and thereby may allow for improved patient selection and treatment planning, but on the other hand, MRI should not replace major duct excision as the gold standard to exclude malignancy in patients with clinically concerning nipple discharge. In a subsequent report from the same institution, in a retrospective review of a highly select group of 475 patients presenting with ND, where the incidence of underlying cancer/high-risk pathology was high (36%), the sensitivity and specificity of MRI was 70% and 44%, respectively, and when performed after a negative standard evaluation, MRI detected 75% of otherwise occult malignant/high-risk lesions (64). However, in all of these cases the lesions were in the central region of the breast that would have been encompassed by standard duct excision. The authors thus concluded that while MRI may have a role in the evaluation of suspicious ND, the low specificity of MRI and the potential to detect "incidental" enhancing lesions that would require follow-up or biopsy should be considered before implementing routine use of MRI in this setting. In 2010, in a report of European Society of Breast Cancer Specialists (EUSOMA) working group on potential indications for the use of breast MRI, the authors found insufficient evidence of benefit to recommend the routine use of MRI in the clinical context of suspicious nipple discharge, recommending systematic reviews and meta-analysis of published studies (65).

Imaging in the Setting of Newly Diagnosed Breast Cancer

The generalized use of MRI in the clinical setting of newly diagnosed cancer remains controversial. The literature is replete with single institution and multicenter, nonrandomized retrospective studies performed over the past 15 years to evaluate MR imaging for preoperative ipsilateral breast cancer staging and contralateral breast cancer screening in patients with newly diagnosed breast cancer. Based on the results of these studies, there is overwhelming evidence that MRI is more sensitive than mammography, ultrasound, and physical examination in the assessment of tumor size and the detection of multifocal or multicentric disease in the ipsilateral breast and detecting unsuspected contralateral synchronous disease. In a recent meta-analysis of 50 such studies (n = 10,811 women) performed between 1996 and 2011 (total of 2,243 studies reviewed), MRI detected additional cancer in the ipsilateral breast in 20% of women and in the contralateral breast in 5.5% of women (66). In another meta-analysis of 22 studies that reported contralateral malignancies detected only by MRI, MRI detected a suspicious finding (TP plus FP) in 9.3% of women, with PPV of 47.9% and TP: FP of 0.92. In 35.1% of cases, the MRI detected cancers were DCIS and in 64.9% were invasive cancer (67).

Given the potential of MRI to detect unsuspected multifocal or multicentric cancer and synchronous bilateral cancer, it has been suggested that MRI should be part of the preoperative assessment of patients with newly diagnosed breast cancer. The assumptions behind adopting MRI in this role include the short-term goal of improved surgical planning, with reduced rate of reexcision surgery in those patients who will ultimately require mastectomy, and the long-term goals of reduced in-breast local recurrence and improved overall survival. At the current time, there is little evidence that preoperative MRI achieves any of these goals. In terms of improving surgical management, while MRI may detect more disease than was suspected based on conventional imaging or clinical examination, limited specificity remains problematic, with false-positive findings resulting in additional benign biopsies, wider excisions, and unnecessary mastectomies. In the aforementioned meta-analysis of 50 studies evaluating MRI for ipsilateral staging, the summary PPV of ipsilateral additional disease was 67% (95% CI 59% to 74%) and for the contralateral breast, the PPV was 37% (95% CI 27% to 47%) (66). While true positive MRI prompted "appropriate" conversion from local excision to wide local excision (WLE) in 4.5% or to mastectomy in 8.3%, the proportion of women with inappropriate conversion to more extensive surgery due to false-positive MRI findings was 4.5% (WLE) and 1.7% (mastectomy).

There remains an ongoing concern that a connection exists between the increasing use of breast MRI for breast cancer staging and increasing rate of mastectomies. At the Mayo Clinic in Rochester, Minnesota, in a study of 5,405 patients who underwent breast cancer surgery between 1997 and 2006, patients who had an MRI were more likely to undergo mastectomy than those who did not. However, mastectomy rates increased from 2004 to 2006 predominantly in patients who did not undergo MRI, suggesting that other factors influencing surgical management are involved (68). In a recent meta-analysis examining the effect of preoperative MRI compared with standard preoperative assessment on surgical outcomes, summary of evidence showed that MRI significantly increased mastectomy rates and suggested an unfavorable harm–benefit ratio for routine use of preoperative MRI in breast cancer staging (69).

In addition to more extensive surgery in the ipsilateral breast, there is also evidence that the use of preoperative MRI may correlate with an increased rate of contralateral prophylactic mastectomy (70–71). In a study of 3,606 women who underwent preoperative staging bilateral breast MRI, women who underwent MRI were nearly twice a likely to have a contralateral prophylactic mastectomy than those who did not undergo MRI (9.2% vs. 4.7%; $p < .001$) (71).

There are multiple potential biases inherent in the nonrandomized trials included in these meta-analyses, making it clear that randomized control trials are needed to gain a clearer understanding of the effects of preoperative breast MRI. The results of the first of such trials, the COMICE (comparative effectiveness of MRI in breast cancer) trial, were published in 2010 (72). This randomized-control multicenter trial, which evaluated the effectiveness of MRI in reducing reexcision rates, enrolled 1623 women in 45 UK centers, with biopsy-proven primary breast cancer that were scheduled for wide excision after triple assessment (clinical, radiological [mammography and ultrasound], and pathological assessment). Patients were randomly assigned to receive either MRI or no further imaging. The addition of MRI was not significantly associated with a reduced reexcision rate, with 19% needing reexcision in the MRI group versus 19% in the no-MRI group. The results of a second randomized control study, the MONET (MR mammography of nonpalpable breast tumors), was published in 2011 (73). This study, performed at four sites in the Netherlands, enrolled 418 patients with a nonpalpable BI-RADS Category 3 to 5 lesion, randomized to MRI versus no MRI. The primary endpoint was the rate of additional surgical procedures in patients with nonpalpable breast cancer. The authors reported that the addition of MRI was paradoxically associated with an increased reexcision rate (reexcision rate performed because of positive margins of resection after primary breast conserving surgery was 18 per 53 [34%] in the MRI group vs. 6 per 50 [12%] in the control group). Based on these results, the authors suggested that breast MRI should not be used routinely for preoperative workup patients with nonpalpable breast cancer.

Thus, at the present time, the short-term goal of MRI, namely improved surgical management with reduced number of surgical procedures, has not been demonstrated. While data are clear that MRI permits detection of mammographically, sonographically, and clinically occult multifocal cancer in selected patients with presumed unifocal disease and detect synchronous contralateral disease, what is not known is whether this will translate into a decreased rate of local recurrence, improved relapse-free survival, and overall survival. Should treatment (i.e., BCT vs. mastectomy) be altered because MRI detects additional foci of cancer, especially in those cases where the foci prove to be tiny areas of DCIS? Would these foci of cancer identified on MRI be successfully treated with postoperative radiation therapy? In those cases where the additional foci of cancer detected on MRI are subsequently excised, might not these patients be ideally suited to BCT? The reported rate of MRI-detected additional foci of cancer of 20% is substantially higher than the rate of recurrence after breast-conserving surgery plus definitive radiation therapy. Presumably, in many cases the additional foci of cancer detected on MRI would have been included in standard breast-conserving surgery or the residual disease would have been treated with postsurgical radiation therapy. To date, there have been no published results from prospective randomized control trials designed to answer these questions. The only information on the impact of staging MRI on outcome comes from single-institution, retrospective studies. In a study of 346 patients, 65% of whom underwent BCT, Fischer et al. reported a reduced rate of local failure for patients who underwent staging MRI compared with those who did not (1.2% vs. 6.5%; $p < .001$) (74). This study, however, is limited by failure to adjust for differences in tumor size, nodal status, and the use of systemic chemotherapy between groups. In a more recent study Solin et al., in a retrospective study of 756 women who underwent BCT (28% of whom had a staging MRI), reported no significant difference in 8-year rates of relapse-free survival (3% with MRI vs. 4% without MRI) and no significant difference in the 8-year rates of overall survival (94% with MRI vs. 95% without MRI) (75). There are limitations to this study. It was a nonrandomized, retrospective study. There was a potential for bias as patients who underwent MRI tended to be young and tended to have dense breast tissue on mammography. The value of MRI may have been underestimated as patients with extensive disease detected on MRI were excluded. Given the low rates of local failure, it may have been difficult to show an improvement in outcome in a single-institution study.

The clinical significance of MRI-only-detected synchronous contralateral cancer also remains unclear, especially the cases that are noninvasive. In approximately one-third to one-half of cases, the MRI-detected contralateral disease was DCIS. Would the contralateral cancers detected on MRI be successfully treated in those patients who undergo systemic chemotherapy and thus never become clinically apparent? Furthermore, the detection of these contralateral cancers must be weighed against the added time, expense, and costs associated with MRI and MRI-guided biopsy in those cases where the MRI-detected lesions prove to be benign.

While published data do not support staging of all patients with newly diagnosed breast cancer, are there subgroups of patients who are most at risk for having multifocal or multicentric cancer and would benefit most from MR imaging? Van Goethem et al. found that unsuspected multifocal or multicentric disease was most often observed in young or perimenopausal women or patients with larger (greater than 5-cm) lesions, dense breast tissue on mammography, a first-degree family history, and invasive lobular cancer (37). The EURSOMA working group suggested potential subgroups that might benefit from staging MRI including patients with newly diagnosed invasive lobular cancer, patients at high risk for breast cancer, and patients under age 60 with a discrepancy in size of greater than 1 cm between mammography and ultrasound with expected impact on treatment decision (65). There are also emerging data that MRI may be of clinical benefit in patients being evaluated for partial-breast irradiation (PBI). In retrospective studies, up to 20% of patients initially considered to be candidates for PBI proved to be unsuitable as a result of the MRI (76–77). One of the major criticisms of MRI staging of breast cancer is that the reported rate of additional foci of cancer detected on MRI is much higher than the reported rate of local recurrence following breast-conservation therapy with lumpectomy followed by whole-breast radiation. However, if whole-breast radiation is replaced with partial-breast radiation, then the additional foci of tumor detected by MRI may become clinically important.

Based on the current success of breast-conserving surgery, it is unlikely that MR imaging of the breast is warranted in all patients with newly diagnosed breast cancer. Furthermore, given the high cost and limited availability of breast MRI, it is unlikely that all patients with newly diagnosed breast cancer will have access to MRI. Even if the cost of MR imaging could be reduced and these imaging modalities do become widely available, which patients with breast cancer should undergo and MRI study prior to surgery? And for those who do undergo this examination, what is the risk–benefit ratio? Additional carefully designed prospective clinical investigation is needed in attempt to find answers to these questions.

Given the uncertainties surrounding the use of MRI in women with newly diagnosed breast cancer, there are two issues that remain paramount. First, it is critical that women are informed of the potential benefits and risks of preoperative MRI and their personal preferences be taken into account prior to ordering the study. Second, MRI-only-detected suspicious lesions require MRI-guided core biopsy or needle localization and excisional biopsy, as the majority of such lesions will prove benign.

MANAGEMENT SUMMARY

- MRI has very high sensitivity for the visualization of both invasive carcinoma and DCIS, and MR imaging can detect breast cancer that is mammographically, sonographically, and clinically occult. MRI, however, has a low specificity leading to a substantial rate of false-positive biopsies. False-positive findings may be minimized by timing MRI appropriately in the menstrual cycle.
- Questions surrounding clinical indications for breast MRI remain. MRI appears to be indicated as an adjunct to mammography in the settings of equivocal mammographic, sonographic, or physical examination findings, malignant axillary adenopathy with unknown site of primary tumor, and monitoring response of locally advanced cancer to chemotherapy.
- Annual screening MRI in addition to annual screening mammography is indicated in women with a known *BRCA1* or *BRCA2* gene mutation, a greater than 20% to 25% lifetime risk of developing breast cancer, or a history of radiation to the chest for Hodgkin disease.

- In other women at increased risk for the development of breast cancer including those with a personal history of breast cancer and those with a history of atypia or LCIS, there is insufficient evidence to recommend routine screening MRI at this time.
- The use of MRI for breast cancer staging remains controversial. MRI is currently the most accurate imaging method for determining extent of disease in the ipsilateral breast. The size of the MRI-detected cancers are also similar to mammographically and sonographically detected breast cancers. However, the detection of additional foci of breast cancer has not translated into a decreased rate of positive margins or improved selection for breast-conserving therapy (BCT). In those patients who do undergo BCT, it remains to be determined if preoperative staging with MRI will result in a decrease in the local recurrence rate. More data are needed. However, MRI detects significantly more disease than current rates of local recurrence. Similar issues exist for contralateral cancer detection.

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CHAPTER 14

New Breast Imaging Techniques

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CHAPTER CONTENTS

More than ever before, the cost of medical care and concern for radiation exposure are being taken into account in the process of deciding which tests and treatments we recommend for our patients. These concerns certainly apply to breast imaging particularly because the examinations we perform are repeated regularly over the course of a woman's lifetime contributing to cumulative radiation exposure. Additionally many of the newer technologies are costly; we need to learn which ones are worth the cost. Fortunately, there is a great deal of research and development in the field of breast imaging geared toward improved diagnostic capability while keeping cost and radiation exposure in mind. This chapter will review the current status of the current and more advanced breast imaging techniques.

Despite the seemingly never-ending controversies regarding its use, screening mammography remains the only breast imaging examination that reduces overall breast cancer mortality. This decrease in mortality is approximately 30%. Mammography is inexpensive and widely available. While there is radiation exposure, it is relatively low: The radiation dose has decreased from analog to digital mammography and is now 3.91 mGy to the breasts and 0.47 mSv to the whole body. The cost of mammography per life saved is less than that of seat belts, approximately $18,000.00.

The overall sensitivity of mammography is 70% to 85%. However, this sensitivity is dramatically decreased in women with denser breast tissue. As medicine becomes more personalized, screening recommendations are adjusted based on individual patient characteristics. Currently patient risk is arbitrarily divided into three categories. Average or normal risk is defined as less than 15% lifetime risk of developing breast cancer. Women at normal risk should begin screening mammography at the age of 40 and have yearly exams until their life expectancy is less than 5 years. Screening should begin earlier in women at intermediate (15% to 20%) risk and high risk (greater than 20%), generally 10 years earlier than the youngest family member who had breast cancer. If the increased risk is due to prior chest radiation, screening should begin 7 years after the completion of radiation therapy. With the application of these recommendations, there are many younger women having mammograms, and they generally have denser breast tissue. Sensitivity of mammography in these higher-risk women with dense breasts is only 30% to 50% (1,2). Boyd et al. have shown that there is a 17.8-fold increase in interval cancers in women with extremely dense breasts compared with women with fatty breasts (3).

In addition to mammography, two other breast imaging tools are commonly used: ultrasound and breast MRI. Ultrasound has primarily been used to further evaluate clinical or mammographic findings and image-guided biopsies. It is inexpensive and widely available. Additionally there is no radiation exposure. Breast ultrasound is increasingly being used for screening in conjunction with screening mammography. However, it is time-consuming, operator dependent, and has a low positive predictive value (PPV). Ultrasound is not useful for the detection of DCIS and breast calcifications.

Breast MRI is an exquisitely sensitive method of breast evaluation with no radiation exposure. As opposed to mammography and breast ultrasound, which only evaluate anatomy, MRI combines physiologic with anatomic evaluation. Contrast-enhanced MRI enables detection of the neovascularity associated with breast cancer, sometimes before a discreet mass can be detected which is why it is so sensitive for detection of breast cancers and for staging cancers within the breast. It is also the most accurate method for following patients after neoadjuvant chemotherapy. However, MRI is very expensive and good-quality MRI is not universally

available. Claustrophobic patients and patients with certain implanted metallic clips and devices are unable to undergo breast MRI. Suboptimal specificity is also a limitation of breast MRI.

Clearly there is a need to develop better technologies for breast cancer detection. Two types of advances have been made. The first type of advancement builds on the standard technologies described above. These include the advance from analog mammography to digital mammography, and, based on the template of digital mammography: tomosynthesis and contrast-enhanced mammography. Advances in ultrasound include automated whole breast ultrasound (AWBU) and elastography. Microbubbles have been used as a contrast agent for ultrasound in various organs and have also been evaluated for breast imaging. MRI advances include improved interpretation criteria by the development of an MRI-specific BI-RADs system. Imaging sequences such as diffusion-weighted imaging and spectroscopy may improve specificity.

The second type of advancement in breast imaging includes new platforms for imaging the breast. These include radionuclide breast imaging, CT of the breast, and optical breast imaging. Both types of advancements will be discussed in this chapter.

MAMMOGRAPHY

Xeromammography was the standard breast imaging modality until the early 1980s. Film screen (analog) mammography replaced xeromammography, leading to improvement in ability to detect soft-tissue lesions. Digital mammography has largely replaced film screen technique. In the United States approximately 70% of mammograms are performed with digital technique. Digital mammography has been shown to improve accuracy in breast cancer detection in women under 50, women with dense breast tissue, and premenopausal and perimenopausal women but has fallen short in improving overall accuracy (4). Radiation exposure is decreased and the interpreting radiologist is able to manipulate the images for better visualization. No hard-copy films are required. Moreover, the digital mammographic technology is the platform on which more advanced breast imaging techniques have been developed. These include digital breast tomosynthesis (DBT) and contrast-enhanced spectral mammography (CESM).

Tomosynthesis

Sometimes referred to as 3-D mammography, this technique was called the most exciting new technology in breast imaging in 2011. DBT is a purely anatomic evaluation of the breast. Multiple projections of the compressed breast are obtained using an x-ray tube that moves along an arc with a stationary detector. Image slices are reconstructed in the plane parallel to the detector both in a mediolateral oblique (MLO) or craniocaudal (CC) plane. A "3-D" volume can be reconstructed when both views are imaged. The theory behind this technique is that by performing these tomographic images, one can peel away the overlying breast tissue that may be obscuring lesions or their characteristics. This improves lesion conspicuity and margin feature analysis (Fig. 14-1). Additionally, false-positive lesions are seen on mammography due to superimposition of breast tissue and DBT can exclude an abnormality in this situation. Because of these capabilities, DBT can be more sensitive and specific than routine mammography. DBT produced by a single vendor is currently FDA approved to be performed in addition to a full-field digital mammogram (FFDM). Other vendors are applying for FDA approval.

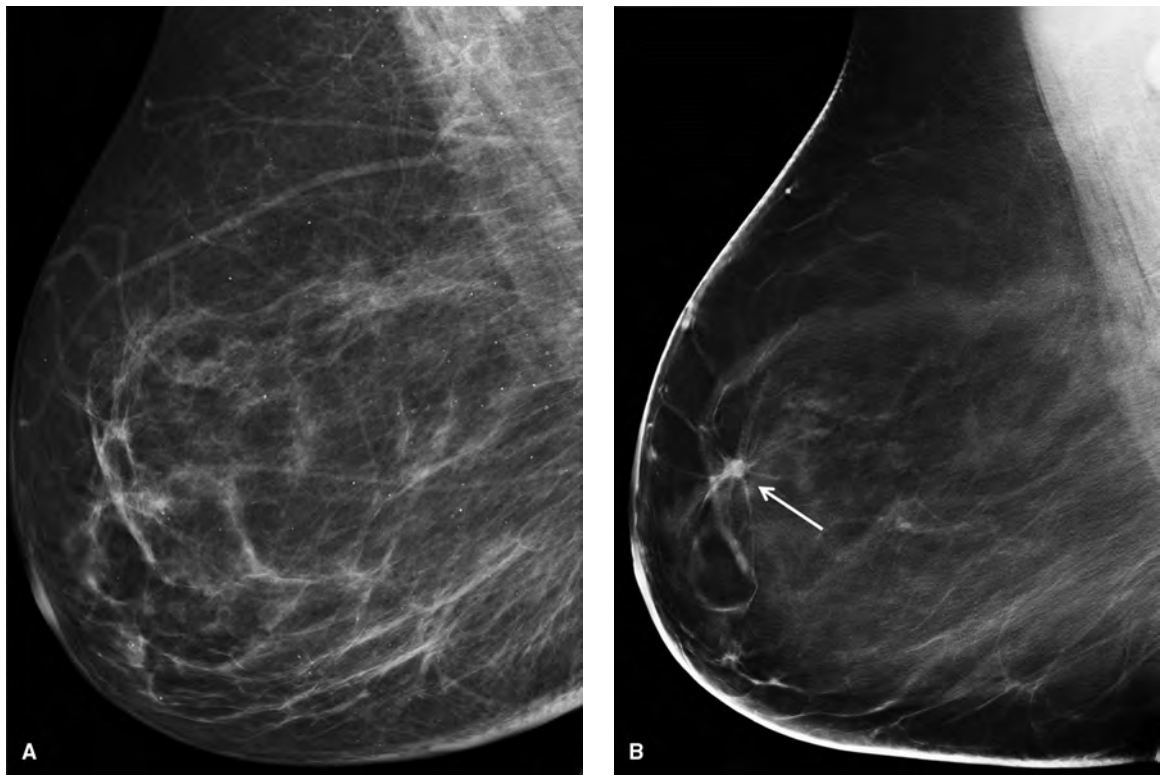

FIGURE 14-1 Tomosynthesis: 61-year-old woman with predominantly fatty breast. **(A)** RMLO: negative mammogram. **(B)** Spiculated cancer detected on tomosynthesis in the MLO view *(arrow)*. (Courtesy of Dr. Gisella Gennaro.)

DBT has been shown to reduce the number of patients called back for additional imaging 40% of the time (4,5). This would be advantageous if DBT alone could be utilized for screening. Used in addition to a screening mammogram, it is essentially a callback of 100% of the patients merely performed at the same time. Noroozian et al. demonstrated that DBT images showed equivalent mass characterization when compared to routine spot films. In 67 patients, DBT detected 7 additional cancers as well as 5 additional false-positive findings (6). Rafferty et al. compared FFDM alone to FFDM plus DBT in two multi-institutional reader studies of 1,192 subjects. Diagnostic accuracy for the combination of tomosynthesis with DBT showed a statistically significant improvement of 6.8% and 7.2% in the two studies (7). Of interest, in a test set of 130 women, two-view tomosynthesis had significantly better accuracy than FFDM but only for readers with the least experience in mammographic interpretation (8).

The benefits of DBT are seen only with soft-tissue lesions. Identification and characterization of calcifications is more problematic. This is partially due to the very thin slices (1 mm) and the blurring inherent to tomosynthesis. Spangler et al. showed superior sensitivity (84% vs. 75%) and specificity (71% vs. 64%) of FFDM over DBT (9). Technological improvements have been made to improve on this, but this remains an area where DBT does not currently offer an advantage over FFDM.

There are many issues to be resolved before any official recommendations can be made for use of DBT. The radiation dose of tomosynthesis is 4 to 8 mGy so that doing both routine mammography and DBT exams doubles or triples overall dose. In an effort to keep radiation dose to a minimum, studies have been and are being performed using various combinations of the two exams: FFDM with a single-view (MLO) tomosynthesis examination was performed in 200 women (376 breasts evaluated). The clinical performance of a single-view tomo was not significantly different from routine mammography (10). Other options being considered include a single-view tomo (i.e., MLO) with the other view (CC) digital mammogram. Another option would be to replace the digital mammogram with a mammogram synthesized from the tomosynthesis examination. Additional research is required to determine the approach with the least radiation and the highest yield.

DBT takes 50% to 70% longer to read than routine mammography which is clearly a significant limitation. Reimbursement does not reflect the additional time expenditure. Storage and display issues must also be resolved. Additionally, it is unclear whether DBT is best used as a screening tool in all patients, screening in selected patients, or as a diagnostic tool after an abnormal screening mammogram. A planned American College of Radiology Imaging Network (ACRIN) trial will address this question. However, it is clear that it will be decades before we are able to determine if screening with DBT will provide reduction of mortality from breast cancer over and above that of routine mammographic screening.

Contrast-Enhanced Mammography

Breast MRI is the most sensitive technique for breast cancer imaging with sensitivities reported to be nearly 100%. The excellent sensitivity is due to its ability to detect abnormal blood flow in a breast cancer in addition to identifying the mass itself. MRI may show vascular enhancement in tumor vascularity even when no discrete mass can be identified: an entity termed nonmass enhancement. With the advent of digital mammography, it was hypothesized that the addition of intravenous contrast to digital mammography could potentially approximate this capability of MRI. Contrast-enhanced mammography would therefore combine physiology with anatomy.

Initial studies were performed using temporal subtraction technique and iodinated contrast material. Patients were injected following a baseline image while the breast was compressed and up to seven additional images were obtained after injection. Subtraction was performed yielding both kinetic curves and a contrast enhanced image. Although this technique was able to detect enhancement associated with breast carcinoma in most patients, there were technical limitations. Motion artifact due to long imaging times limited the quality of the images. Additionally only a single view of one breast could be imaged per injection.

An alternative solution utilizing dual-energy imaging was proposed. Hardware and software adaptations to a digital mammography unit automate the dual-energy technique. Approximately 3 minutes after the injection of iodinated contrast material a mammogram is performed. For each exposure, two images are obtained in each view: a low-energy image that is below the K-edge of iodine (33.2 keV) and a high-energy image that is just above. The two images are combined and processed so that the background breast tissue is subtracted out, maximizing the ability to see the iodine enhancement. The low-energy image is essentially a digital mammogram, although at the moment it cannot be used as such. This procedure was initially called dual-energy contrast-enhanced digital mammography (DE CEDM) and is now called contrast-enhanced spectral mammography (CESM). Using this technology, Dromain et al. compared contrast-enhanced mammography plus noncontrast mammography to mammography alone or to mammography with ultrasound in the evaluation of 142 lesions in a single breast in 120 patients. Sensitivity for contrast-enhanced mammography with mammography was 93% versus 78% for mammography alone ($p < .001$). Specificity was unchanged. There was a trend toward improvement in sensitivity and specificity when DE CEDM plus mammography was compared to ultrasound with mammography, but this did not reach statistical significance (11).

Jochelson et al. then evaluated the feasibility of performing bilateral contrast-enhanced mammography in 10 patients with known carcinoma using the same technique described above. Bilateral DE CEDM was easily accomplished and well tolerated. The order in which the images were obtained did not matter. The bilateral examination was completed within 8 to 10 minutes. While contrast enhancement in MRI washes out quickly, contrast enhancement with DE CEDM remained for up to 10 minutes after injection. It is presumed that this may be due to the use of a different type of contrast material. Radiation dose from this dual-energy technique is 20% more than a routine digital mammogram or the equivalent of one extra mammographic image.

Once feasibility was demonstrated, DE CEDM was compared to breast MRI and digital mammography for the ability to identify the primary tumor in 52 patients with untreated unilateral breast cancer. Contrast-enhanced mammography was also compared to MRI for its ability to stage the cancer within the breast. DE CEDM and breast MRI were equivalent in their ability to detect the index tumors: 50 per 52 (96%) and significantly better than mammography 42 per 52 (81%) at $p < .05$ (Fig. 14-2). The lesions detected by DE CEDM ranged from 4 to 67 mm, median 17 mm. The size of the lesions approximated pathologic size in all but two patients in whom DE CEDM overestimated the size of the lesions. The two cancers not seen on DE CEDM included a 2-cm infiltrating lobular carcinoma (ILC) and a 5-mm infiltrating ductal carcinoma with ductal carcinoma *in situ* (IDC and DCIS). The two lesions

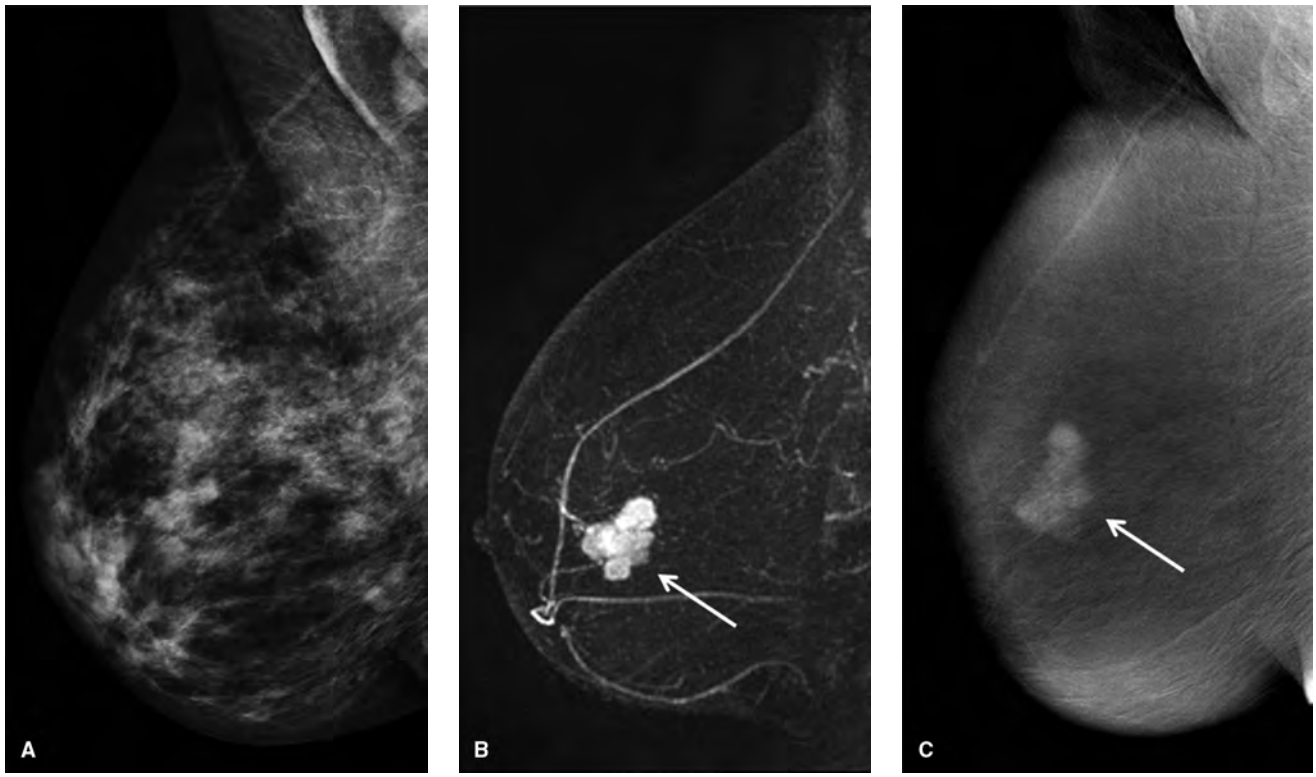

FIGURE 14-2 Contrast-enhanced mammography: 51-year-old woman with a palpable mass that was mammographically occult. Cancer detected on ultrasound. **(A)** Right MLO: negative mammogram. **(B)** Sagittal subtraction view from breast MRI demonstrates enhancing lobulated breast cancer *(arrow)*. **(C)** Contrast-enhanced mammogram; mediolateral oblique projection demonstrates lobulated breast cancer similar to MRI *(arrow)*.

occult on MRI, which were in patients whose cancers were detected on DE CEDM, included a 7-mm IDC/DCIS and an area of DCIS that measured 14 mm on DE CEDM. The only contralateral cancer was Paget's disease which was not evident on either DE CEDM or MRI, but was detected when the patient underwent a prophylactic contralateral mastectomy.

MRI surpassed DE CEDM in the ability to detect additional sites of malignancy. Sixteen patients had multifocal or multicentric cancers and MRI detected 15 per 16 (94%) while DE CEDM detected additional disease in 9 per 16 (56%). Twenty-five additional lesions were detected in these 16 patients. MRI detected 22 per 25(92%) and DE CEDM 14 per 25 (56%). The clinical impact of this difference in detection of additional lesions was seen in three patients who were originally thought to be candidates for breast conservation, but were demonstrated to have multicentric disease thus requiring mastectomy. The addition of DE CEDM or MRI to digital mammography conveyed a considerable advantage in the determination of which women required mastectomy.

One of the greatest limitations of MRI is its low specificity. DE CEDM was more specific than MRI in this series: 4% of patients undergoing DE CEDM had one false-positive finding while 25% of patients undergoing MRI had one false-positive finding. Two patients demonstrated false-positive lesions in the ipsilateral breast on DE CEDM, and biopsy of both of these lesions was also recommended on the corresponding MRI. On pathology, one was a radial scar and the other a fibroadenoma. No contralateral false-positive lesions were found on DE CEDM. There were 13 false-positive findings on MRI: 8 in the ipsilateral breast and 5 in the contralateral breast. Eight core biopsies and 8 additional surgical procedures were performed as a result of these false-positive findings on MRI. Biopsies yielded the following: 1 radial scar, 2 fibroadenomas, 2 papillary lesions, 3 cases of ADH, 1 ALH, and 4 cases of benign tissue. None of the high-grade lesions were upgraded at surgery.

An enhancing lesion seen on DE CEDM was significantly more likely to be malignant than one seen on MRI, with a positive predictive value for DE CEDM of 97% (64 per 66) and for MRI of 85% (72 per 85) ($p < .01$) (12).

Since the initial trials, improvements to the software, hardware, and filters of the CEDM unit have been made. It is now FDA approved and called contrast-enhanced spectral mammography (CESM) because there is the potential to use more than two energies. With these changes, there is less time needed between exposures enabling a shorter examination time and less chance for motion. The processing mechanism has also been improved yielding better images. It remains to be seen if the improved technique will improve accuracy. At this time the ability of CESM to detect cancers in a pure screening setting has not been tested, but that study is underway.

Contrast-Enhanced Digital Breast Tomosynthesis

The natural next step from the latter two technologies is to combine them. Chen et al. performed a pilot study involving 13 patients with BI-RADS 4 or 5 lesions using tomosynthesis performed in the MLO projection and temporal subtraction technique (13). Ten of 11 cancers were detected. Neither of the two benign lesions enhanced. More recently, Carton et al. (14)

performed both temporal subtraction and dual-energy contrast enhancement with DBT on a single breast with a known cancer. The cancer was identified with both contrast techniques and was found to correlate with MRI images in that same patient. Not surprisingly there was less motion artifact when using dual-energy technique when compared to temporal subtraction. Dual energy also allowed for both breasts to be imaged. As this chapter is being written there is ongoing development of this promising technology.

ULTRASOUND

Targeted breast ultrasound is a standard method of evaluating mammographic and clinical breast abnormalities. It is used to characterize a mass seen on mammography as cystic or solid and may distinguish malignant from benign features. Ultrasound is also used to investigate a mammographically occult palpable mass and to guide core biopsies.

Screening ultrasound has gained increasing popularity as an adjunct to screening mammography, particularly in women at increased risk for breast cancer. It is a method of cancer detection that is predominantly anatomic. Ultrasound is relatively inexpensive and widely available. There is no radiation exposure. Since ultrasound is operator dependent, reproducibility is suboptimal.

ACRIN trial 6666 evaluated the performance of screening breast ultrasound in addition to mammography in over 6,000 women who had dense breast tissue in at least one quadrant of the breast and at least one other risk factor. Interpretation was blinded to mammographic findings. There were 4.2 mammographically occult cancers detected per 1,000 women. These were primarily invasive cancers. Ultrasound was not shown to be useful for the detection of DCIS or microcalcifications. In this study, biopsy was recommended in 9% of the women and short-term follow-up was recommended in another 9%. PPV was only 9% (15).

In the last few years many states have passed legislation requiring patients to be directly informed that they have dense breasts with an associated increased risk for breast cancer. Additional imaging will likely be suggested or desired by the patient and currently this has primarily been screening ultrasound. The first state to enforce this legislation was Connecticut. Weigert et al. have reported the first data regarding the use of screening ultrasound in women with dense breast tissue and no other risk factors. In this retrospective study of six practices there were 72,030 mammograms and 8,647 screening ultrasounds. Twenty-eight cancers were diagnosed with an additional cancer detection rate of 3.25 per 1,000. PPV was only 6.7%, 9% of patients were called BI-RADS 3 requiring 6-month follow-up. 5% were BI-RADS 4 or 5. In their population the average cost of a breast ultrasound was $250 for which average insurance reimbursement was $72. Professional fee was $85 and reimbursement was $30. Ultrasound core biopsies were $2,400. Using these numbers the cost per breast cancer found was $110,241 (16).

Automated Whole Breast Ultrasound (AWBU)

AWBU is a technique developed to decrease the operator dependency of handheld ultrasound and thereby improve reproducibility. The device is placed over the breast and static images are obtained in a standard fashion which also allows 3-D reconstruction. The static images do not need to be interpreted in real time. This may improve efficiency, but patients will need to be called back if there are findings requiring additional evaluation. Kelly et al. reported their experience with the performance of AWBU with mammography in 6,425 studies in women with dense breasts. They demonstrated an improvement in cancer detection from 3.6 per 1,000 with mammography alone to 7.2 per 1,000 by the addition of AWBU. In their hands the PPV of AWBU was 38.4% versus 39% for mammography. Twenty-one cancers less than 10 mm were detected by ultrasound versus 7 by mammography (17). Shin et al. evaluated 55 patients with 121 lesions detected with handheld ultrasound. An additional 36 lesions were detected with AWBU. Lesion detection rate increased with size. It was 92% when mean lesion diameter was greater than 1.2 cm. Their false-positive detection rate was 6% (18). Should these data be confirmed in larger studies, this technology could potentially provide improved screening results with a more efficient method of imaging.

Elastography

Differentiation of benign and malignant ultrasound masses is based on mass and margin characterization. Malignant appearing masses have irregular margins, microlobulation, posterior shadowing, and a heterogeneous echo pattern. They are classically taller than wide or have a round shape. Vascularity is increased. Despite these seemingly adequate criteria, specificity remains a major limitation. Another characteristic of breast cancer that may potentially improve lesion characterization is that cancers are generally harder or stiffer than the surrounding breast tissue. Elastography is a technique that can be used to better differentiate benign from malignant masses using this attribute. There are two different types of elastography: static and shear strain.

Static or compressive elastography uses manual compression to detect tissue "hardness." The operator compresses the breast and a color map that reflects tissue hardness is generated. Fluid-filled lesions have a trilaminar appearance, benign or soft tumors are green, and malignant tumors are blue and may appear larger than their size on the B-mode scan itself. However, the accuracy depends on the degree of compression, rendering this an operator-dependent technique. Chang et al. performed a prospective study of 312 breast masses: 245 benign and 67 malignant. Fifty percent of the static exams were either technically inadequate or low quality. Multivariate analysis revealed that breast thickness in the location of the target lesion was the most important factor that affected quality. The ability to differentiate benign from malignant lesions differed significantly (p = .015) between high-quality exams (87%) and lower-quality exams (56.8%) (19). Yi et al. compared B-mode ultrasound to elastography in 1,786 women. They showed that B mode was more sensitive (98.5% vs. 93.2%) and elastography more specific (42.6% vs. 16.3%) (20). Cho et al. combined elastography with Doppler, improving the area under the receiver operating characteristic (ROC) curve from 0.771 to 0.844. When both tests were negative, the specificity of the ultrasound exam improved from 25% to 34% (p < .001). They concluded that an anatomically low suspicion mass with a negative elastogram and Doppler interrogation could be called probably benign and undergo 6-month follow-up rather than biopsy (21).

Shear-wave elastography is less operator dependent and more reproducible. It is also quantitative. It works by measuring the propagation of the speed of the sound waves which is directly related to tissue stiffness. Chang et al. studied 158 consecutive women with this technique and demonstrated that mean elasticity values were significantly higher in malignant masses than in benign masses (p < .0001) (22). Berg et al. performed a multinational trial evaluating 939 breast masses, 289 of which were malignant. Median mass size was 12 mm and 837 of the masses were greater than or equal to BI-RADS 3. By using the visual color generated by the stiffness

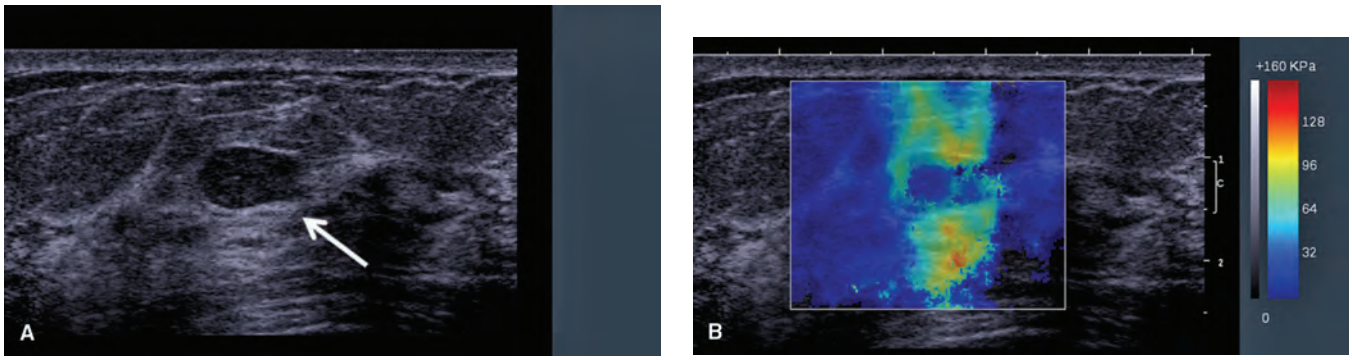

FIGURE 14-3 Shear-wave elastography: 53-year-old woman. **(A)** Predominantly circumscribed mass on standard B-mode ultrasound *(arrow)* originally called probably benign BI-RADS 3. **(B)** Surrounding tissue was shown to be stiff on shear-wave elastography. Therefore, biopsy was performed. Pathology revealed grade 1 infiltrating ductal carcinoma with ductal carcinoma *in situ*. (Courtesy of Dr. Christophe Tourasse via Dr. Wendie Berg.)

measurement to upgrade BI-RADS 3 and using lack of stiffness to downgrade BI-RADS 4a masses, specificity improved from 61.1% to 78.5% ($p < .001$). Area under the curve improved from 0.950 to 0.962 ($p = .005$) (23) (Fig. 14-3).

Contrast-Enhanced Ultrasound (CEUS)

Evaluation of tumor angiogenesis with ultrasound has primarily been performed with Doppler flow imaging. However, specificity remains suboptimal due to demonstration of vascularity within benign tumors. Gas microbubbles within lipid microspheres have been injected in an attempt to improve sensitivity and specificity of ultrasound. The microbubbles oscillate and emit signals that can be detected by the ultrasound probe. This type of contrast is different from iodinated contrast in that the microbubbles do not diffuse from the blood vessels into surrounding tissues. Newer ultrasound imaging techniques have been developed to better image these microbubbles. These include intermittent power Doppler and pulse inversion harmonic imaging. Early studies have shown improved sensitivity of up to 100% using this technique, but with specificities of 5.6% to 100%. Limitation of specificity is likely due to increase in the detection of small, nonmalignant vessels.

Liu et al. have recently reported results in 104 patients with known breast masses in whom the results of contrast-enhanced ultrasound (CEUS) correlated with histologic features (24). Possible applications include the follow-up of patients after neoadjuvant chemotherapy or as a method to deliver drugs directly to a tumor site.

While potentially very exciting, the use of microbubbles is currently limited due to the technical difficulty involved in performing this procedure.

BREAST MRI

Breast MRI is among the most commonly used breast imaging modalities. With regard to sensitivity, it is the examination against which all other breast imaging exams are compared. There is no radiation exposure. Images are obtained prior to and at several time points after infusion of a gadolinium chelate contrast material (except when evaluating implants). Subtraction images are produced and kinetic information is generated. Technology has continued to evolve with magnet field strength increasing from 1.5T (tesla) to 3T for current routine use. Exploration of the utility of a 7T magnet has begun as well.

A full discussion of MRI can be found elsewhere in this book. There are a few new concepts and techniques that bear mentioning.

MRI Screening

It is well known that breast MRI is more sensitive for the detection of breast cancer in women at increased risk for breast cancer than clinical breast exam, mammography, and ultrasound combined. However, its use is limited by cost and availability. Cost is high due in part to contrast material, length of time for examination, and interpretation. Studies are being performed to determine if the time involved in scanning and interpreting breast MRI can be decreased. Kuhl et al. prospectively read 932 breast MRIs for screening or assessment. Interpreting the first postcontrast subtraction views took 58 seconds to read with a sensitivity of 98.7% and specificity of 92.9%. Interpretation of the subtraction MIP took 2 seconds to read. Sensitivity was 88.6% and specificity 85.7% (25). Mango et al. evaluated the sensitivity and timing of interpretation of three postcontrast MRI sequences in 100 women with known breast carcinoma by two readers. When interpreted with no history or prior examinations, one reader detected 98% of the cancers on the first postcontrast images and first postcontrast subtraction images while the second reader detected 95% and 93%. Sensitivity for the subtraction MIP was 96% and 84% for these two readers. Results improved to 100% detection with history and prior examinations. The time to perform these limited sequences is approximately 15 minutes, reduced from the full protocol which takes 30 to 40 minutes. Interpretation time was 0.5 to 3 minutes (mean 56 seconds) (26). This is a promising area of exploration, although a great deal more work needs to be done.

Diffusion-Weighted Imaging (DWI)

While the sensitivity of MRI is exquisite, reportedly close to 100%, specificity is moderate—in the 70% range. Improvements in specificity have occurred in part with the adoption of BI-RADS for MRI which is a combination of both morphologic and kinetic features as well as the use of standardized descriptors. Morphologic criteria include mass shape and margin characteristics. Lesions with irregular, microlobulated, or spiculated margins are more likely to be malignant. Rim enhancement also suggests malignancy. Segmental or ductal distribution of nonmass enhancement also increases the likelihood of malignancy. Kinetic characteristics assess

the rapidity of initial enhancement and the changes in enhancement afterwards. Rapid initial enhancement followed by washout of contrast is more highly suggestive of carcinoma compared to a plateau or continual increase in enhancement.

Despite the use of these criteria, there remains a need for improved specificity. Diffusion-weighted imaging (DWI) has been evaluated in this regard. DWI is a sequence that is available on most MRI scanners. However, results are felt to be better with greater field strength. Imaging time is short and importantly, no contrast is required. DWI has been used successfully in many other organs including the brain. It is a pulse sequence that essentially measures the random motion of water molecules within a lesion. Motion is affected by cellularity and extracellular characteristics such as viscosity, membrane permeability, and blood flow. In addition to the DWI, diffusion can be quantified by apparent diffusion coefficient (ADC) characteristics. An ADC map can be generated, although accurate mapping can be technically challenging. This is particularly true in smaller lesions.

The ADC value is inversely proportional to cellularity, edema, viscosity, and the presence of extensive fibrosis which all restrict the movement of water molecules. Since most cancers are cellular (with the exception of the rare mucinous cancers), they classically have lower ADC values. Kul et al. investigated the contribution of DWI added to dynamic contrast-enhanced MRI in 84 patients with 47 breast cancers. They demonstrated an improvement in specificity of breast MRI from 75.7% to 89.2% (p = .063) when adding DWI (27). Ei Khouli et al. showed improved characterization of breast lesions using ADC normalization by using glandular tissue rather than an absolute ADC value. They demonstrated an improvement in the area under the receiver operating curve from 0.89 to 0.98 and a decrease in the false-positive rate of MRI from 36% to 24% in 93 patients (28) (Fig. 14-4).

Investigators are attempting to further characterize the meaning of ADC values. Martincich et al. showed that ADC values varied among different breast biomarkers. They demonstrated that patients with more aggressive subtypes of breast cancer had lower ADC values. They proposed that this could be due to the more aggressive tumors having increased mitotic activity and therefore cellularity which would decrease ADC values (29). In a similar vein, Parsian et al. evaluated ADC values of benign and high-risk lesions in 165 women. They demonstrated that high-risk lesions were more likely to have a lower ADC value while other lesions such as many fibroadenomas, fibrosis, usual ductal hyperplasia, and inflammation had higher values (30). If this study is validated with larger patient populations, DWI could be used in conjunction with contrast-enhanced MRI to differentiate which benign-appearing lesions require biopsy.

Data suggest that DWI may also improve the ability to assess treatment response in patients undergoing neoadjuvant chemotherapy. However, limitation in accuracy of DWI with smaller tumors and current technical complexity in obtaining accurate mapping limit its widespread application at this time. Therefore use of this sequence remains primarily investigational. An ACRIN trial has been designed to further assess the utility of DWI for breast imaging.

MR Spectroscopy

Another MRI tool with the potential to improve specificity is MR spectroscopy (MRS). This is a technique of molecular breast imaging that is currently a measurement of the total composite choline (tCho) within a breast lesion detected on MRI. This function is based on the fact that choline is a precursor of phosphatidylcholine which composes cell membranes and increases with tumor growth. It has been well established that choline peaks can be detected in most breast cancers and generally not in normal breast tissue. This knowledge can potentially be used to improve the positive predictive value of breast MRI. There is, however, some overlap in choline values between benign and malignant tumors. Using primarily 1.5T MRI units sensitivities of 70% to 100% and specificities of 67% to 100% have been reported. Recently, Mizukoshi et al. have shown that using quantitative MRS provides higher specificity than qualitative MRS when differentiating benign from malignant breast tumors. In their evaluation of 208 breast lesions (169 malignant and 39 benign), sensitivity decreased from 84.6% to 68.1% while specificity increased from 51.3% to 79.4% using the quantitative measurements (31).

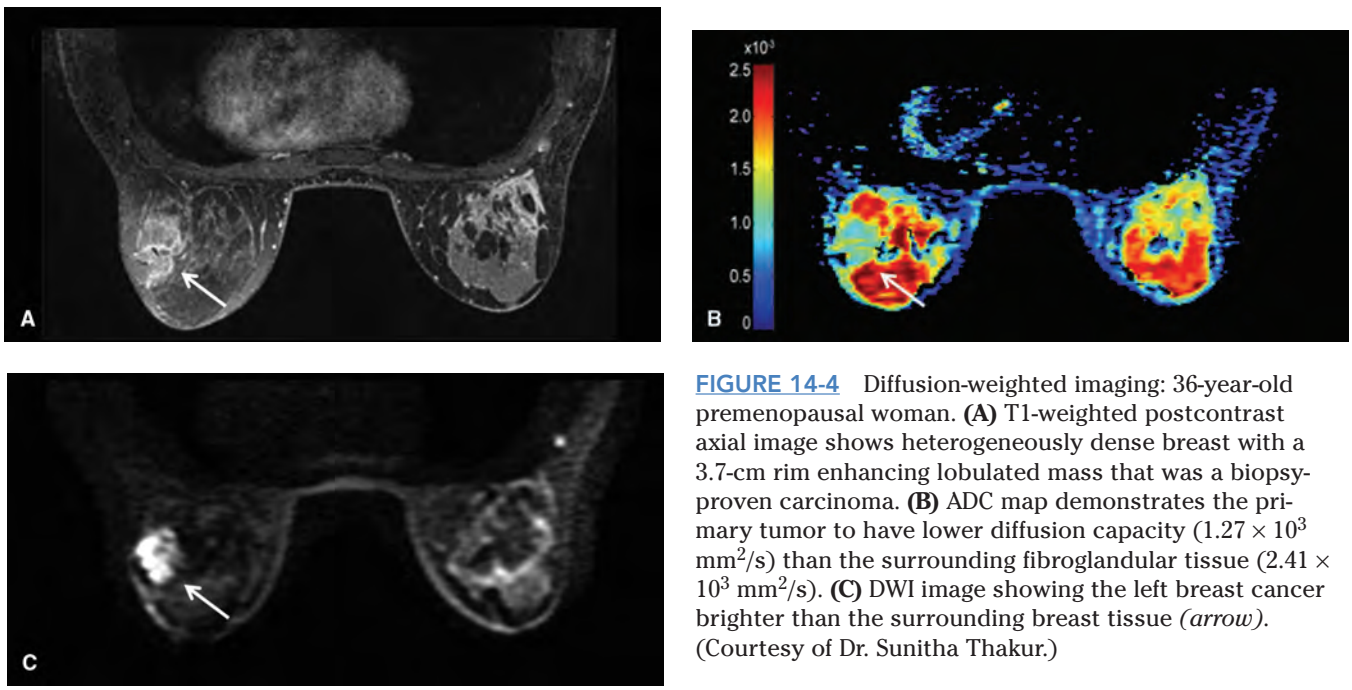

FIGURE 14-4 Diffusion-weighted imaging: 36-year-old premenopausal woman. **(A)** T1-weighted postcontrast axial image shows heterogeneously dense breast with a 3.7-cm rim enhancing lobulated mass that was a biopsy-proven carcinoma. **(B)** ADC map demonstrates the primary tumor to have lower diffusion capacity (1.27×10^3 mm^2/s) than the surrounding fibroglandular tissue (2.41×10^3 mm^2/s). **(C)** DWI image showing the left breast cancer brighter than the surrounding breast tissue *(arrow)*. (Courtesy of Dr. Sunitha Thakur.)

Tozaki et al. demonstrated that choline levels correlated with standardized uptake values obtained with PET/CT. They also found that both results correlated significantly with nuclear grade, estrogen receptor negativity and triple-negative lesions (32).

As intellectually promising as MRS seems, there are limitations precluding routine use. In order to measure tCho, it is necessary to place a volume of interest in the region of the suspected cancer seen on MRI. Lipid signals from the surrounding adipose tissue may contaminate this measurement and precise placement requires the breast imager to be available to determine the area to be measured at the time of scanning which can hamper use in a busy clinical setting. The possibility of automating this process is under consideration. Measurements in lesions under a centimeter are likely to be inaccurate limiting use in both the diagnostic setting as well as the evaluation of residual disease after treatment.

Wijnen et al. have reported quantification of levels of phosphorylated metabolites rather than tCho using a 7T magnet. They have shown that there is less likely to be contamination from surrounding tissues using this technique with the different metabolites which would therefore not require such precise identification of the area to be measured. Thus, smaller lesions could theoretically be measured as well (33). In conclusion, MRS is currently primarily a research tool. A great deal more investigation is required to make this a viable routine clinical adjunct to breast MRI.

RADIONUCLIDE BREAST IMAGING

Radionuclide breast imaging is a method of detecting breast abnormalities that is independent of breast density and images physiology over anatomy. There are currently two tracers commonly used: sestamibi (MIBI) and 18F-fluorodeoxyglucose (18F-FDG).

MIBI or Gamma Imaging

In the early 1990s incidental breast and other cancers were occasionally detected during cardiac imaging with technetium-99m-sestamibi (MIBI). Attempts at dedicated imaging of the breasts with MIBI at that time were limited by the large collimators that were distant from the breasts. Sensitivity was excellent (greater than 90%) for large lesions but abysmal for small lesions. Thus MIBI imaging of the breast was stalled until new technological advances enabled high-quality dedicated breast imaging to be performed. There are two different systems using high-resolution detectors: molecular breast imaging (MBI) using a semiconductor base and breast-specific gamma imaging (BSGI) which uses a scintillating crystal detector. There does not appear to be a significant clinical difference between the two technologies. Both may detect cancers occult on mammography and both may detect additional cancers within the breast once cancer is diagnosed (Fig. 14-5). With both techniques the breasts are positioned as with mammography using mild breast compression.

Although MIBI imaging is independent of breast density, it is dependent on the patient's hormone status. Therefore it is ideal to image premenopausal women between days 2 and 14 of their cycles. The patient receives between 740 and 1,110 MBq of tracer. Imaging begins 10 minutes after tracer administration. Each of the four routine images requires 5 to 10 minutes of imaging and if axillary views are necessary an additional 10 to 20 minutes are needed.

The group at the Mayo Clinic has reported on its use of a dedicated semiconductor-based gamma camera system: molecular breast imaging (MBI). The detector is made of cadmium zinc telluride elements (CZT). Initially a single gamma camera was used but Mayo now uses a dual-head system. Sensitivity for breast cancer detection improved from 85% overall and 29% for tumors 5 mm or less to 91% overall and 69% for tumors 5 mm or less (34) in 150 women prior to their breast biopsies (34). Rhodes et al. screened 936 women with dense breast tissue and at least one other risk factor with both mammography and MBI. There were 11 cancers. Yield of mammography was 3.2 per 1,000, yield of MIBI imaging was 9.6 per 1,000, and combining both technologies had a detection rate of 10.7 cancers per 1,000 women (35).

Breast-specific gamma imaging (BSGI) is the other modality employed for MIBI imaging. This uses a scintillating crystal detector with a single camera. Initial work performed by Brem et al. showed a sensitivity of 96.4% overall but slightly less for lesions less than 1 cm, 88.9%. Specificity was only 59.5% (36). Multiple other studies also reported sensitivities of approximately 90% and specificities of approximately 60%. In a BSGI multicenter registry that included 1,042 patients, Weigert et al. reported a sensitivity of 91% and a specificity of 77%. However, in this report high-risk lesions such as atypical ductal hyperplasia, lobular carcinoma *in situ*, radial scars, and papillomas were classified as true positives, not false positives, as they are in other breast imaging studies. This is likely to account for the improved specificity (37).

Indications for performing MIBI imaging have included high-risk screening, evaluation of extent of disease in known breast cancers, problem solving, and imaging patients for whom MRI is recommended but can't be done. However, it is important to note that at the dose of tracer currently in use, while patients receive only 2 mGy to the breast (compared to 3.91 from a digital mammogram), they receive 8.9 to 9.4 mSv as a whole body effective dose (compared with 0.47 mSv from a digital mammogram) and in particular 50 mGy to the lower large intestine. These high extramammary doses should obviate repeated use of this technology for an individual patient (i.e., use as a yearly screening tool). Preliminary studies suggest possible equivalency at a reduced dose, but even at half the dose the radiation exposure is considerable.

Positron Emission Mammography (PEM)

Whole body PET/CT using 18F-fluorodeoxyglucose (18F-FDG) is widely used for staging and follow up of lymphomas and multiple solid tumors including breast carcinoma. Investigations of its ability to detect the primary breast cancers were disappointing with sensitivity as low as 30%, even though most breast cancers are FDG avid. As with MIBI imaging, this was due to the distance of the collimators from the breasts. PEM was developed to better image the breast with FDG. As with MIBI imaging, PEM involves positioning patients in the same manner as with mammography. The breasts are gently compressed between two collimators and the detectors have high (1.5 to 2.0 mm) spatial resolution. The results of PEM imaging are independent of breast density and hormone status.

Preparation for PEM is similar to whole body PET scans. Patients fast for 4 to 6 hours prior to injection of approximately 10 mCi (403.3 MBq) of 18F-FDG. They rest for 1 hour after which imaging is performed with 10-minute acquisitions per view. Tomographic slices are provided with 12 images for each view of the breast providing a three-dimensional set of images. PEM can also be performed after a single FDG dose following a whole body examination and there are data to suggest that the longer period of time after injection may actually improve specificity. Unfortunately, PEM following whole body imaging is not reimbursed as a separate study.

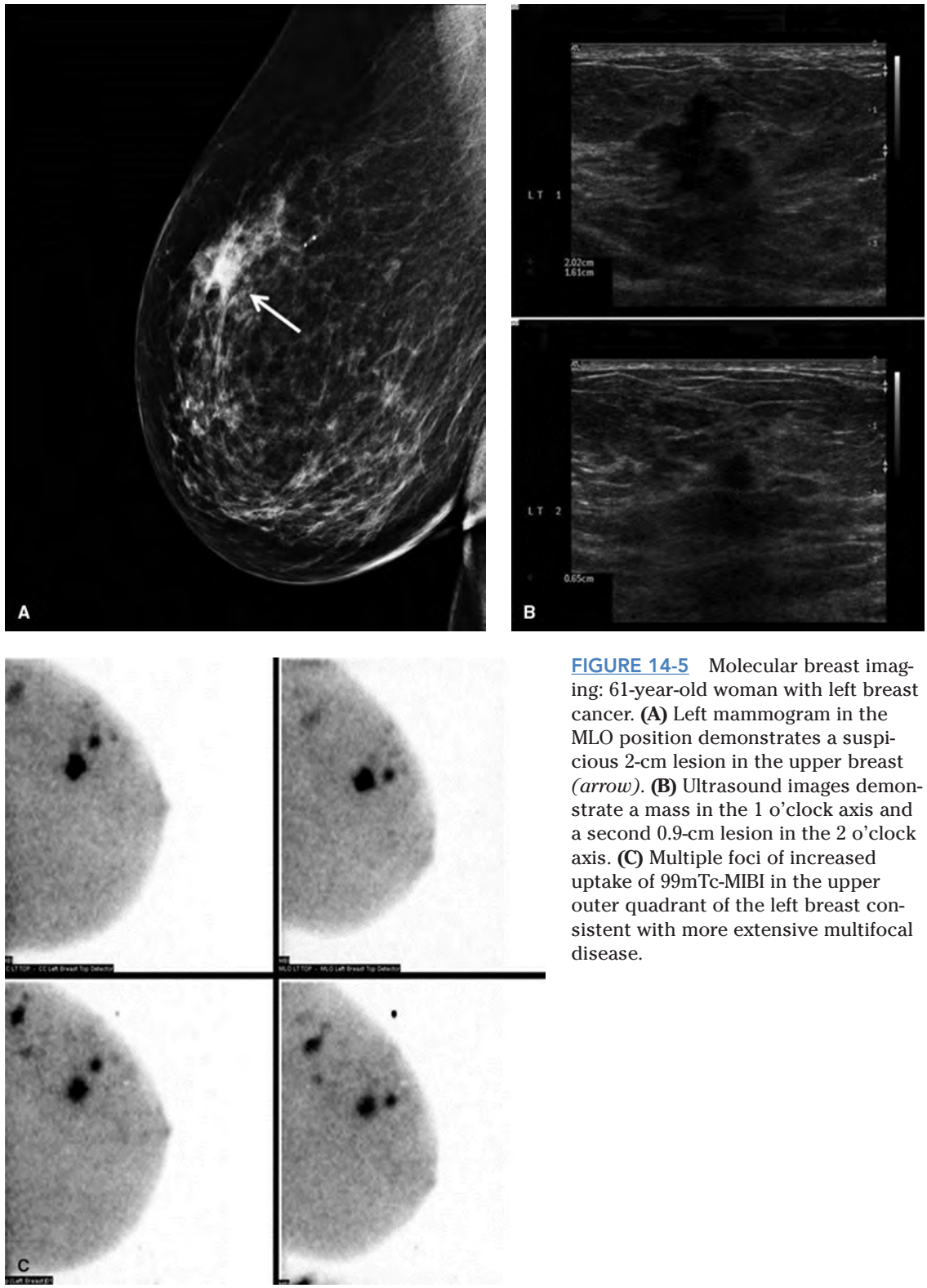

FIGURE 14-5 Molecular breast imaging: 61-year-old woman with left breast cancer. **(A)** Left mammogram in the MLO position demonstrates a suspicious 2-cm lesion in the upper breast *(arrow)*. **(B)** Ultrasound images demonstrate a mass in the 1 o'clock axis and a second 0.9-cm lesion in the 2 o'clock axis. **(C)** Multiple foci of increased uptake of 99mTc-MIBI in the upper outer quadrant of the left breast consistent with more extensive multifocal disease.

PEM differs from whole body evaluation in that there is no correlative CT to provide attenuation correlation or anatomic correlation. Therefore the units of uptake for PEM are not standard uptake value (SUV). The unit used for PEM is the PEM uptake value or PUV, which measures uptake in a lesion against the background of the breast itself.

Schilling et al. have reported PEM to have a sensitivity of 90% for the detection of DCIS and 93% for invasive cancers, even for small lesions (38). Berg et al. reported their experience comparing PEM to MRI in staging the breast in 388 patients with recently diagnosed breast cancer. They demonstrated that the two modalities had comparable breast level sensitivity while MRI was more sensitive at the

lesion level. However, PEM was more specific at both the patient and lesion levels. The positive predictive value of PEM was 66%, which was significantly better than that of MRI, which was 53% (p = .016) (39). In a group of 367 patients with known breast cancer, PEM was less sensitive in detecting cancers in the contralateral breast. Fifteen (4.1%) patients were found to have contralateral breast cancer. PEM diagnosed 3 of 15 (20%) prospectively. Uptake in three other cancers had been called benign and two other cancers were visible retrospectively. On a blinded retrospective review 11 of 15 (73%) were called suspicious (40).

Whenever a new technique is developed that can detect a breast cancer not seen on any other breast imaging test, a mechanism for biopsy is critical to document that the abnormality is actually cancer. PEM was the first of the radionuclide imaging modalities to develop a technique for breast biopsy. The technique is performed with the patient seated, but is otherwise similar to the method employed with stereotactic and MRI guided biopsies: in this case the lesion is targeted and guided by FDG uptake. Once the samples are obtained, they can be placed under the detector to confirm adequate sampling of the hypermetabolic lesion.

Although PEM appears to be a sensitive and specific modality for detection of cancer(s) within the breast, its use must also be limited due to radiation dose. Just as with MIBI dose to the breast is low: 2.5 mGy. However, at current tracer doses whole body dose is 6.2 to 7.1 mSv with 59 mGy to the bladder wall. Manufacturers are evaluating whether adequate results can be obtained using lower tracer doses, but even so regular use of this technology as for yearly screening is not warranted. Other uses for radionuclide breast imaging might include follow-up after neoadjuvant treatment using either FDG or other tracers, staging the breast once a diagnosis of cancer has been made or for problem solving when other clinical and or imaging parameters are indeterminate.

Breast CT

Dedicated computerized tomography (CT) of the breast is another tool developed to evaluate breast tissue without the interference of overlying structures; in principal similar to tomosynthesis. The patient lies prone on the scanning table. One breast is scanned at a time. No breast compression is used. The scan field of view is approximately 21 cm, which is large enough to accommodate most breasts. Since there is no breast compression, patients find breast CT more comfortable than mammography. Scans of each breast take approximately 17 seconds.

O'Connell et al. evaluated a cone-beam CT system to evaluate dose, breast coverage, and image quality compared with conventional mammography. They demonstrated overall equivalent radiation doses ranging from 4 to 12.8 mGy, mean 8.2, compared with mammography 2.2 to 15mGy with a mean of 6.5. Breast coverage was superior with CT except in the axilla and axillary tail. Overall detection of masses and calcifications was similar (41).

Adding physiology to this otherwise purely anatomic technique, Prionas et al. evaluated the performance of breast CT after administration of nonionic iodinated intravenous contrast material. Fifty-four lesions (25 benign and 29 malignant) in 46 patients were analyzed. Not surprisingly, malignant masses were significantly better seen after contrast enhancement than on nonenhanced CT and mammography. Previous studies showed inferior detection of calcifications on nonenhanced CT when compared with mammography. In this study, malignancies presenting as microcalcifications were significantly better seen on contrast-enhanced CT than on non-contrast-enhanced CT but not better than on mammography, while benign calcifications remained better detectable on mammography than on CT either enhanced or nonenhanced (42).

CT of the breast is a potentially promising technology that is better tolerated by patients due to lack of compression and shows equivalent radiation exposure as mammography. More work is required to improve the spatial resolution necessary to detect smaller lesions and microcalcifications.

Optical Imaging of the Breast

Optical imaging is a primarily physiologic method of evaluating the breast that utilizes near infrared light to detect breast lesions based on determination of differential light absorptions of tissue hemoglobin and oxygen saturation. Malignant tumors develop neovascularity and therefore have increased concentration of hemoglobin which is detected with optical scanning. The hemoglobin concentration correlates well with mean vessel density (MVD). Despite the increased vascularity, however, there is decreased oxygen saturation also theoretically detectible by diffusion imaging. The scanner has poor spatial resolution and is unable to penetrate into deeper breast tissues at this time. Therefore, while a few small studies show tumor detection rates of up to 90%, optical imaging cannot currently be used as a stand-alone examination.

Investigators have evaluated using optical imaging to supplement other imaging tests such as ultrasound and breast MRI for both diagnosing breast cancer and evaluation of response to treatment. Moon and colleagues performed a prospective study combining optical diffusion breast imaging with ultrasound in 193 women with 217 breast lesions. The group was evenly divided between benign and malignant lesions. Ultrasound alone showed 100% sensitivity, 27.5% specificity, PPV of 57.8%, and NPV of 100% in distinguishing benign from malignant lesions. With the supplemental use of optical imaging, sensitivity was 98%, specificity 41.3%, PPV 62.4%, and NPV 95.7%. The investigators found that utilization of the hemoglobin level was superior to utilization of oxygen saturation. When evaluating patients with a BI-RADS 4A, the addition of optical imaging improved specificity from 27.5% to 76.1% (43).

Early data have shown that using optical imaging as a surrogate biomarker can predict for pathologic complete response in women receiving neoadjuvant chemotherapy for locally advanced breast cancer since it measures hemoglobin/MVD within the tumors: CD-105 is a glycoprotein expressed on the surface of highly proliferating endothelial cells that is not detected in normal breast tissue. Pakalniskis et al. demonstrated that there was a significant correlation between the MVD of pretreatment biopsy CD-105 expressing vessels and pretreatment hemoglobin levels in women achieving pathologic complete response, not those with a partial response. There was also a significant difference in the MVD of CD-105 expressing vessels and mean levels of hemoglobin after treatment in patients achieving a complete pathologic response (44).

The use of optical imaging has also been investigated during surgery, but again results are premature. It is a technology with early promise particularly if used as an adjunct with other imaging modalities, but at the moment requires validation of early results before it can be brought into routine use. A comparison of this and the various technologies discussed above is provided in Table 14-1.

In conclusion, I have described an array of promising breast imaging modalities that are currently to be considered primarily as adjuncts to the three standard breast imaging tools: mammography, ultrasound, and MRI. These modalities are in varying stages of development. It is not feasible to perform every test on every patient, and rigorous scientific

TABLE 14-1

New Imaging Techniques: Characteristics and Potential Benefits

Technique	*Characteristics*	*Potential Benefits*
Mammography		
Tomosynthesis	Thin slices peel away overlying tissue.	Improved lesion conspicuity and margin analysis; decreased callbacks.
Contrast mammo	Neovascularity can be visualized by contrast enhancement.	Can visualize mammographically occult cancers even without discrete mass; improved sensitivity.
Contrast tomo	Combines tomosynthesis with contrast.	Improved analysis of characteristics of enhancing lesions.
Ultrasound		
Automated US	Machine performs static images with 3-D reconstruction.	Not operator dependent; improved reproducibility; no need to interpret in real time.
Elastography	Differentiates lesions based on their hardness or stiffness.	Improved specificity of ultrasound; decreased biopsies.
Contrast US	Gas microbubbles with neovascularity can be detected by ultrasound probe.	Improved sensitivity; ability to assess response to chemotherapy; potential mechanism for drug delivery.
MRI		
Diffusion weighted	Can quantify random motion of water molecules within a lesion.	Improved specificity when evaluating breast lesions.
Spectroscopy	Measures total composite choline within breast lesions.	Improved specificity of MRI.
Radionuclide Imaging		
BSGI/MBI	Tumors are detected by uptake of sesta-MIBI.	Sensitive method to detect cancer limited by whole body radiation exposure.
PEM	Tumor detection is related to uptake of FDG.	Sensitive and specific method of breast cancer detection limited by whole body radiation exposure.
Other		
Breast CT	Can evaluate tissue without overlying structures; no breast compression; IV contrast improves sensitivity.	Sensitive and more tolerable method to evaluate for breast cancer.
Optical imaging	Near infrared light is used to detect breast lesions based on tissue hemoglobin and oxygen saturation related to neovascularity.	Used as adjunct to ultrasound or MRI to improve specificity; may aid in assessment of response to therapy.

principals must be applied to determine which of these will be the most useful in each clinical situation (screening, diagnosis, staging, response to treatment, and follow-up) while also trying to limit costs, unnecessary biopsies, and radiation dose. Perhaps with greater knowledge of tumor biology and genetics, we will be able to tailor our approach to the use of specific tests for specific biologic situations.

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CHAPTER 15

Image-Guided Biopsy of Nonpalpable Breast Lesions

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CHAPTER CONTENTS

IMAGE-GUIDED BIOPSY OF NONPALPABLE BREAST LESIONS

The increasing use of mammography, ultrasound, and breast MRI to screen asymptomatic women has resulted in the increased detection of clinically occult, nonpalpable breast lesions. Despite technological advances and improvements in image resolution, the imaging features of most breast lesions remain indeterminate, requiring tissue sampling for definitive diagnosis. Initially, surgical excision following image-guided needle localization was the gold standard for biopsy. However, because up to 70% to 80% of lesions for which biopsy is recommended represent benign etiologies, newer cost effective methods were investigated as alternatives to surgical biopsy (1).

Nonpalpable breast abnormalities were initially sampled using fine-needle aspiration (FNA). FNA is a fast, relatively inexpensive technique that patients tolerate well. However, significant limitations of FNA include the frequency of insufficient sampling, frequency of false positives, and limited accuracy compared to core biopsy or surgical excision. In the multicenter randomized Radiology Diagnosis Oncology Group V trial, there was a 35% insufficient sample rate with FNA of nonpalpable breast lesions, and the accuracy rate for ultrasound-guided FNA was 77% compared to 98% with ultrasound-guided core biopsy (2,3). In addition, distinguishing between *in situ* or invasive carcinoma and determining receptor status may be difficult on cytology from FNA. For these reasons, FNA is primarily used to sample axillary nodes or lesions not amenable to core biopsy, including lesions that are superficial or abutting the chest wall.

Simple and complicated cysts are benign and do not require aspiration except when requested for symptomatic relief. In general, the fluid should be discarded due to the frequency of false positives unless the aspirate is not typical of cyst contents. Ciatto et al. examined the cytology following aspiration of 6,782 consecutive cysts and found that the 5 papillomas detected in this series all had bloody aspirates. Therefore, the fluid from a cyst aspiration is typically discarded and cytology obtained only with bloody aspirate (4). In cases when the ultrasound findings cannot distinguish between a complicated cyst versus a solid mass, initial aspiration is recommended for those masses that would require biopsy if solid (i.e., new or enlarging). Complete resolution with aspiration confirms that the lesion in question represented a complicated cyst. If a suspected cyst does not completely resolve with aspiration, the fluid should be discarded and the procedure converted to a core biopsy due to its increased accuracy.

In the late 1980s and 1990s, automated large core needle biopsy using stereotactic or ultrasound guidance was demonstrated to be an accurate method to sample imaging-detected abnormalities with comparable results to surgical biopsies and decreased costs and patient morbidity (1). Stereotactic biopsy is most commonly used to sample mammographic microcalcifications. Less frequently, stereotactic biopsy is performed to sample a mammographic mass, asymmetry, or area of architectural distortion with no sonographic correlate. However, stereotactic biopsy of noncalcified lesions should be performed only after a thorough high-quality breast ultrasound has been performed, as these may be more difficult to target using stereotactic guidance. A focused ultrasound should also be performed if mammographic calcifications are associated with a mass or increased density as targeting the associated soft tissue density has a higher likelihood of diagnosing an invasive component (Fig. 15-1). Percutaneous biopsy using ultrasound guidance is the preferable method for sampling any lesion that is evident sonographically.

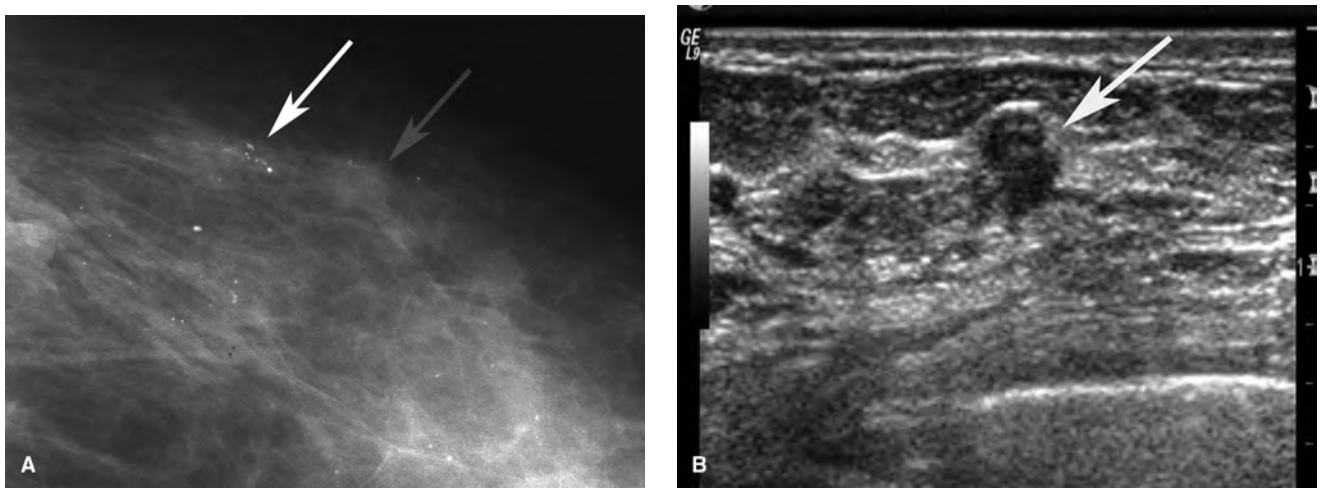

FIGURE 15-1 Ultrasound-guided biopsy of an invasive ductal carcinoma. **(A)** Mammogram demonstrates calcifications (*white arrow*) and adjacent soft tissue mass (*grey arrow*). **(B)** Targeted ultrasound identified a sonographic correlate to the mammographic density (*arrow*). Ultrasound-guided biopsy yielded invasive ductal carcinoma with DCIS. Calcifications were associated with the DCIS.

Compared to stereotactic or MRI-guided biopsy, ultrasound-guided biopsy is faster, more comfortable for the patient, and allows greater access to breast tissue, especially for far posterior and medial lesions that may not be amenable to either stereotactic or MRI-guided biopsy. In addition, adequate sampling is more consistently obtained because the needle can be seen traversing the target in real time. Parker et al. first described the accuracy of ultrasound-guided core biopsy using a 14-gauge automated needle. In this study, there was 100% concordance between the pathology obtained with ultrasound-guided core biopsy of 49 lesions and subsequent surgical excision. Of the 132 benign ultrasound-guided biopsies, no malignancies were identified at 12- to 36-month follow-ups (5).

Subsequently, vacuum-assisted devices were developed that improved diagnostic accuracy compared to automated devices and are now routinely used in all stereotactic percutaneous biopsies. Automated and vacuum-assisted devices were also modified to sample lesions detected only on MRI. Percutaneous biopsy using imaging guidance has been demonstrated to be a safe, accurate, less deforming, less invasive, and less expensive alternative to surgical biopsy and is the preferred method for sampling nonpalpable breast lesions. However, accurately performing percutaneous biopsies requires an understanding of all breast imaging modalities and an ability to correlate spatially between them despite differences in technique and patient positioning.

This chapter will review the indications and techniques for performing biopsies using stereotactic, ultrasound, and MRI guidance as well the potential pitfalls in both performing these procedures and the management of the pathology obtained from percutaneous biopsy.

PATIENT SELECTION AND PREPARATION

Patient Selection

Mammography, ultrasound, and breast MRI examinations are classified using the American College of Radiology Breast Imaging Reporting and Data System (BI-RADS), which gives a final assessment category indicating the level of suspicion for malignancy for each study (6).

BI-RADS 3 lesions have imaging features that suggest a less than 2% chance of malignancy. The criteria of a BI-RADS 3 mammographic lesion are largely based on two studies that collectively include over 80,000 mammograms (7,8). In these studies, a 6-month follow-up mammogram identified interval progression of those few BI-RADS 3 lesions that were actually malignant and diagnosed these cancers early enough to maintain a favorable prognosis (9). At the same time, close follow-up of BI-RADS 3 lesions reduces the false negative rate of biopsy and decreases health care costs. Examples of BI-RADS 3 mammographic lesions include a nonpalpable low-density solid mass with a round or oval shape and predominantly circumscribed margins on a baseline mammogram or clustered microcalcifications with a punctate morphology on a baseline study. New or enlarging solid masses should not be categorized as BI-RADS 3 lesions but should undergo biopsy.

The BI-RADS lexicon for lesions detected on ultrasound and MRI are less widely validated than for mammography. Stavros et al. initially developed a classification scheme to differentiate benign from malignant lesions on ultrasound with a 98.4% sensitivity and a 99.5% negative predictive value for malignancy (10). Subsequent studies have confirmed the low rate of subsequent malignancy in BI-RADS 3 masses (11,12). An incidental homogeneously hypoechoic oval mass with circumscribed margins and parallel orientation is an example of an ultrasound BI-RADS 3 lesion.

The specific morphologic and/or kinetic features of lesions appropriate for a BI-RADS 3 recommendation on MRI have not been well established but are generally based on the principles used to characterize BI-RADS 3 lesions on mammography. The cancer yield of BI-RADS 3 lesions on MRI has varied between 0% and10% (13,14). Eby et al. evaluated the characteristics of probably benign MRI lesions and found that foci, defined as lesions less than 5 mm in size that are too small to further characterize, comprise 46% of BI-RADS 3 lesions (14). Liberman et al. also found a 3% malignancy rate in suspicious lesions less than 5 mm in size (15). Studies have suggested that unique foci with a high T2 signal intensity correlate may safely be followed on a 6-month follow-up MRI given the low rate of malignancy of these lesions.

BI-RADS 4 lesions have between a 2% and 95% chance of representing malignancy and can be further subdivided

into BI-RADS 4a (low suspicion of malignancy), 4b (moderate suspicion), and 4c (high suspicion) categories. BI-RADS 5 lesions are highly suspicious with a greater than 95% chance of malignancy. Percutaneous biopsy is recommended for all examinations with BI-RADS 4 or 5 recommendations. Percutaneous biopsy is most useful for BI-RADS 4 lesions because surgery can be avoided in 70% to 80% of cases where biopsy yields benign and concordant pathology. Percutaneous biopsy of BI-RADS 5 lesions is recommended due to improved surgical outcomes at lumpectomy, including decreased positive margin rates (16).

Patient Preparation

Patients are asked to discontinue aspirin, warfarin, nonsteroidal anti-inflammatory agents, vitamin E, or other anticoagulation or antiplatelet drugs for at least 5 days prior to the procedure. However, patients who are anticoagulated for a medical reason are advised to consult their ordering physician to determine whether the medication can be safely discontinued. Studies have demonstrated that core biopsy can safely be performed without clinically significant complications if anticoagulants cannot be discontinued or if urgent results are required (17). Premedication with antibiotics in patients with prosthetic valves or joint replacements is generally not necessary.

SELECTION OF BIOPSY DEVICE

Both the gauge of the biopsy needle and the type of biopsy device are important factors to consider when performing percutaneous core biopsies. Percutaneous biopsies should be performed using a 14-gauge or larger bore needle due to increased accuracy compared to 16- or 18-gauge needles (18).

Two types of biopsy devices are available: automated spring-loaded devices or vacuum-assisted biopsy devices. Vacuum-assisted devices are standard for stereotactic or MRI-guided biopsies. Vacuum-assisted devices are faster and more accurate due to the larger size of specimens and the ability to obtain contiguous samples. The median specimen weight is approximately 17 mg with a 14-gauge automated needle, 35 mg with a 14-gauge vacuum-assisted biopsy probe, and 100 mg using an 11-gauge vacuum-assisted needle (1). Successful calcification retrieval rate and the rate of histologic underestimation are improved using a vacuum-assisted device compared to a 14-gauge automated large core biopsy device.

Although vacuum-assisted devices are routinely used during stereotactic and MRI-guided biopsies, most ultrasound-guided biopsies can be accurately performed using an automated spring-loaded device (19). A vacuum device may be preferred when sampling complex masses when lesion conspicuity may decrease due to loss of the fluid component once the needle is inserted or in cases of a suspected fibroepithelial lesion or papilloma when larger specimens may improve pathologic accuracy.

BIOPSY METHODS

Stereotactic Biopsy

Stereotactic biopsy may be performed on either dedicated prone tables or an upright add-on unit. Add-on units convert a standard diagnostic mammography unit, and the biopsy is performed with the patient in a sitting or decubitus position. Add-on units require less space, are less expensive, and allow the room to be used for routine mammography when a biopsy is not being performed, but they are associated with an increased risk of vasovagal reactions. Advantages of prone tables include that the biopsy is performed out of the patient's view, that vasovagal reactions are uncommon, and that more working space between the biopsy gun and the patient is permitted (1). The cost and space requirement for a dedicated room make prone tables impractical for centers that perform a low volume of stereotactic biopsies, and both types of units are considered acceptable and commonly used.

The technique for performing stereotactic biopsy is similar regardless of the type of unit used. The direction of approach is selected based on lesion location and/or visibility. A scout image is taken with the target centered in a cutout compression plate. A stereotactic pair in which images are taken at +15 and –15 degrees from a center line is obtained. Stereotactic biopsy is based on the concept that a lesion can be localized in three dimensions—the *x*, *y*, and *z* axes—based on the apparent change in position on the stereotactic pair (parallax). Once the target is selected, the housing unit is moved to the x and y coordinates. The skin is cleansed and anesthetized, and the biopsy needle inserted into the breast to the predetermined depth. Another stereotactic pair is obtained with the needle in the prefire position to confirm accurate targeting, and then the needle is typically fired (Fig. 15-2). A postfire stereotactic pair may be obtained to confirm needle position prior to sampling. If the target is calcifications, a specimen radiograph is taken to confirm retrieval of some of the targeted calcifications. If the target is a mass or asymmetry, a postfire image should be obtained to confirm that the needle trough is within the mammographic abnormality. Finally, a localizing clip is placed at the biopsy site and an image obtained to confirm clip deployment. After completion of the biopsy, a 2-view mammogram is performed to confirm clip placement and position relative to the biopsy site. This postbiopsy mammogram is also useful to confirm sampling of a mammographic mass or asymmetry, although these may be obscured by postbiopsy change.

Pitfalls of Stereotactic Biopsy

Several factors may complicate successful stereotactic biopsy, including the following:

- Error in targeting: Localization requires targeting the same lesion on both stereotactic pairs. Targeting two different lesions on the stereotactic pairs will miscalculate the depth (*z* axis), resulting in unsuccessful retrieval of the target.
- Skin calcifications: Skin calcifications mistakenly may be thought to be within the breast parenchyma. The possibility that the target represents skin calcifications should be considered when the calculated Z value (depth) is approximately 5 mm (Fig. 15-3).
- Negative stroke margin: Stroke margin is the distance between the postfire needle position and image receptor. A negative stroke margin indicates that the breast thickness is insufficient and that the needle will strike the image receptor when fired (Fig. 15-4). Standard biopsy needles typically have a needle trough of 18 to 20 mm, and the calculated depth (Z value) centers the target within the needle trough. With thin breasts, devices with a shorter cutting chamber of 12 mm and a blunt tip may be employed. However, these petite devices decrease the sample size and require more precise targeting. Minimizing compression to ensure maximal breast thickness may also permit sampling in thin breasts. If the stroke margin error is only a few millimeters because the calculated Z value

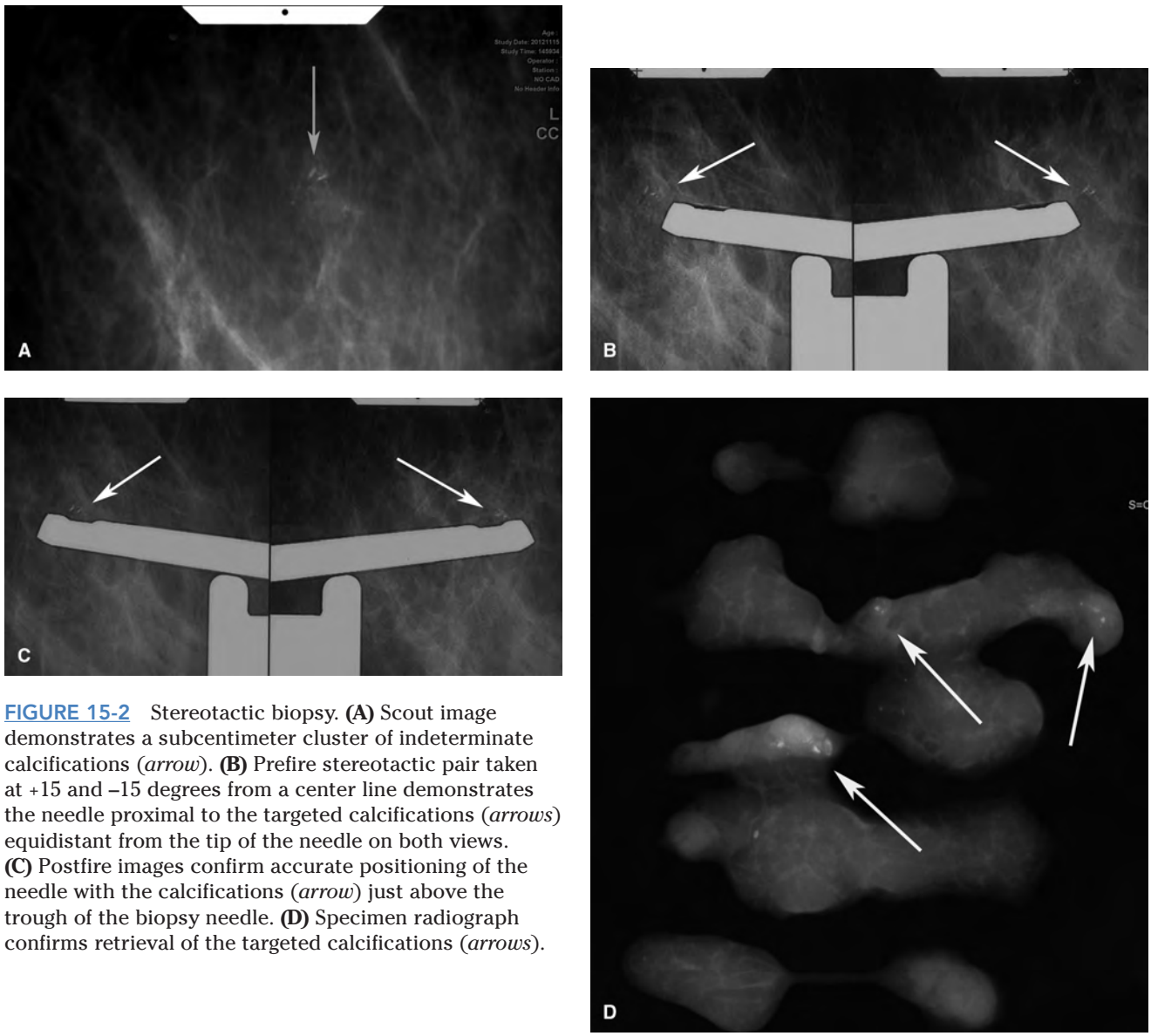

FIGURE 15-2 Stereotactic biopsy. **(A)** Scout image demonstrates a subcentimeter cluster of indeterminate calcifications (*arrow*). **(B)** Prefire stereotactic pair taken at +15 and –15 degrees from a center line demonstrates the needle proximal to the targeted calcifications (*arrows*) equidistant from the tip of the needle on both views. **(C)** Postfire images confirm accurate positioning of the needle with the calcifications (*arrow*) just above the trough of the biopsy needle. **(D)** Specimen radiograph confirms retrieval of the targeted calcifications (*arrows*).

centers the target in the middle of the needle trough, which is typically 18 to 20 mm, the needle can be pulled back to prevent the tip from striking the image receptor while keeping the target within, but not centered in, the trough. A reversed compression paddle, which has an aperture allowing tissue to push through, also may be placed on the far side of the breast to increase breast thickness.

- Axillary tail or posterior lesions: Lesions in the posterior breast may be difficult to target. Positioning the patient in an oblique position may facilitate access to the posterior parenchyma. Targeting the anterior edge of the lesion with preferential sampling posteriorly can be attempted. Alternatively, biopsy can be performed with the patient's arm and shoulder positioned through the table aperture and supported in order to better access the axillary tail (Fig. 15-5).
- Calcifications on specimen radiograph but not identified by pathology: Mammographic calcifications representing calcium oxalate may be difficult for pathologists to visualize and may require analysis with polarized light to improve their conspicuity. In addition, after tissues cores are embedded into paraffin, only a small proportion is sectioned into slides for analysis. If no calcifications are identified, the paraffin blocks can be x-rayed to determine whether additional sections are needed (Fig. 15-6).

Despite these maneuvers, some lesions will not be amenable to stereotactic biopsy, usually due to lesion location or breast thickness. In these situations, mammographic-guided localization prior to excisional biopsy will be required.

Ultrasound Guided Biopsy

Ultrasound-guided core biopsy is the preferable method for sampling any lesion that is evident sonographically. Ultrasound-guided biopsy is more technically challenging than either stereotactic or MRI-guided biopsy as hand-eye coordination is required to accurately target the lesion while the breast is mobile and not compressed.

During an ultrasound-guided core biopsy, the patient is positioned either in the supine or supine oblique position with the ipsilateral arm raised over the head. The skin is

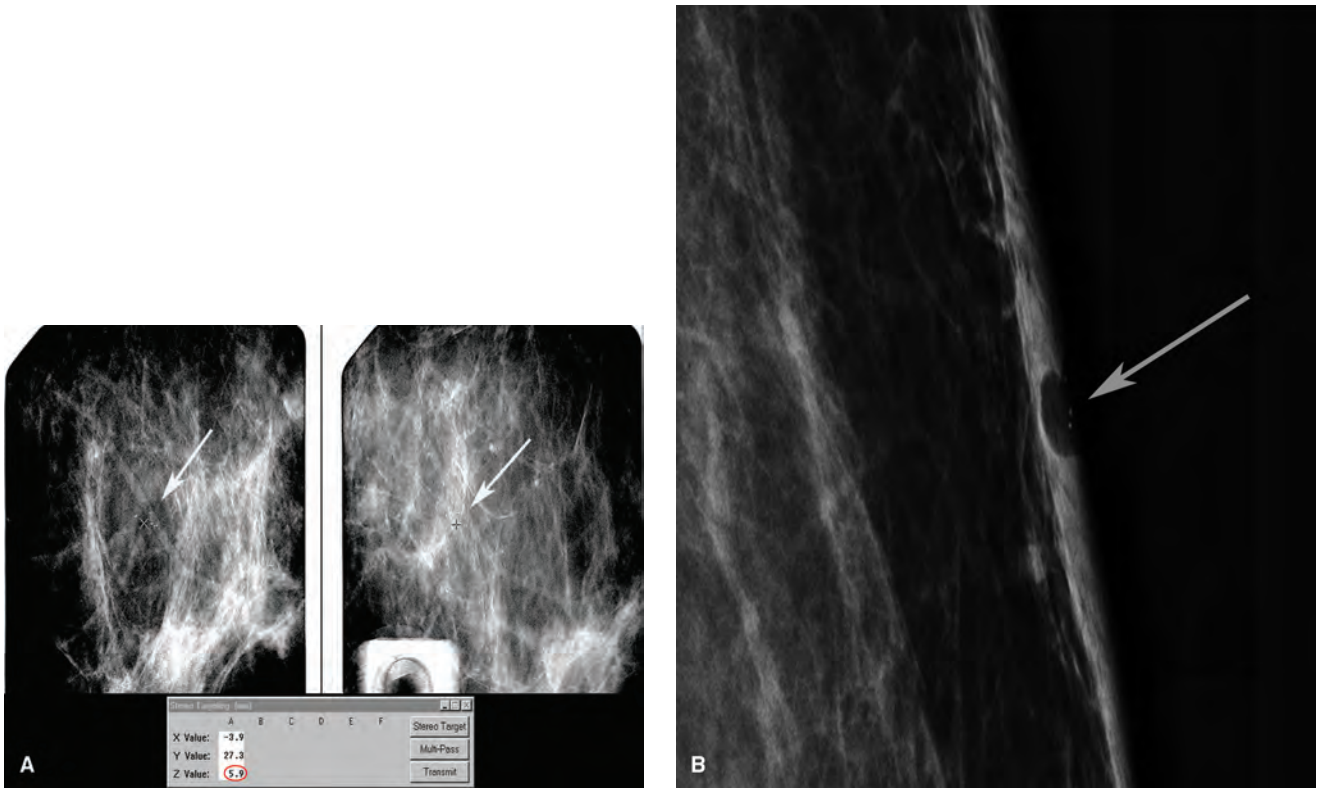

FIGURE 15-3 Stereotactic biopsy of dermal calcifications. **(A)** Initial targeting localizes a cluster of calcifications (*arrow*) to a depth of 5 mm (*red circle*), suggesting that the calcifications are within the skin. No calcifications were present on the specimen radiograph. **(B)** Tangential view postbiopsy confirms that the calcifications are within the skin, which now contains postbiopsy changes including air (*arrow*).

cleansed, and local anesthesia injected. After a skin incision is made, the needle is inserted parallel to the long axis of the transducer so that the entire length of the needle is visualized as it is advanced to the target. With automated core biopsy devices that are fired into biopsy position, the needle tip should be positioned just proximal to the lesion edge before it is fired. With a nonfiring vacuum-assisted device, the needle is typically positioned deep to the target. The angle of the needle greatly affects visualization, and the needle should be directed parallel to the transducer and chest wall to avoid injury.

Pitfalls of Ultrasound-Guided Biopsy

The major limitations to ultrasound-guided biopsy are as discussed below:

- Lesion visualization: A lesion must be sonographically evident to undergo ultrasound-guided biopsy. Therefore, ultrasound-guided biopsy may not be feasible for calcifications or small masses for which no sonographic correlate can be identified.
- Inaccurate targeting: An advantage of ultrasound-guided biopsy is that the biopsy needle can be seen in real time traversing the desired target. However, when sampling subcentimeter lesions, the needle may appear to be accurately positioned through the target, but, due to volume averaging, the needle is actually in the adjacent tissue. Turning the transducer in the orthogonal plane to image the needle in cross section through the target confirms accurate targeting.
- Injury to the chest wall: The core biopsy needle should always be positioned parallel to the chest wall. With automated core biopsy devices, the tip of the needle should be visualized at all times and when firing the needle. There must be adequate distance away from vital structures to accommodate the throw of the needle once fired. A rare but potential complication of ultrasound-guided biopsy is pneumothorax.
- Inaccurate identification of a sonographic correlate to a mammographic abnormality: When sampling a potential sonographic correlate to a mammographic abnormality, a localizing clip should be placed in the biopsied lesion. The postbiopsy mammogram should confirm correlation between the biopsied lesion and the mammographic abnormality (Fig. 15-7).
- Inaccurate identification of a sonographic correlate to a MRI abnormality: Targeted ultrasound is often performed to evaluate for a sonographic correlate to a MRI finding in order to facilitate biopsy. A potential correlate is more frequently identified for enhancing masses compared to nonmass enhancement (20,21). However, true ultrasound-MRI correlation can be confirmed only if a follow-up MRI is performed, demonstrating the localizing clip placed at the time of ultrasound-guided biopsy within the area of enhancement on MRI. One study found that the presumed sonographic correlate biopsied yielding a benign, concordant diagnosis did not correspond to the lesion originally detected on MRI in 12% of cases (21). For this reason, a 6-month follow-up MRI is recommended following benign concordant biopsy of a sonographic correlate to a

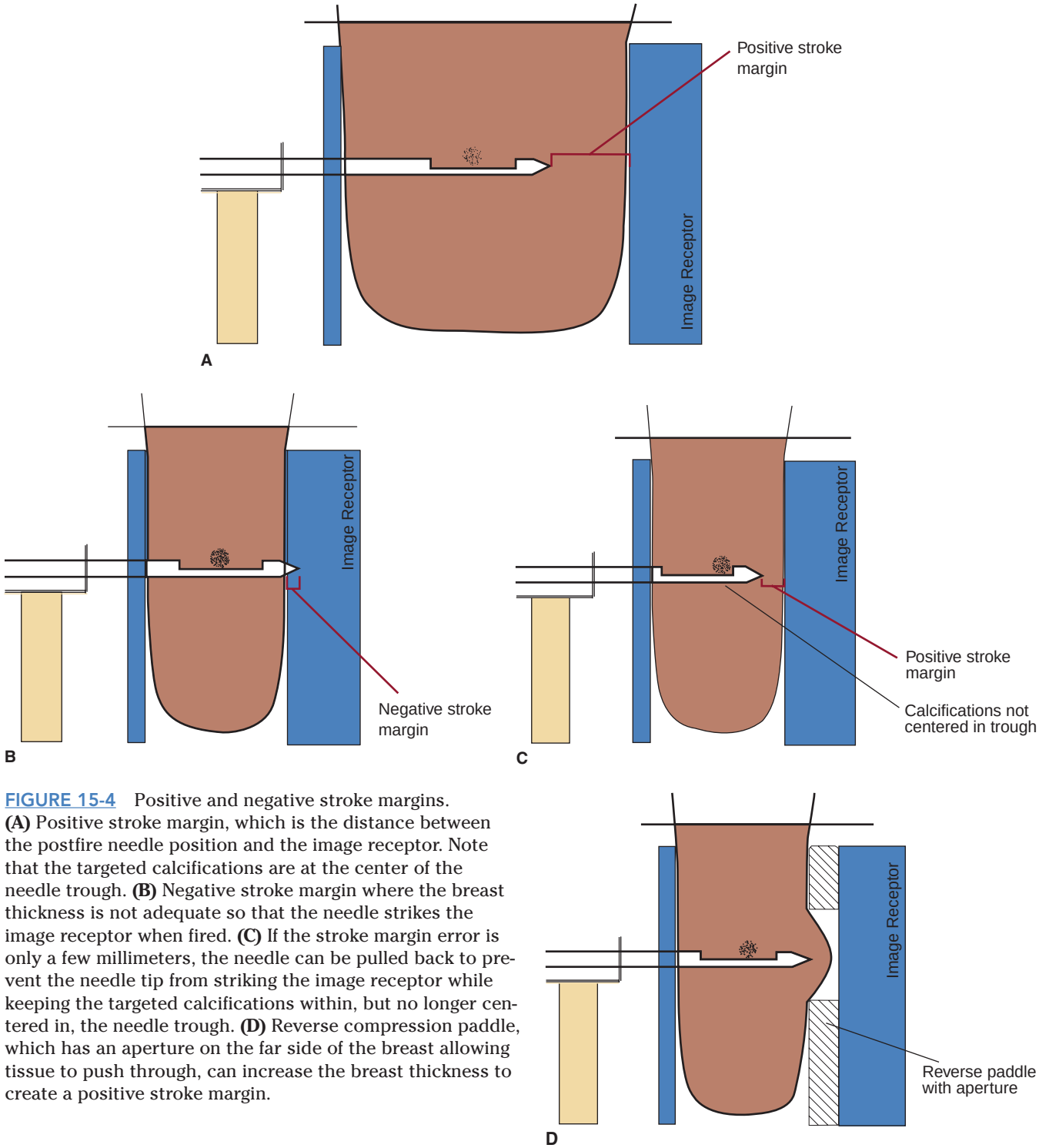

FIGURE 15-4 Positive and negative stroke margins. **(A)** Positive stroke margin, which is the distance between the postfire needle position and the image receptor. Note that the targeted calcifications are at the center of the needle trough. **(B)** Negative stroke margin where the breast thickness is not adequate so that the needle strikes the image receptor when fired. **(C)** If the stroke margin error is only a few millimeters, the needle can be pulled back to prevent the needle tip from striking the image receptor while keeping the targeted calcifications within, but no longer centered in, the needle trough. **(D)** Reverse compression paddle, which has an aperture on the far side of the breast allowing tissue to push through, can increase the breast thickness to create a positive stroke margin.

MRI-detected lesion (22). This pitfall likely is related to differences in patient positioning with the patient positioned prone during the MRI but supine and oblique during the ultrasound.

MRI-Guided Biopsy

Breast MRI is increasingly being performed as an adjunct to mammography to screen patients who are at high risk for developing breast cancer. The sensitivity of breast MRI for detecting invasive and *in situ* breast cancer is high, but the specificity is lower (23,24), necessitating the use of percutaneous biopsy for a definitive diagnosis.

Breast MRI should be performed on only a 1.5 or 3.0 T magnet using a dedicated breast coil. During biopsy, the patient is positioned prone and the breast immobilized in light compression. Tight compression may inhibit blood flow and is not recommended. Depending on the location of the target, either a medial or lateral approach is selected. Pre- and postcontrast images are first obtained to identify

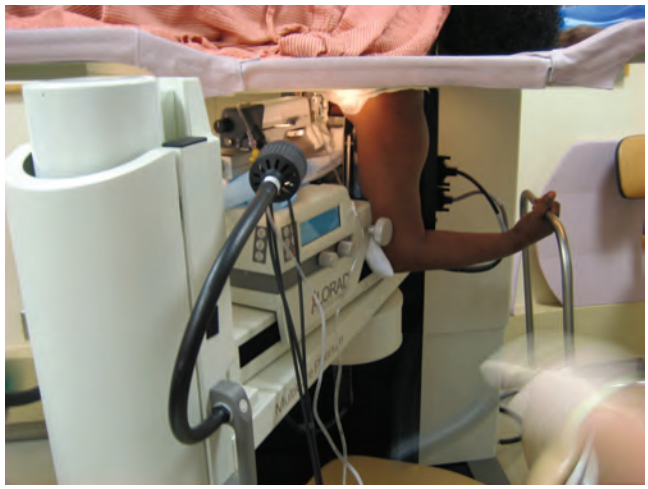

FIGURE 15-5 The patient's arm and shoulder can be positioned through the table opening to facilitate access to posterolateral lesions. The patient's arm should be stabilized during the procedure to minimize motion.

the target. The skin overlying the lesion is cleansed and anesthetized. A sheath is placed over a trocar and inserted to the appropriate depth. The trocar is removed, a plastic obturator inserted, and repeated imaging performed to confirm accurate positioning. Samples are obtained using a vacuum-assisted device. A postbiopsy series is then obtained to confirm biopsy site changes. Following biopsy, a localizing clip is placed at the biopsy site. A postbiopsy mammogram is obtained to confirm clip placement and position with respect to biopsy site changes.

Pitfalls

Potential factors complicating accurate MRI-guided biopsy include the following:

- Lesion nonvisualization: Cancellation of MRI-guided biopsy occurs in approximately 8% of patients. Factors associated with a higher cancellation rate include moderate or marked parenchymal enhancement and lesion size less than 1 cm (25). Lesion nonvisualization may be due to excessive compression of the breast parenchyma. Therefore, if a target is not identified at the time of biopsy, compression is reduced and delayed sequences obtained. If the target is still not visualized, the biopsy is canceled and a 6-month follow-up MRI should be obtained (22,25).
- Decreased lesion conspicuity: Decreased lesion conspicuity is likely related to compression, which is applied only at the time of biopsy and may alter perfusion and the appearance of the target. If a lesion is visualized but appears less conspicuous at the time of MRI-guided biopsy, biopsy should still be performed.
- Errors in targeting: Unlike ultrasound-guided biopsy where the needle is seen traversing the target in real time or stereotactic biopsy where the specimen radiograph confirms sampling of the targeted calcifications, confirmation of accurate sampling during MRI-guided biopsy is less accurate and relies on identifying postbiopsy changes at the expected location of the target (Fig. 15-8). One study reports a 2.5% false negative rate of MRI-guided biopsy

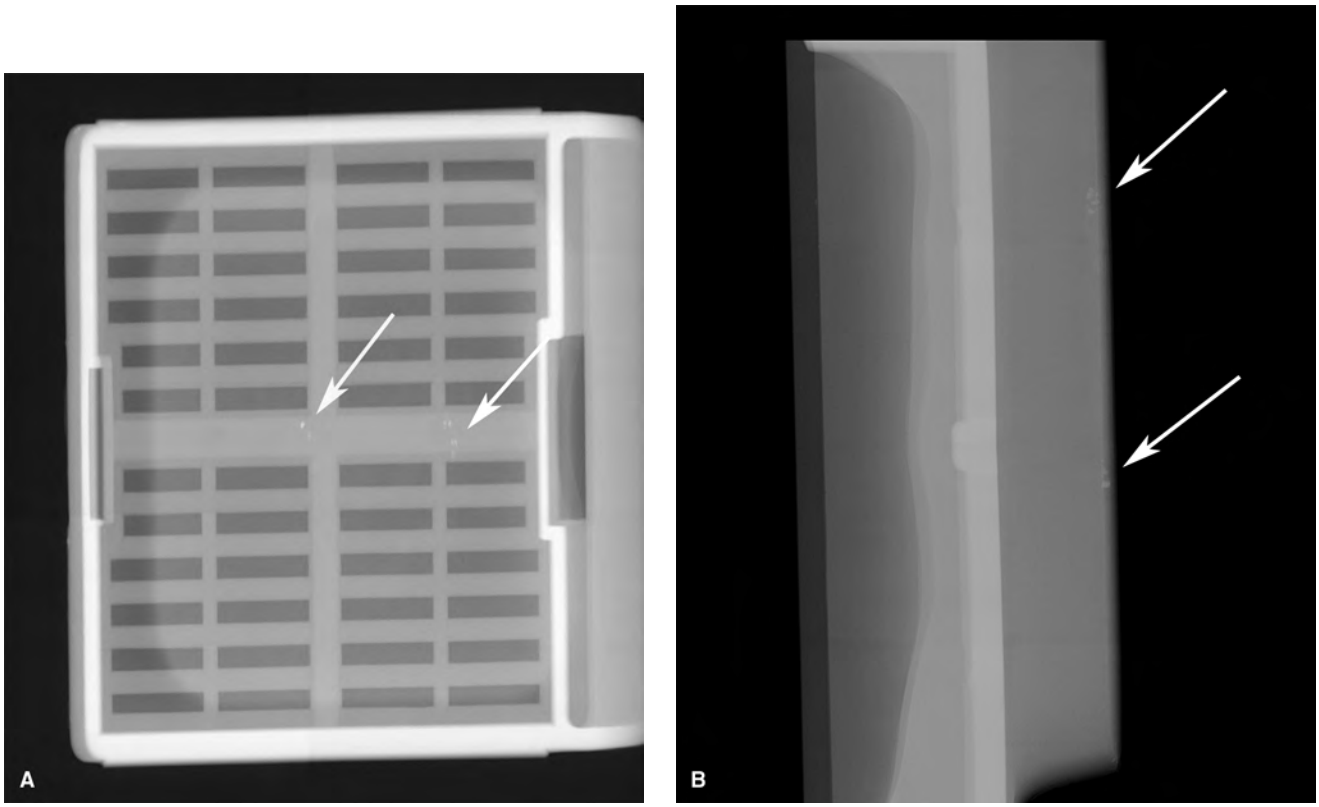

FIGURE 15-6 Imaging specimen paraffin blocks. Frontal (**A**) and lateral (**B**) x-rays of specimen blocks confirm the presence of calcifications (*arrows*) retrieved on stereotactic biopsy. Additional sections can be obtained from those blocks containing calcifications.

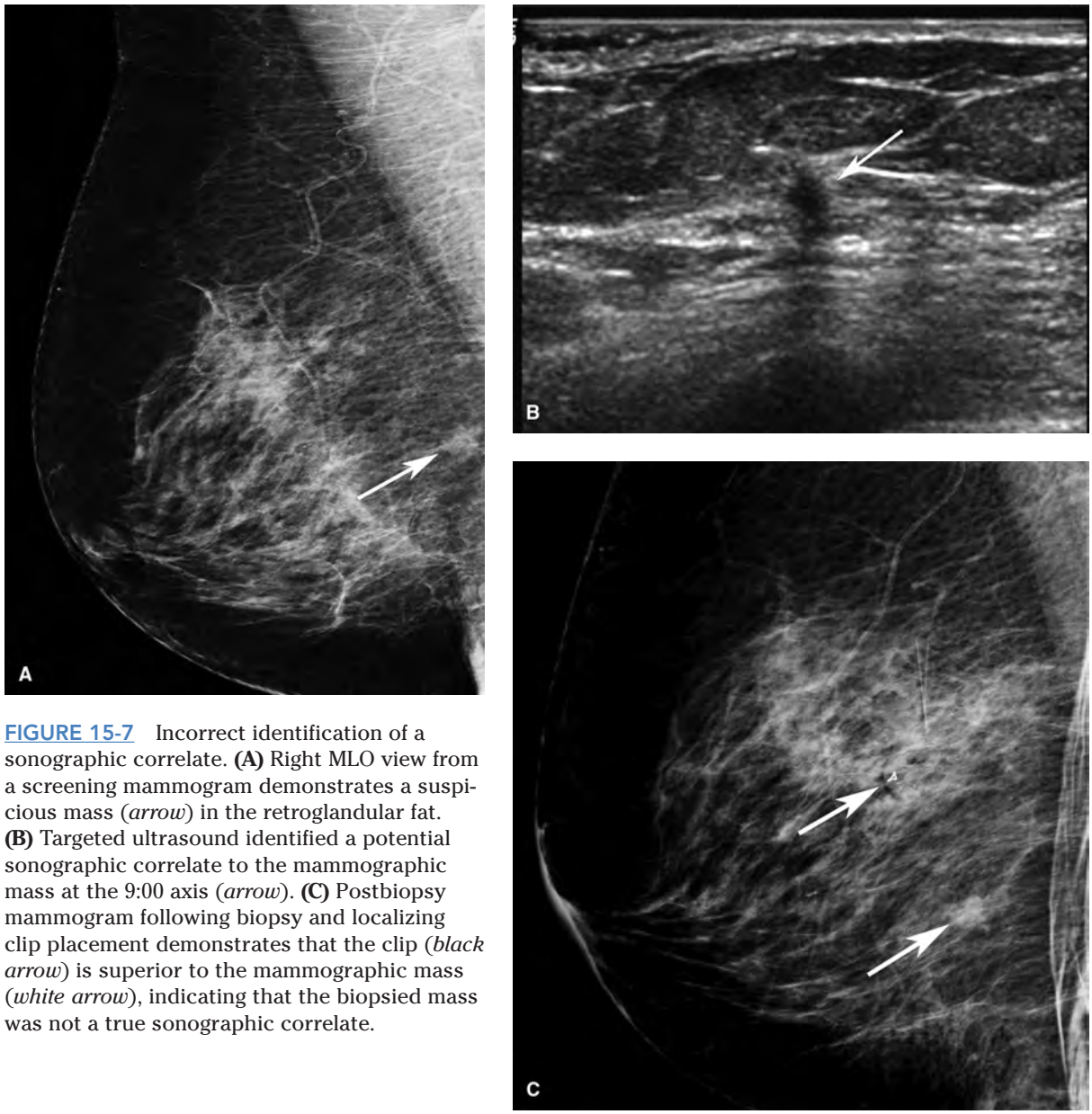

FIGURE 15-7 Incorrect identification of a sonographic correlate. **(A)** Right MLO view from a screening mammogram demonstrates a suspicious mass (*arrow*) in the retroglandular fat. **(B)** Targeted ultrasound identified a potential sonographic correlate to the mammographic mass at the 9:00 axis (*arrow*). **(C)** Postbiopsy mammogram following biopsy and localizing clip placement demonstrates that the clip (*black arrow*) is superior to the mammographic mass (*white arrow*), indicating that the biopsied mass was not a true sonographic correlate.

(22,26). Therefore a 6-month follow-up MRI is recommended after benign concordant MRI-guided biopsy to confirm accurate targeting and sampling.

CLIP PLACEMENT

A localizing clip should routinely be placed during almost all percutaneous biopsies, particularly for subtle lesions or lesions that are less conspicuous or no longer evident after sampling. Clip placement also assists in correlating lesions between modalities. A postbiopsy mammogram should be performed following clip placement in order to document clip deployment and the position of the clip relative to the expected location of the targeted lesion. Clip displacement when the clip position is significantly distant from the site of the imaging abnormality is an infrequent complication. This occurs predominantly during stereotactic or MRI-guided biopsies along the biopsy tract when the breast is released from compression. If a clip is displaced and surgical excision is necessary, the original imaging abnormality (i.e., residual calcifications) can be targeted if still visible following biopsy. Otherwise, localization can be performed by targeting anatomic landmarks and the location of biopsy changes, which are best assessed on the immediate postbiopsy mammogram.

COMPLICATIONS

Complications following percutaneous biopsy procedures are infrequent. Bleeding is the most common complication and has been reported in up to 3% of cases using an 11-gauge vacuum-assisted system. Hemostasis can usually be obtained with direct compression for 10 to15 minutes. Hematomas are rarely clinically significant and can be managed conservatively. Infection is another potential but rare complication.

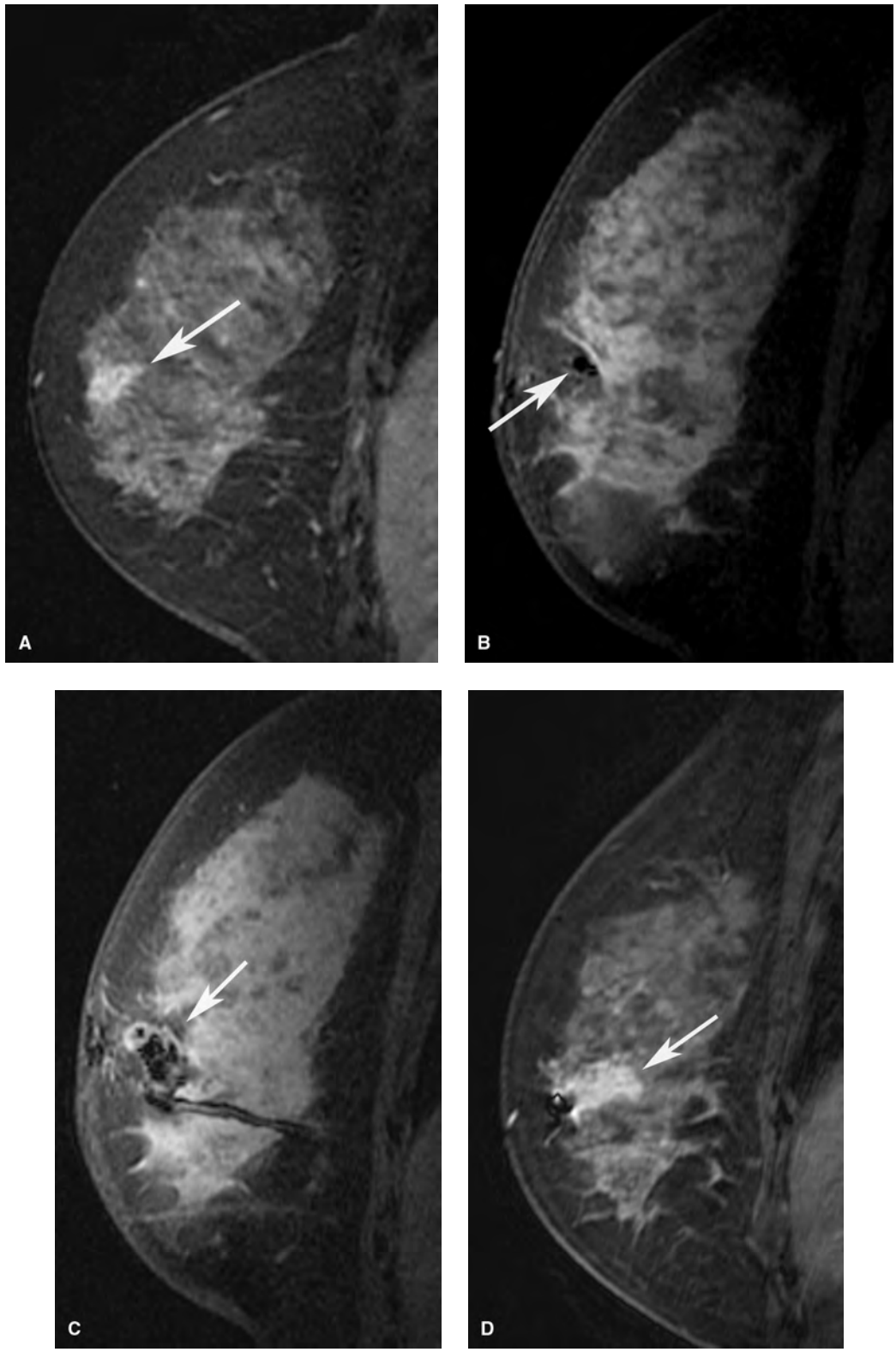

FIGURE 15-8 False negative MRI-guided biopsy. **(A)** Biopsy was recommended for an indeterminate area of nonmass enhancement (*arrow*) on screening breast MRI. **(B)** Sagittal fat saturated T1-weighted image demonstrates low signal from the obturator (*arrow*) at the anterior aspect of the nonmass enhancement that has become difficult to visualize. **(C)** Sagittal fat saturated T1-weighted image demonstrates expected postbiopsy changes (*arrow*) after sampling. Pathology-yielded stromal fibrosis, which was thought to be concordant. **(D)** Sagittal fat saturated T1-weighted image on the 6-month follow-up MRI demonstrates the localizing clip at the anterior aspect of the area of nonmass enhancement (*arrow*), which has now increased in size. Repeat MRI-guided biopsy yielded invasive ductal carcinoma.

HISTOPATHOLOGIC CONCORDANCE

Correlation of the imaging appearance of a biopsied lesion with the histopathology is an integral part of percutaneous breast biopsy to maintain high accuracy and a false negative rate comparable to surgical excision. Communication with the pathologist may be helpful in cases of questionable imaging-pathologic concordance.

Benign breast histopathology encompasses a broad range of conditions, including nonspecific findings such as fibrocystic change, apocrine hyperplasia, sclerosing adenosis, stromal fibrosis, and ductal hyperplasia. Examples of more specific benign histology include fibroadenoma, lymph nodes, and fat necrosis. The mammographic and sonographic features of many of these pathologies have been well described.

There is no consensus regarding the follow-up imaging protocol after benign concordant percutaneous biopsy, and practices vary by institution. Lee et al. recommended a 6-month follow-up for nonspecific benign results on stereotactic biopsy and yearly screening mammography if specific benign results were obtained; another retrospective study recommended imaging at 6, 12, and 24 months after all benign concordant biopsies (27,28). A more recent study reported that a 6-month imaging follow-up did not impact either cancer detection or rebiopsy rates and therefore yearly follow-up may be more appropriate (29).

At our institution, the patient returns to routine annual screening mammography after benign and concordant stereotactic biopsy of calcifications if the calcifications appear to be adequately sampled on the specimen radiograph. If multiple morphologically similar clusters of calcifications are present and sampling of one representative cluster yielded benign and concordant pathology, a 6-month follow-up mammogram is recommended to confirm stability of the remaining clusters. A 6-month follow-up mammogram is also recommended after obtaining benign, concordant pathology after stereotactic biopsy of masses or asymmetries as assessing for adequate sampling may be more difficult than with biopsy of calcifications. Similarly, a 6-month follow-up ultrasound is also sometimes recommended after ultrasound-guided biopsy of a low-suspicion lesion that yields a benign but nonspecific pathology.

Determining histopathologic concordance following MRI-guided biopsy is more challenging as all of these lesions can appear as focal areas of enhancement, distinct from the remainder of the breast parenchyma. Because there is considerable overlap in the morphologic features of benign and malignant lesions on MRI, it is possible that a lesion thought to be benign and concordant is, in fact, malignant. Therefore, a 6-month follow-up MRI is routinely performed following benign concordant MRI-guided biopsy.

HIGH RISK LESIONS DIAGNOSED AT CORE BIOPSY

Controversy exists regarding the need for surgical excision after percutaneous core biopsy yielding certain high risk lesions, including atypical ductal hyperplasia, lobular neoplasia, radial scar, and papillary lesions. Excision of a high risk lesion is often recommended (Table 15-1) due to potential histologic underestimation when a high risk lesion diagnosed at percutaneous biopsy is upgraded to either *in situ* or invasive carcinoma at the time of surgery.

Atypical Ductal Hyperplasia

Atypical ductal hyperplasia (ADH) is the most common of the high risk lesions, identified in approximately 5% of all biopsies and in up to 20% of biopsies performed for amorphous calcifications (3). Histologic underestimation of ADH diagnosed on stereotactic biopsy is reduced by acquiring a larger volume of tissue. The upgrade rate of ADH to carcinoma at excision is approximately 20% to 56% when using a 14-gauge automated core biopsy device but is reduced to 20% with an 11-gauge vacuum-assisted device (1). This upgrade rate is high enough that surgical excision is generally recommended.

Surgical excision is also recommended when ADH is diagnosed on MRI-guided biopsy. Although histologic underestimation is reduced to approximately 20% with an 11-gauge vacuum-assisted device using stereotactic guidance, studies have reported a 38% upgrade rate of ADH diagnosed at MRI-guided biopsy using a 9-gauge vacuum-assisted biopsy device (30). This higher rate may reflect the increased risk of malignancy in patients undergoing a breast MRI, which is usually performed for either high risk screening or preoperative staging.

TABLE 15-1

Management Recommendations of High Risk Lesions on Percutaneous Biopsy

High Risk Lesion	*Management Recommendation*
Atypical ductal hyperplasia	Excision
Lobular neoplasi(a)	
- ALH	Controversial
- Classic LCIS	Controversial
- Pleomorphic LCIS	Excision
Radial scar/ Radial sclerosing lesion	Excision
Papilloma	Excision
Microscopic radial scar and papilloma	Controversial

Lobular Neoplasia

Lobular neoplasia (LN) includes both atypical lobular hyperplasia (ALH) and lobular carcinoma *in situ* (LCIS). ALH and LCIS are often considered to be along a spectrum of a disease. Currently LN is thought to represent a marker for increased risk of breast cancer at any site in either breast as opposed to a true precursor of malignancy.

Lobular neoplasia can be subdivided into classical and pleomorphic types with the pleomorphic type having a higher likelihood of upgrade to malignancy (31). The upgrade rate for lobular neoplasia varies widely in the literature—between 0% and 50%. This wide range is likely related to the fact that most of these studies are retrospective, have small numbers of patients included due to the low incidence of the pathology, and do not include radiologic-pathologic concordance. In one of the largest retrospective studies that included 278 cases of lobular neoplasia from 14 institutions, Brem et al. reported a 23% upgrade rate (32). Conversely, Hwang et al. reviewed 136 cases of LN and reported a 2% upgrade rate of ALH and 23% upgrade rate of LCIS (33). However, the upgrade rate of LCIS was reduced to less than 2% when nonclassic or pleomorphic variants of LCIS or cases with imaging-pathology discordance were excluded. Another consideration is whether the LN represents an incidental finding or is related to the imaging abnormality. Given the conflicting

data, surgical excision for classic LCIS and ALH continues to be controversial. Surgical excision is recommended for all cases of pleomorphic LCIS.

Radial Scar

Radial scars are rare—reported in less than 1% of all percutaneous biopsies. These may present mammographically as spiculated masses, classically with a lucent center, or as incidental microscopic lesions unrelated to the imaging abnormality for which biopsy had been performed. Historically, the standard management of radial scars diagnosed at core biopsy has been excision due to a reported association with DCIS and invasive carcinomas. A multiinstitutional trial published in 2002 reported an overall upgrade rate of 8% at surgical excision (34). The upgrade rate was higher if there was associated atypia on core biopsy. There was no upgrade if at least 12 specimens were obtained at stereotactic biopsy using an11-gauge vacuum-assisted device, if there was no associated atypia, and when the mammographic findings were concordant. Microscopic radial scars also have a low upgrade to malignancy and may not require excision (35). Although the data are limited, some institutions reserve surgical excision for radial scars that are mammographically evident or for radial scars associated with atypia.

Benign Papillomas

Papillary lesions are diverse, ranging from benign papillomas to papillary lesions with atypia to invasive papillary carcinomas. Papillary tumors are found in up to 4% of percutaneous biopsies (36). Papillomas are considered atypical papillomas if there are foci of ADH or DCIS. Atypical papillomas or papillomas with DCIS warrant excision. However, there is continuing controversy as to whether surgical excision is required for a benign papilloma on core biopsy. Surgical excision has traditionally been recommended due to the limited sample obtained and concern that percutaneous biopsy might sample a nonrepresentative portion of the lesion. Similar to other high risk lesions, the reported upgrade rate of papillomas ranges widely in the literature between 0% and 25%, largely due to the small number of patients included in each study, their retrospective design, and differences in assessing imaging-pathologic concordance (31,36). Most of these studies involved papillomas diagnosed at either ultrasound or stereotactic biopsy. Communication with the pathologist is important to distinguish microscopic papillomas that are entirely contained within the core specimens as these may not require excision (35). Surgical excision is recommended when papilloma is obtained on MRI guided biopsy due to a 5% upgrade rate in papillomas without atypia (36).

CONCLUSION

Image guided percutaneous breast biopsy has become the preferred method for evaluating nonpalpable lesions in the breast. Percutaneous core biopsy is a safe, less invasive, and less costly alternative to surgical biopsy with comparable accuracy. However, understanding potential pitfalls that may occur with image guided biopsy is important in order to maintain its effectiveness. Accurate targeting is critical with any image guided biopsy in order to minimize false negative rates. In addition, imaging-pathologic concordance is essential after biopsy. Management of high risk lesions continues to be debated, and additional studies need to be performed to standardize management of these lesions.

MANAGEMENT SUMMARY

- Most nonpalpable breast lesions can be successfully and accurately biopsied using imaging guidance.
- Ultrasound-guided biopsy is the preferred method of percutaneous biopsy for any sonographically evident lesion as it is faster, less expensive, and more comfortable for the patient compared to stereotactic or MRI-guided biopsy. Ultrasound-guided biopsy also avoids radiation exposure or intravenous contrast administration.
- Definite indications for surgical excision following percutaneous biopsy include malignancy, pathology that is discordant from the imaging appearance, and certain high risk lesions, such as ADH, radial scars, and papillomas.

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SECTION IV

Epidemiology and Assessing and Managing Risk

CHAPTER 16

Inherited Genetic Factors and Breast Cancer

Alan Ashworth

CHAPTER CONTENTS

Although much remains to be learned about the heritable factors involved, enormous strides have been made in the past two decades in understanding inherited susceptibility to breast cancer. These advances are based on the discovery and characterization of a number of high-risk, relatively uncommon genes responsible for the clustering of breast cancer in certain families. More recently, a large number of common variants having a modest effect on individual risk have been defined by the use of genome-wide association studies. As clinical utility is currently largely restricted to high-risk genes, this chapter will focus largely on this category but in the future it seems possible that low-risk common variants will also be utilized to inform risk and management of breast cancer. Other relevant information can be found in Chapter 17.

One measure of familial clustering is the familial relative risk (FRR) which is defined as the ratio of the risk of breast cancer for a relative of an affected individual to that of the general population. Multiple observations including simulation and twin studies suggest that the FRR for breast cancer largely reflects the genetic influence on the disease.

Although genetics are clearly important, there is a tendency to assume that familial clustering of disease invariably results from inherited predisposition. However, other explanations for familial clustering of breast cancer should be considered including (a) geographically limited environmental exposure to carcinogens, which might affect an extended family living in close proximity; (b) culturally motivated behavior that alters risk factor profile, such as age at first live birth; and (c) socioeconomic influences that, for example, might result in differing dietary exposures. In addition, multiple, complex inherited genetic factors likely influence the extent to which a risk factor for breast cancer plays a role in any one individual; such modifying effects are likely to be shared among genetically related members of an extended family.

HISTORICAL EPIDEMIOLOGIC STUDIES OF FAMILIAL BREAST CANCER

The first attempts to determine the influence of family history on breast cancer risk were published in the first half of the twentieth century (1,2). Although many of these studies have methodological flaws, they consistently demonstrated a twofold to threefold increase in breast cancer risk in mothers and sisters of patients with breast cancer. The first large population-based study to estimate breast cancer risk associated with a family history was conducted in Sweden and involved 2,660 women (3). Within this study cohort, women with an affected relative had an increased breast cancer risk of 1.7 compared to those without. Anderson (4) suggested that a small subset of families with a very high risk of developing breast cancer due to a single genetic defect might be obscured in studies in which most breast cancer cases were multifactorial in origin. By 1980, a significant

body of evidence had accumulated supporting the presence of inherited factors responsible for familial clustering of breast cancer, and efforts shifted to determining the inheritance pattern of breast cancer within these families. In 1984, Williams and Anderson (5) provided the first evidence for an autosomal dominant breast cancer susceptibility gene with age-related penetrance finding supported by Newman et al. (6) in 1988.

MODE OF INHERITANCE

To date, all studies of inherited susceptibility to breast cancer suggest that breast cancer susceptibility is transmitted in an autosomal dominant mendelian fashion, and the identification of an increasing number of genes has born out this modeling (7,8) (Table 16-1). With a pattern of autosomal dominant inheritance, an individual can have one of three possible genotypes: carrier of two nonmutant alleles (homozygous normal), or carrier of one (heterozygous) or two (homozygous) mutant alleles. The actual risk of developing breast cancer in a mutation carrier is based on the penetrance of the gene. Penetrance is the likelihood that the effect (phenotype) of a mutation (genotype) will become clinically apparent. Individuals carrying two copies of an autosomal dominant disease–related gene are rare, partly because of the relative rarity of heterozygotes and partly because of the potential for a lethal defect in a homozygous affected fetus. However, biallelic (homozygous) deleterious mutations in *BRCA2* have been reported in patients with Fanconi anemia type D1, a rare recessive disorder characterized by leukemia and birth defects (9). Finally, there are several reports of individuals who have both *BRCA1* and *BRCA2* mutations (10). Anecdotal observations suggest that these women develop more frequent and earlier cancers than single mutation carriers, but the number of such individuals identified is too small for definitive studies.

There is a 50% chance that an individual offspring will inherit a mutant copy of any given gene from a heterozygous parent. Therefore, on average, 50% of the related individuals in a family carry the mutant gene being transmitted. If the penetrance of the gene is high, the pedigree pattern for an autosomal dominant disease is quite striking, with vertical inheritance and half the children of an affected parent also being affected, whereas none of the offspring of a homozygous normal parent are affected. This pedigree pattern also

TABLE 16-1

Allele Frequency and Effect Sizes Associates with High-, Moderate-, and Intermediate-Penetrance Variants

Locus	*Genes in/Near Region*	*Variant*	*MAF*	*RR*
High-penetrance mutations				
17q21	*BRCA1*		0.0006	5-45
13q12.3	*BRCA2*		0.001	9-21
17p13.1	*TP53*		rare	2-10
10q23.3	*PTEN*		rare	2-10
19p13.3	*STK11*		rare	2-10
16q22.1	*CDH1*		rare	2-10
Moderate-penetrance variants				
11q22.3	*ATM*		0.003	2-3
22q12.1	*CHEK2*		0.004	2-3
17q22-q24	*BRIP1*		0.001	2-3
16p12.1	*PALB2*		rare	2-4
Low-penetrance variants				
10q26	*FGFR2*	rs 2981582	0.38	1.26
16q12	*TOX3*	rs 3803662	0.25	1.20
5q11	*MAP3K1*	rs 889312	0.28	1.13
8q24	*FAM84B/c-MYC*	rs 13281615	0.40	1.08
11p15	*LSP1*	rs 3817198	0.30	1.07
3p24	*NEK10/SLC4A7*	rs 4973768	0.46	1.11
17q23.2	*COX11*	rs 6504950	0.27	0.95
10p14	*CASP8 (D302H)*	rs 1045485	0.13	0.88
2q35	*TNP1/GFBP5/IGFBP2/TNS1*	rs 13387042	0.52	1.12
1p11.2	*NOTCH2/FCGR1B*	rs 11249433	0.40	1.14
14q24.1	*RAD51L1*	rs 999737	0.24	0.84
5p12	*MRPS30/FGFR10*	rs10941679	0.26	1.19
6q25.1	ESR1	rs 2046210	0.35	1.29

MAF, minor allele frequency from European populations; RR, relative risk.
From Mavaddat N, Antoniou AC, Easton DF, et al. Genetic susceptibility to breast cancer. *Mol Oncol* 2010;4:174–191.

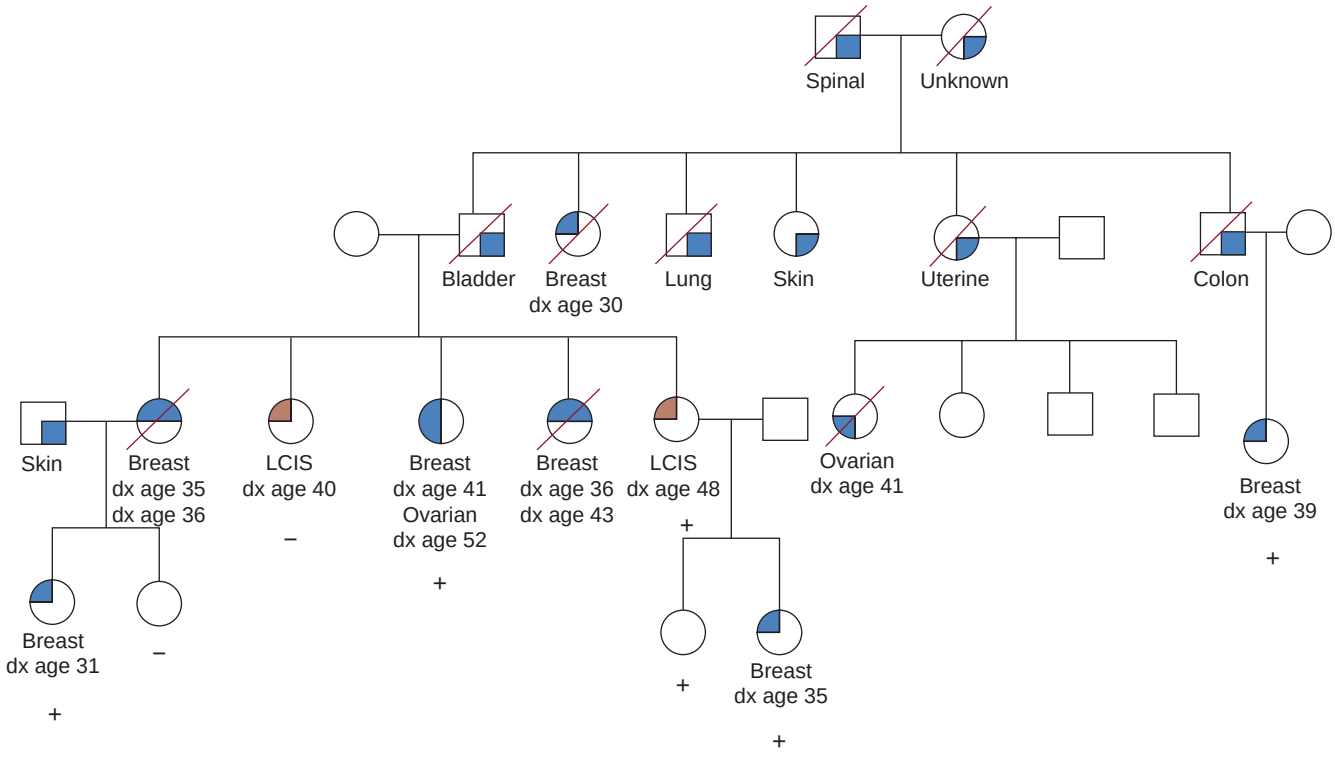


FIGURE 16-1 A kindred with a *BRCA1* mutation. □, Unaffected cancers are indicated with dark shading of symbols;(+), known *BRCA1* mutation carriers;(–), individuals who tested negative; all others are untested. Deceased individuals are indicated with a diagonal line through the symbol. One family member with lobular carcinoma *in situ* (LCIS) tested positive, and the other tested negative, consistent with previous reports suggesting LCIS is not a component of *BRCA1*-related cancer susceptibility.

presupposes a low risk in the general population, which is not the case for breast cancer. As a result, breast cancer in women from families that have a known *BRCA1* mutation but who do not themselves carry the mutation is not uncommon. Such women are termed *phenocopies,* because they have the phenotype associated with the gene mutation but are noncarriers. This situation is illustrated in the pedigree shown in Figure 16-1, a typical pedigree of a family known to carry a mutation in *BRCA1.* As long as the gene being examined is not on the X or Y sex-related chromosomes, the sex of the carrier is irrelevant. However, in the case of autosomal dominant inheritance of breast cancer, significant sex-related differences in the penetrance of mutations exist. Therefore, although mutations occur equally in male and female populations, breast cancer is much more common in women with *BRCA1* or *BRCA2* mutations than in men, but male breast cancer is part of the spectrum of both *BRCA1* and *BRCA2.*

TUMOR SUPPRESSOR GENES

Two fundamental types of genetic alterations responsible for the development of the malignant phenotype are found in cancer cells: (a) activation of protooncogenes producing a "gain of function" in the affected cell and (b) inactivation of tumor suppressor genes producing a "loss of function" in the cell. Some tumor suppressor genes are important in cell-cycle regulation, normally functioning as checks on cell growth; others are critical elements in the cellular response to DNA damage, preventing the propagation of mutations in other critical genes. Mutated tumor suppressor genes lose these regulatory functions, leading to malignant transformation. However, because all individuals are born with two alleles of every gene, an explanation was needed for the development of cancer in large numbers of individuals who had only a single inherited mutation in a tumor suppressor gene. In 1971, Knudson (11) put forward the "two-hit hypothesis," suggesting that cancer arises as a result of two genetic events occurring in the same cell, inactivating both copies of a given tumor suppressor gene. In the case of sporadic cancer (i.e., cancer occurring in women without a family history of the disease), the likelihood that two events would occur in the same gene in the same cell is quite low. However, individuals from "cancer families" inherit an inactivating mutation in one allele of the implicated tumor suppressor gene in all cells (i.e., a germline mutation); therefore, only one somatic (noninherited) event is required to inactivate the single remaining copy, making the development of cancer a much more common event than in individuals born without the "first hit." Of particular relevance to breast cancer are the tumor suppressor genes *TP53, BRCA1,* and *BRCA2.*

HEREDITARY BREAST CANCER SYNDROMES

The study of clinical syndromes that include an increased incidence of breast cancer has provided insight into the mechanisms by which genetic mutations result in the development

of cancer. The most frequently identified pedigrees contain site-specific breast cancer (i.e., breast cancer in these families is not found in association with inherited susceptibility to other cancers, such as ovarian) and are thought to represent the effect of a single genetic abnormality; *BRCA1* and *BRCA2* are the best studied examples. Breast cancer also has been noted to occur in association with other cancers. The occurrence of breast cancer in association with diverse childhood neoplasms in the Li-Fraumeni/SBLA (*soft-tissue* and bony sarcomas, *b*rain tumors, *l*eukemias, and *a*drenocortical carcinomas) (12) syndrome and the association between breast and ovarian cancer represent some of the most intensively studied examples. An elevated frequency of breast cancer may occur in patients with hereditary syndromes that include nonmalignant manifestations as well, such as Cowden's disease and Muir-Torre syndrome (13–15). An increasing number of moderate-risk genes—*ATM, CHEK2, PALB2,* and *BRIP1*—are being identified that lead to an increased risk of cancer of twofold to fourfold (8). Finally, numerous common variants (population frequency 5% to 50%) in genes, which cause a very modest (1.1–1.5 fold) elevation in risk, are just starting to become part of the landscape of breast cancer susceptibility (8) (Table 16-1).

BRCA1 and *BRCA2*

In 1990, chromosome 17q21 was identified as the location of a susceptibility gene for early onset breast cancer, now termed *BRCA1* (16). Shortly thereafter, linkage between the genetic marker D17S74 on 17q21 and the appearance of ovarian cancer in several large kindreds was also demonstrated (17). Initial estimates suggested that *BRCA1* mutations were responsible for more than 90% of breast cancer cases in families with apparent autosomal dominant transmission of breast cancer and at least one case of ovarian cancer, and 45% of cases in families with breast cancer only. However, the percentage of site-specific breast cancer cases attributed to *BRCA1* mutations rose to almost 70% if the median age at onset of breast cancer in the families was younger than 45 years (18), demonstrating the critical importance of the characteristics of a family to the likelihood that a *BRCA1* mutation will be detectable. The *BRCA1* gene was identified in 1994 (19) and encodes a novel protein now known to be important in the cellular response to DNA damage (20).

Initial progress toward the identification of a second breast cancer susceptibility gene came from a linkage analysis of 22 families with multiple cases of early onset female breast cancer and at least one case of male breast cancer. Linkage between male breast cancer and polymorphic genetic markers on chromosome 13q12-13 identified the *BRCA2* locus (21). In 1995, the partial sequence of *BRCA2* and six germline mutations that truncated the putative *BRCA2* protein were identified (22). Shortly thereafter, the complete structure of the *BRCA2* gene was published (23).

BRCA1 is composed of 24 exons (coding regions) and is translated into a protein consisting of 1,863 amino acids (Fig. 16-2A). The coding region of *BRCA2* is 11.2 kb in length and is made up of 26 exons that produce a protein of 3,418 amino acids. The size of these genes is important from a clinical standpoint in the context of genetic testing, because this has made screening for mutations technically demanding and costly. Furthermore, the *BRCA1* gene contains a large number of repetitive elements that facilitate the generation of large deletions and duplications. For example, disease-associated deletions account for 36% of *BRCA1* mutations in the Netherlands (24). However, the use of modern next-generation DNA sequencing methodologies are already overcoming these technical and cost issues.

More than 500 coding region sequence variations have been detected in *BRCA1* and 250 in *BRCA2*. A listing and description of most known mutations is available on the Breast Cancer Information Core (BIC) website (research.nhgri.nih.gov/bic/). Several similarities between *BRCA1* and *BRCA2* are apparent. No mutation hot spots in either have been detected. Most unequivocally confirmed mutations reported to date are truncating mutations, adding little in the way of clues for defining functional regions. Finally, few mutations have been identified in either gene in sporadic breast cancers. However, it has been suggested that the pathways in which the *BRCA1* and *BRCA2* proteins act may be disrupted in sporadic cancer, a phenotype that has been termed "BRCAness" (25).

Estimates of *BRCA1* and *BRCA2* mutation prevalence in unselected patients with breast cancer are in the range of 2% to 3%. In a large population-based study of white and black cases (n = 1,628) and controls (n = 674) in North America for ages 35 to 64, *BRCA1* mutations were detected in 2.4% of cases and 0.04% of controls while *BRCA2* mutations were detected in 2.3% of cases and 0.4% of controls. *BRCA1* mutations were more common in white (2.9%) than black (1.4%) of cases, while *BRCA2* mutations were slightly more frequent in black (2.6%) than white (2.1%) cases (7).

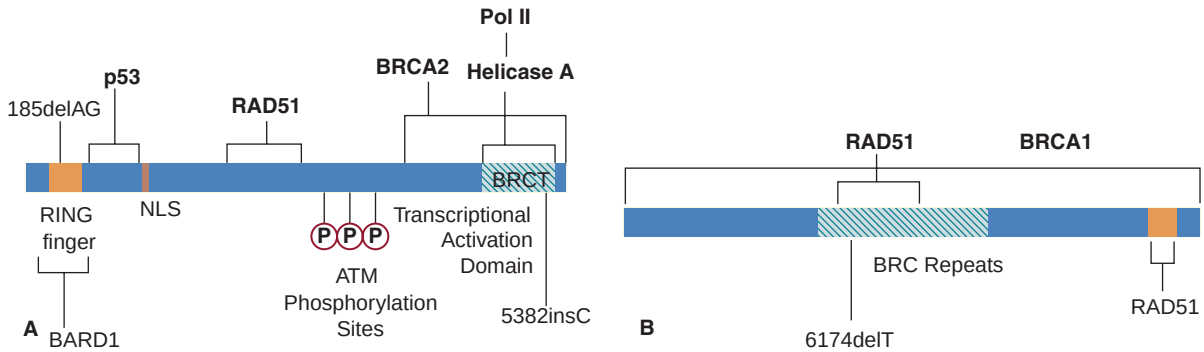


FIGURE 16-2 **(A)** Functional domains of *BRCA1*. An idiogram of the 220-kd *BRCA1* protein depicting known functional domains. Domains are shown as filled areas within the diagram. The two common mutations found in the Ashkenazi Jewish population (185delAG and 5382insC) are indicated. **(B)** Functional domains of *BRCA2*. The carboxy terminal RAD51 binding site, and the central RAD51 binding BRC repeats are as depicted. The common mutation (6174delT) found in the Ashkenazi Jewish population is indicated (51,52).

In families identified through clinics treating high-risk breast cancer, *BRCA1* and *BRCA2* mutations are found in up to 55% of families with both breast and ovarian cancer and up to 75% of families with both breast and ovarian cancer in the same individual, underscoring the importance of the family history in determining the likelihood that a *BRCA1* mutation is present (26). Population-based DNA sequencing studies, now feasible due to new technology, should give much more accurate estimates of mutation prevalence.

Population Genetics of BRCA1 *and* BRCA2

The population genetics of *BRCA1* and *BRCA2* reflect several basic evolutionary principles. Each gene has undergone multiple independent mutations and these mutations have migrated with the populations in which they originally occurred. Certain "founder mutations" are known to exist in *BRCA1* and *BRCA2,* which have occurred in specific ethnic populations many generations in the past. They persist because the development of disease usually occurs after childbearing age, so individuals carrying these mutations are able to pass them on to subsequent generations with little impact of the mutated alleles on survival of the species.

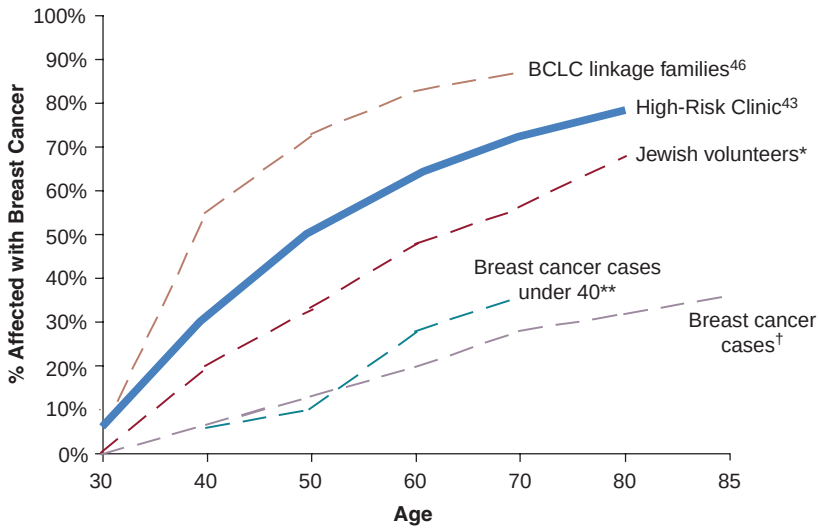
Founder mutations have been identified in a number of populations. A comprehensive review by Szabo and King (27) reveals the similarities and differences in mutation rate, penetrance, and nature of the mutations among various population groups. The proportion of high-risk families with breast or ovarian cancer appears to vary widely by population group. Mutations in *BRCA1* are most common in Russia (79% of families with breast and/or ovarian cancer), as compared to Israel (47% of families) and Italy (29%). *BRCA2* mutations appear to be more common than *BRCA1* mutations only in Iceland, where a single mutation accounts for virtually all of the *BRCA2*-associated breast and ovarian cancer cases (28).

BRCA1 and *BRCA2* mutations among the Ashkenazi Jewish population are among the most intensively researched, as the presence of founder mutations facilitates these studies. The two Ashkenazi Jewish founder mutations in *BRCA1* are 185delAG and 5382insC, occurring in 1 in 8 and 1 in 12 individuals of Ashkenazi descent, respectively (29,30). One of these two mutations, 6174delT in *BRCA2,* occurs in more than 2% of the Ashkenazi Jewish population. When compared to the estimated frequency of *BRCA1* mutations in an unselected white population of about 0.1% (31), this finding suggested the presence of a "founder effect" in the Ashkenazi Jewish population, documented with haplotype studies (32). Analysis of germline *BRCA1* mutations in several cohorts of Jewish women suggests that more than 20% of Jewish women developing breast cancer before age 40 carry the 185delAG mutation (33). Even more strikingly, estimates suggest that 30% to 60% of all Ashkenazi Jewish women with ovarian cancer carry one of the *BRCA1* or *BRCA2* founder mutations (34). Up to 90% of mutations identified in women of Ashkenazi Jewish descent are one of the three founder mutations, although other *BRCA1* and *BRCA2* mutations have also been detected (35). Based on these data, individuals of Ashkenazi descent choosing to undergo genetic testing should first be tested for the three Ashkenazi Jewish founder mutations. Full sequencing can be reserved for those individuals at particularly high risk of having a *BRCA1* or *BRCA2* mutation.

Though still limited, data are now available on the prevalence of *BRCA1* and *BRCA2* mutations in some nonwhite populations. Interestingly, many *BRCA1* and *BRCA2* mutations in African Americans appear unique to this ethnic/racial group (36) and in addition, genetic testing for *BRCA1* and *BRCA2* mutations in the African American population is complicated by a high rate of variants of unknown significance. More data are also becoming available from the Hispanic population, with similar features predicting pathogenic mutations (37). Comprehensive data from other ethnic groups or geographic areas are lacking.

Cancer Risks for BRCA1 *and* BRCA2 *Mutation Carriers*

Cancer risk estimates for *BRCA1* and *BRCA2* mutation carriers have been controversial (38). Estimates based on the highly penetrant families used to find these genes are high (as they were selected to be), likely due to coexistent genetic and environmental modifiers that may increase the risk of disease. However, in studies of lower-risk cohorts, such as population-based studies or cohorts of women with breast cancer unselected for family history, the lifetime risk of breast cancer was much lower (39). For this reason, the estimation of the risk of breast cancer in *BRCA1* mutation carriers has been variable with an estimate of pooled data of 65% (40) (Fig. 16-3). Estimates of contralateral breast cancer occurrence are as high as 60% (41). Cumulative risk of ovarian cancer in *BRCA1* carriers has been reported to be



*Data from Struewing JP, Hartge P, Wacholder S, et al. *N Engl J Med* 1997;336:1401–1408.
**Data from Fodor FH, Weston A, Bleiweiss IJ, et al. *Am J Hum Genet* 1998;63:45–51.
†Data from Hopper JL, Southey MC, Dite GS, et al. *Cancer Epidemiol Biomarkers Prev* 1999;8:741–747.

FIGURE 16-3 Breast cancer risk estimates associated with *BRCA1* mutations vary depending on sample ascertainment. Breast cancer risks (penetrance) will be highest in families selected to have multiple affected family members for use in linkage studies (27) and lowest in population-based ascertainments (29). Sample sets collected in breast cancer risk evaluation clinics would be expected to be intermediate between these two ascertainments; recent data have confirmed that hypothesis (30). An ascertainment of Ashkenazi Jewish volunteers also falls between high- and low-risk penetrance estimates, again because this sample is likely a mix of population-based ascertainment and individuals who volunteer because they were aware of a strong family history (31).

between 27% (40) and 45% (42,43), and there is also a significantly increased risk of fallopian tube cancer and reports of an increase in uterine and cervical cancer, stomach cancer, a twofold to threefold increase in pancreatic cancer, a possible twofold increase in colon cancer, and a 17-fold risk of testicular cancer (43,44); however, these risks have not been consistently seen across studies. Prostate cancer risk does not appear increased, although the disease may occur at an earlier age. Male breast cancer is also seen in association with *BRCA1* mutations (43).

BRCA2 has a cancer risk profile similar, but not identical, to *BRCA1*. Lifetime breast cancer risk for *BRCA2* mutation carriers is estimated to be 45% to 84%, with lifetime ovarian cancer risk in the range of 10% to 20% (40,45) and *BRCA2* mutations are associated with a 6% lifetime risk of male breast cancer (7). Male *BRCA2* mutation carriers have an increased risk of prostate cancer. Pancreatic cancer also is associated with *BRCA2* mutations (46), with an RR of 3.5. The incidence of *BRCA2* germline mutations in patients with familial pancreatic cancer (two first-degree relatives with pancreatic cancer) may be as high as 20% (47). *BRCA2* mutation carriers also appear to have an increased risk of stomach cancer (RR = 2.6), gallbladder and bile duct cancers (RR = 5.0), and malignant melanoma (RR = 2.6) (46).

Modifiers of BRCA1 *and* BRCA2 *Mutations*

Although germline mutations in *BRCA1* and *BRCA2* confer a high risk of breast cancer, a great deal of variability in cancer risk among individuals both between and within families has been observed. The discovery of environmental or genetic factors that modify the penetrance of *BRCA1* and *BRCA2* mutations may clarify our understanding of their mechanism of action and provide additional information with which to counsel individuals with *BRCA1* and *BRCA2* mutations. Furthermore, factors that affect familial breast cancer risk in the general population could presumably affect breast cancer risk in *BRCA1* and *BRCA2* mutation carriers. By far the most important modifiers identified for *BRCA1* and *BRCA2* mutation carriers are prophylactic oophorectomy and the use of tamoxifen for chemoprevention. Prophylactic oophorectomy decreases the risk of ovarian cancer by 95% but importantly also decreases the risk of breast cancer by 50% (48,49). The magnitude of the benefit of oophorectomy (and estrogen deprivation) on breast cancer risk is seen in both in *BRCA1* and *BRCA2* mutation carriers, despite that 90% of *BRCA1*-related breast cancers are ER negative. In retrospective studies, tamoxifen has been shown to decrease the risk of contralateral breast tumors by 50% in both *BRCA1* and *BRCA2* mutation carriers (50). To date, many reproductive factors have been examined as modifiers in *BRCA1* and *BRCA2* mutation carriers, including parity, age at first pregnancy, oral contraceptive use, and tubal ligation (51). Of all these, perhaps the most clinically relevant are the protective effects of oral contraceptives on ovarian cancer risk.

Genetic factors are likely to modify the risk of cancer in *BRCA1* and *BRCA2* mutation carriers. However, most studies examining this have been limited in size and statistical power. Convincingly validated modifiers of *BRCA1* and *BRCA2* penetrance have yet to be identified. However, consortia of investigators are now being established to systematically investigate candidate genetic modifiers. One such group, the Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2* (CIMBA), contains about 30 affiliated groups who together have collected DNA and clinical data from approximately 10,000 *BRCA1* and 5,000 *BRCA2* mutation carriers (52). Initial results have provided support for the role of a number of gene variants in affecting penetrance in mutation carriers. The identification of proven genetic modifiers of breast cancer risk for *BRCA1* and *BRCA2* mutation carriers may prove useful for the determination of individualized risk of cancer among carriers.

Biological Function(s) of BRCA1 *and* BRCA2

BRCA1 and BRCA2 Proteins: BRCA1 is a nuclear protein with two important regions of sequence similarity to known functional motifs. These regions are the RING domain at the beginning of BRCA1 and the BRCT motif at the carboxyl terminus (Fig. 16-4A). The 42 amino acid RING domain (so called because it was initially described in a *R*eally *I*nteresting *N*ew *G*ene) near the amino terminus of BRCA1 binds zinc (7). RING domains mediate interactions between proteins involved in polyubiquitination, a key cellular process regulating protein degradation that is essential in cell growth and differentiation (53). The BARD1 (BRCA1-associated RING domain-1) protein binds the BRCA1 RING domain (54) which confers substantial ubiquitin ligase activity on the complex. The BRCA1–BARD1 heterodimer can therefore add polyubiquitin chains to specific lysine residues of target proteins, targeting those proteins for modification and degradation (55). The BRCT (*br*east *c*ancer-1 *t*erminus) domain was first recognized as a cellular motif by its presence in BRCA1, but it is now known to be highly evolutionarily conserved and present in more than 40 other proteins involved in response to DNA damage, including scRAD9 in yeast and BARD1; this domain functions as a phospho-protein docking motif (56).

Like BRCA1, BRCA2 is a nuclear protein. However, the structure of BRCA2 initially provided fewer insights into its function (Fig. 16-2B). Subsequently, major structural motifs recognized in BRCA2 are the eight tandem BRC repeats in the central portion of the protein which mediate

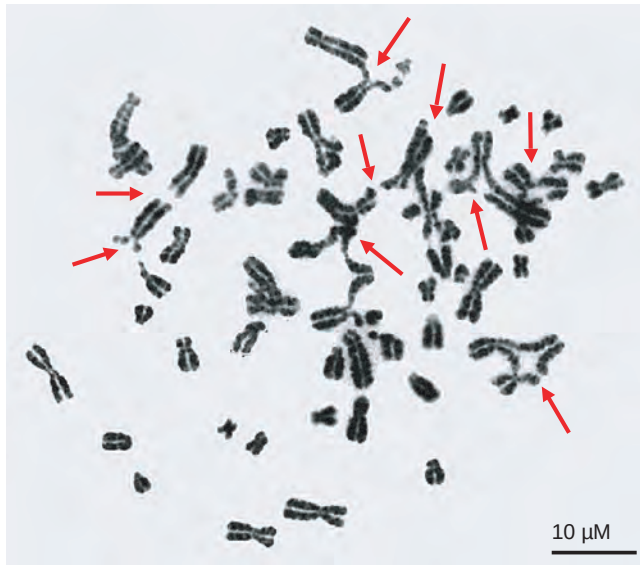


FIGURE 16-4 *BRCA2*-deficient cells are highly sensitive to DNA cross-linking agents. Cells defective in *BRCA2* function show a high degree of chromosome instability, including chromosome breaks and radial chromosomes (51,52,139). These aberrations accumulate spontaneously but are highly exascerbated by DNA-damaging agents that induce DSBs, in particular DNA cross-linking agents. Shown here are the effects of treating CAPAN1 cells, which carry a loss of function c.6174delT *BRCA2* allele and no wild-type allele, with the DNA cross-linking agent mitomycin C. *Arrows* indicate chromosomal aberrations.

the critical interaction of BRCA2 and RAD51 (22,23). TR2, another binding site for RAD51 exists at the carboxyl terminus of BRCA2 (57). The structure of a large portion of the C-terminus of *BRCA2* has been determined, which revealed the presence of a single-strand and double-strand DNA binding domain (58).

Roles of BRCA1 and BRCA2 in the Response to DNA Damage: The *BRCA1* and *BRCA2* genes encode large proteins that likely function in multiple cellular pathways including transcription, cell cycle regulation (59). However, it is the roles of BRCA1 and BRCA2 in the maintenance of genome stability DNA repair that have been best documented (20). Both proteins suppress illegitimate recombination and play important roles in the repair of double-stranded DNA breaks as a central part of this function. BRCA1 participates more broadly in this process than BRCA2, with a role both in sensing and signaling the presence of damaged DNA and in assisting in repair of the damage locally. When present in normal cells, BRCA1 enhances transcription of other important genes in the process, regulates the S, G_1, and G_{2M} checkpoints, ensuring that cells with damaged DNA damage do not replicate, alters chromatin structure and nucleosome organization at the local site of damage, facilitating access by repair complexes, and promotes use of the error-free repair pathway of homologous recombination (HR) -mediated repair rather than the error-prone process of nonhomologous end joining (NHEJ) (20).

BRCA2 has a more limited role in maintaining genome stability, functioning only at the local site of repair by regulating the activity of RAD51, an essential component of error-free HR-mediated repair of double-stranded breaks (20). In particular, BRCA2 affects the choice between the two HR subpathways—the conservative gene conversion (GC) mechanism and the error-prone single-strand annealing (SSA). In BRCA2 mutant cells, GC is suppressed leading to the preferential use of NHEJ and SSA. The physical interaction between BRCA2 and RAD51 is essential for error-free DSB repair. BRCA2 is required for the localization of RAD51 to sites of DNA damage, where RAD51 forms the nucleoprotein filament required for recombination. Foci of RAD51 protein are apparent in the nucleus after certain forms of DNA damage and these likely represent sites of repair by HR; BRCA2-deficient cells do not form RAD51 foci in response to DNA damage (60).

For both BRCA1 and BRCA2 it is the failure to faithfully repair DNA breaks that underlies the genomic instability in BRCA1 and BRCA2 mutant cells (Fig. 16-5). Cells defective in BRCA1 and BRCA2 function show a high degree of chromosome instability, including chromosome breaks and radial chromosomes (60–62). These aberrations accumulate spontaneously but are exacerbated by DNA damaging agents that induce DSBs, in particular DNA cross-linking agents (Fig. 16-4). These observations eventually provided critical information for the identification of *FANCD2*, mutated in Fanconi's anemia type D2, as BRCA2 (9). This discovery was made in part due to the observation that cells from patients from the Fanconi complementation group D2 have the same unusual chromosomal structures seen in BRCA2-deficient cells.

Other Functions of BRCA1: The role of BRCA1 as a transcriptional coactivator—a protein that facilitates transcription of genes in the presence of direct transcriptional activators—is a critical component of its ability to transduce signals, activating DNA damage response pathways. In unraveling this function, BRCA1 first was shown to interact with two key components of the cell transcription machinery of the cell including the RNA polymerase holoenzyme (63). In addition, the carboxy-terminus BRCT repeats act as transcriptional activation domains (64). *BRCA1* has been shown to be an important factor in the transcriptional regulation of ER (65). In the absence of functional *BRCA1* ER is no longer expressed and this is could be the explanation of the ER negative, basal, phenotype of tumors arising in *BRCA1* mutation carriers (25). Recently additional novel functions have been proposed (66).

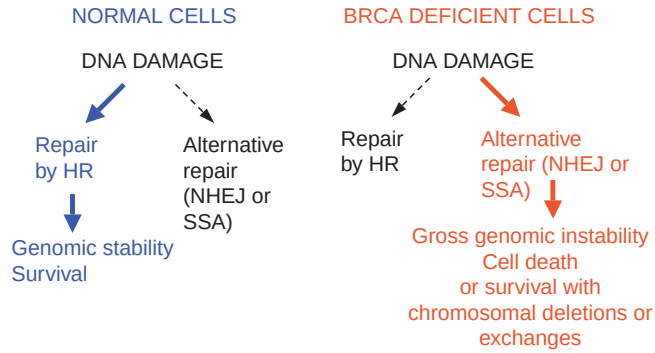


FIGURE 16-5 Loss of functional BRCA1 or BRCA2 affects the choice of DNA double-strand break repair pathway. DNA DSBs are repaired in normal cells, in part, by HR-based mechanisms. Functional *BRCA1* and *BRCA2* proteins are required for efficient repair by HR and genomic stability. In the absence of BRCA1 or BRCA2 alternative repair pathways, such as NHEJ and SSA, are utilized leading to cell death or survival with genomic damage (20).

CLINICAL FEATURES OF HEREDITARY BREAST CANCER

Breast cancers caused by mutations in high-penetrance susceptibility genes have several distinctive clinical features: Age at diagnosis is considerably younger than in sporadic cases, the prevalence of bilateral breast cancer is higher, and associated tumors are noted in some families. Associated tumors may include ovarian, colon, prostate, pancreatic, and endometrial cancers, among others, as well as sarcomas and breast cancer in male family members. Evidence reviewed later in this chapter also supports the notion that tumors arising in the setting of inherited mutations in susceptibility genes have different characteristics with regard to grade, estrogen receptor (ER) status, and molecular profile. Whether these cancers respond differently to treatment or are associated with a worse prognosis than sporadic tumors remains controversial.

Histopathology of *BRCA1*- and *BRCA2*-Associated Breast Tumors

In contrast to sporadic breast cancers, those arising in *BRCA1* mutation carriers are frequently, although not exclusively, negative for the estrogen receptor (ER) and the growth factor receptor, HER2, but mostly express basal cytokeratins (67–68). In support of this, gene expression profiling analysis indicates relative downregulation of ER response genes and the upregulation of proliferation associated genes and basal cytokeratins. This phenotype leads to the clustering of these tumors with sporadic cancers of the basal-like subtype (25,69). A mechanism by which loss of *BRCA1* function likely mandates lack of ER and ER regulated

gene expression has been suggested. Functional *BRCA1* appears necessary for the expression of ER by directly binding and transactivating the *ER* gene promoter. When *BRCA1* is lost in tumors, ER can no longer be expressed and, as a result, resistance to tamoxifen and other ER-directed therapies arises (65).

BRCA2 mutation associated breast cancers are typically quite different to those arising in *BRCA1* mutation carriers and are generally much more similar to sporadic cases. Specific morphological features such as pushing margins and a greater degree of tubule formation have been noted. The ER and HER2 status of tumors, are not obviously different from the spectrum of sporadic cancers invasive ductal cancers (70). However, a recent study has suggested that *BRCA2* associated tumors are of higher grade, are more frequently ER positive and are less likely to overexpress HER2 compared to control sporadic tumors matched for age and ethnicity. In summary *BRCA2* cancers tend to be a high grade proliferative form of luminal breast cancer.

Influence of *BRCA1* or *BRCA2* Mutation Status on Breast Cancer Prognosis

This remains a controversial issue in part because of the diversity of the design of the studies that have been used. A review of most of these concluded that there was no convincing data, in women with breast cancer, that *BRCA1* or *BRCA2* mutation status conferred adverse prognosis, other than for contralateral breast cancer occurrence (71). Since this review was published two other relevant studies have been reported. Moller et al. (72) studied patients who developed breast cancer while enrolled on prospective breast cancer surveillance programs because of strong family history of breast cancer and mutation status was confirmed by re-sequencing. *BRCA1* mutation was associated with worse prognosis even in classically low risk node negative patients. Rennert et al. (73) conducted a very large population study in Israel in which all new cases of invasive breast cancer in the country in 1987 and 1988 were sought. Case records and pathology samples were available on 1545 women and tumor DNA was extracted and analyzed for the three Ashkenazi founder mutations in *BRCA1* and *BRCA2*. No difference in overall or breast cancer specific survival was noted for *BRCA1* or *BRCA2* mutation carriers when compared with non-carriers.

Influence of *BRCA1* or *BRCA2* Mutation Status on Response to Therapy

Rennert et al. noted two important observations in subgroups of their large Israeli study (73). First, there was a statistically significant correlation between *BRCA1* mutation status and a more favorable prognosis in women receiving adjuvant chemotherapy when compared with non-carriers. Second, women presenting with tumors less than 2 cm had a worse prognosis if they were *BRCA1* carriers. This is intriguing given the similar results of another retrospective study of similar design conducted in 505 Jewish women in New York and Montreal with small tumors suitable for breast conserving surgery (74). Robson et al. (74) found the presence of an Ashkenazi founder mutation in *BRCA1* to be associated with adverse breast cancer survival when compared with non-carriers (62% at 10 years versus 86%; $p < .0001$). *BRCA1* status predicted breast cancer mortality only among women who did not receive chemotherapy (hazard ratio 4.8, 95% confidence interval 2.0–11.7; $p = .001$). Whether this phenomenon relates directly to *BRCA1* gene function or some other aspect of the basal-like breast cancer phenotype associated with *BRCA1* mutated breast cancer is not clear. A similar adverse prognosis normalized by an apparent increase in sensitivity to chemotherapy in sporadic "basal-like" breast cancer has also been reported in a small study (75) and sporadic "basal-like" breast cancers have been noted to have high response rates to anthracycline based chemotherapy, in common with the other major ER negative subtype, the HER2 positive cancers (76). There are few data relating to *BRCA1* or *BRCA2* genotype specific effects on normal tissue chemotherapy toxicity. Retrospective data suggest no evidence of increased complications (77). Taken together these data suggest that *BRCA1* mutation carriers who present with small and node negative breast cancers may be at more significant risk of micro-metastatic breast cancer than noncarriers. This may explain a worse prognosis if chemotherapy is avoided in what is regarded as a classically lower-risk population. A greater sensitivity to adjuvant chemotherapy seems to correct for any adverse baseline prognosis.

A potential concern, because of the role of *BRCA1* and *BRCA2* in the DNA damage response, is response to radiotherapy. A mature analysis of *BRCA1* and *BRCA2* carriers and matched controls treated with breast-conserving therapy and radiotherapy and followed for a median of 6 to 8 years has shown no increase in ipsilateral breast tumor recurrence in carriers who had had a prophylactic oophorectomy when compared to matched controls. An increase was noted in women who did not have prophylactic oophorectomy (78). As stated above, contralateral breast cancers were significantly more common in *BRCA1* and *BRCA2* mutation carriers than controls whether or not prophylactic oophorectomy was performed. There is, however, no evidence of increase in normal tissue radiation toxicity associated with carrier status (78,79).

What Is the Most Effective Chemotherapy for *BRCA1*- and *BRCA2*-Associated Breast Cancer?

A number of clinically used agents appear to be selective for killing cells defective in *BRCA1* or *BRCA2*. These include the DNA cross-linking agents (e.g., carboplatin, cisplatin, and mitomycin C) (60). This suggests an increased sensitivity to lesions that damage DNA in ways that interfere with DNA replication forks and which subsequently require DNA repair by homologous recombination for fork restart. This is consistent with the key role that *BRCA1* and *BRCA2* play in the Fanconi anaemia network (66), the hallmark of which is extreme cellular sensitivity to DNA cross-linking agents. The sensitivity of *BRCA1*- and *BRCA2*-deficient cancers to platinum salts is strongly supported by observations in genetically modified mice (80).

It has been suggested that *BRCA1* may be required to mediate paclitaxel induced cell death as loss of *BRCA1* function leads to microtubule stabilizing agent resistance (81). This contention is supported by uncontrolled retrospective data from patients treated with taxane-based neoadjuvant therapy (82). An randomized phase II clinical study testing the efficacy of carboplatin and docetaxel in *BRCA1* and *BRCA2* carriers with advanced breast cancer (www.breakthrough.org.uk/researchcentre/clinical_trials/brca_trial/index.html)(60) is ongoing.

New Therapeutic Approaches to the Treatment of *BRCA1*- and *BRCA2*-Associated Cancers

New therapeutic strategies, based on synthetic lethality, have recently been put forward for the treatment of cancers arising in carriers of mutations in *BRCA1* or *BRCA2* (20,83).

Synthetic lethality is defined as the situation when mutation in either of two genes individually has no effect but combining the mutations leads to death (20). This effect can arise because of a number of different gene–gene interactions. Examples include two genes in separate semiredundant or cooperating pathways and two genes acting in the same pathway where loss of both critically affects flux through the pathway. The implication is that targeting one of these genes in a cancer where the other is defective should be selectively lethal to the tumor cells but not toxic to the normal cells. In principal, this should lead to a large therapeutic window (20).

The synthetic lethal pair in the approach that is being developed is the interaction between HR and the single-strand break (SSB) DNA repair pathway (84). Endogenous base damage, including SSBs, is the most common DNA aberration and it has been estimated that the average cell may repair 10,000 such lesions every day. Base excision repair (BER) is an important pathway for the repair of SSBs and involves the sensing of the lesion followed by the recruitment of a number of other proteins. PARP-1 (Poly[ADP]Ribose Polymerase) is a critical component of the major "short-patch" BER pathway. PARP-1 is an enzyme, discovered over 40 years ago (20), that produces large branched chains of poly(ADP) ribose (PAR) from NAD^+ which senses and binds to DNA nicks and breaks. This results in activation of catalytic activity causing poly(ADP) ribosylation of PARP-1 itself as well as other acceptor proteins such as histones. This modification potentially signals the recruitment of other components of DNA repair pathways as well as modifying the activity of proteins (84).

PARP-1 inhibition causes failure of the repair of SSB lesions but does not affect DSB repair (20). However, a persistent DNA SSB encountered by a DNA replication fork will cause stalling of the fork and may result in either fork collapse or the formation of a DSB (20). Therefore, loss of PARP-1 increases the formation of DNA lesions that might be repaired by GC. As loss of function of either *BRCA1* or *BRCA2* impairs GC, loss of PARP-1 function in a *BRCA1* or *BRCA2* defective background likely results in the generation of replication-associated DNA lesions normally repaired by sister chromatid exchange. This is likely to be the explanation of the observation that small molecules PARP inhibitors are highly selectively lethal to cells lacking functional *BRCA1* or *BRCA2* (Fig. 16-6).

These observations suggested a potential new mechanism-based approach for the treatment of patients with *BRCA1*- and *BRCA2*-associated cancers. In these patients, tumor cells lack wild-type *BRCA1* or *BRCA2* but normal tissues retain a single wild-type copy of the relevant gene potentially providing a large therapeutic window. This difference provides the rationale for inhibiting PARP to generate specific DNA lesions that require functional *BRCA1* and *BRCA2* for their repair. This approach is likely to be more specific and to have fewer side effects than standard cytotoxic chemotherapy, as PARP inhibitors are relatively nontoxic and do not directly damage DNA. A number of PARP inhibitors are in clinical development (20).

Phase 1 studies have established the safety of olaparib, a potent PARP inhibitor, as a single agent and shown that significant and durable antitumor responses can be established in patients with BRCA-mutant breast, ovarian, or prostate tumors (85). Furthermore, olaparib does not seems to cause many of the side effects associated with standard chemotherapies. In subsequent phase 2 clinical studies, 40% of patients with breast or ovarian cancer with germline BRCA mutations had a favorable response to the drug (86,87). This is a particularly high response given that the patients in these trials had been heavily pretreated and had become resistant to a range of chemotherapies. Such work has led to a series of additional PARP inhibitors being tested in clinical trials (20). Not all of these trials have shown positive results, which in part may be due to differences in the pharmacological properties of the PARP inhibitors used, the nature of the study population and the trial design (20).

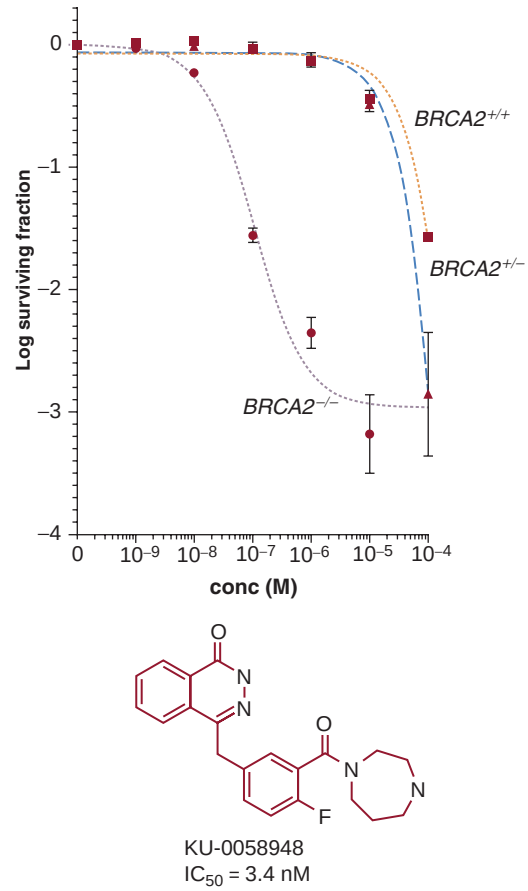


FIGURE 16-6 *BRCA2* mutant cells are exquisitely sensitive to a potent PARP inhibitor (20,83). Clonogenic survival curves of *BRCA2* wild-type, heterozygous, and deficient mouse ES cells after exposure to a range of concentrations of the potent PARP inhibitor KU0058948. *BRCA2*-deficient cells are over 1,000-fold more sensitive than wild-type or heterozygous cells. KU0058948 is based around a phthalazin-1-one core and is a competitive inhibitor with respect to the PARP substrate NAD+ (20).

Mechanisms by which *BRCA2* mutated cells can acquire resistance to PARP inhibitors and platinum salts have been studied (88). These experiments have shown that mutagenic DNA pathways that are up-regulated in the absence of *BRCA2* function may drive intragenic deletion events. These can rarely correct the effect of mutation on the open reading frame and restore expression of a functional *BRCA2* gene (88). These rare events may then be selected for over time in a sensitive population. This potential mechanism of resistance to PARP inhibitors has now been observed clinically in humans (89).

OTHER BREAST CANCER SUSCEPTIBILITY GENES

TP53

Germline mutations in *TP53* result in Li-Fraumeni syndrome (LFS), which was first identified in 1969 in four kindreds with multiple childhood sarcomas and excessive cancer risks (12). Subsequent epidemiologic efforts have identified the major component neoplasms, including breast cancer, soft-tissue sarcomas and osteosarcomas, brain tumors, leukemia, and adrenocortical carcinomas; several additional tumor types are likely to merit inclusion (90). Segregation analysis confirmed the autosomal dominant pattern of transmission of cancer susceptibility, with age-specific penetrance estimated to reach 90% by age 70 years (91). In 1990, germline *TP53* mutations were identified as the cause of LFS (92); approximately 50% of carefully defined families have alterations in *TP53*. The prevalence of germline *TP53* mutations in women with breast cancer diagnosed at younger than 40 years has been estimated at approximately 1%. Although an initial report suggested *CHEK2* mutations were responsible for some cases of LFS and LFS-like syndrome, this finding was not supported by much larger studies showing that *CHEK2* is a low-penetrance cancer susceptibility gene (93).

ATM

Ataxia-telangiectasia is an autosomal recessive disorder characterized by oculocutaneous telangiectasias, cerebellar ataxia, immune deficiency, and a predisposition to leukemia and lymphoma. Both copies of *ATM* (*A-T*, mutated) are mutated in patients with ataxia-telangiectasia (94). *ATM* is a member of a large family of protein kinases, and functions as a checkpoint in response to DNA damage, phosphorylating *TP53* and *BRCA1* in the presence of damaged DNA (94). Conflicting data have existed about whether female *ATM* heterozygotes have an increased risk for breast cancer. Initial studies examining family members of patients with ataxia-telangiectasia observed an increased number of breast cancer cases in obligate and predicted heterozygotes (95). However, the controls in the two largest studies had an unusually low incidence of breast cancer. Other studies have been inconclusive due to two factors: only small numbers of cases were included and in general the whole *ATM* gene was not screened due to its large size. In an attempt to overcome these limitations, Renwick et al. (96) screened the whole *ATM* gene in 443 *BRCA1 and BRCA2* mutation negative familial breast cancer cases and 521 controls. Significantly more *bona fide* ataxia-telangiectasia causing mutations were found in the cases than the controls. These results convincingly establish *ATM* as a breast cancer susceptibility gene.

One controversy that has emerged as a result of the question of breast cancer risk in *ATM* heterozygotes is the use of mammography in women younger than 50 years. Concern over repeated mammography was raised based on data that *ATM* homozygotes (i.e., that have ataxia-telangiectasia) have increased DNA damage from ionizing radiation. This biological defect suggested that the use of mammography for cancer detection should be weighed against the possibility of inducing cancer as a result of radiation exposure. However, *ATM* mutations do not appear to contribute to breast cancers diagnosed following radiation therapy for Hodgkin disease (97) and do not seem to play a role in recurrence following radiation for breast cancer (98). Therefore, magnitude of increased risk for breast cancer due to mammography in *ATM* heterozygotes is unknown and presumably small, and the benefit of detecting a neoplasm in its early stages is large. There has, thus, been almost uniform agreement that screening mammography should be initiated when clinically appropriate regardless of concern over the presence of *AT* mutations.

PTEN

Cowden's syndrome is a rare inherited syndrome in which mutations in *PTEN* are transmitted in an autosomal dominant pattern with variable penetrance. Malignant and benign lesions of the breast along with hamartomas in the gastrointestinal tract; mucocutaneous lesions (including trichilemmomas, papillomatosis of the lips and oral mucosa, and acral keratoses); thyroid abnormalities including goiters, adenomas, and follicular cancer; macrocephaly; uterine fibroids; and ovarian cysts and carcinomas characterize Cowden's syndrome (13). Approximately 75% of affected women have either fibrocystic breasts or mammary fibroadenomas. A marked increase in breast cancer incidence as compared to the general population was first observed in a series of cases of families with Cowden's disease, and subsequently it has been estimated that up to 25% to 50% of women with Cowden's disease may develop invasive breast cancer (13). Male breast cancer also has been reported in families with Cowden's syndrome, although infrequently (13).

STK11 LKB

Peutz-Jeghers syndrome, first described in the 1920s, is characterized by the occurrence of hamartomatous polyps in the small bowel and pigmented macules of the buccal mucosa, lips, fingers, and toes (99). It is an autosomal dominant disorder that has been reported to occur in approximately 1 in 20,000 live births. More recently, it has been associated with an excess incidence of tumors involving the breast, gastrointestinal tract, ovary, testis, and uterine cervix (99). The gene mutated in Peutz-Jeghers syndrome has been identified on chromosome 19 (100) and is *STK11/LKB1,* a tumor suppressor gene that encodes a protein kinase. Two studies have attempted to define the degree of cancer risk associated with the syndrome. Giardiello et al. (99) described a cohort of 31 patients followed from 1973 to 1985. Forty-eight percent of the patients developed cancer during that interval: Four developed gastrointestinal tract cancer and 10 developed non–gastrointestinal tract cancer, representing an RR 18 times that of the general population (99). An elevated risk of breast and gynecologic cancers has been reported in women with Peutz-Jeghers syndrome (101).

CHEK2

CHEK2 is located on chromosome 22, and encodes a cell-cycle checkpoint kinase that is implicated in DNA repair. An initial study suggested that families with LFS that lacked an identifiable *TP53* mutation had germline *CHEK2* mutations (93). However, there are now data providing strong evidence that *CHEK2* is not a high-penetrance cancer susceptibility gene in these families (101). The possibility that *CHEK2,* specifically the *CHEK2* 1100delC mutation, is associated with an increased risk of breast cancer was explored in a large multi-institutional study (102). Of those individuals with familial non-*BRCA1* and *BRCA2* breast cancer, 5.1% carried a *CHEK2* 1100delC mutation, compared to 1.4% of sporadic breast cancers, and 1.1% of controls ($p < 10^{-7}$) providing evidence that germline *CHEK2* mutations confer a twofold risk of breast cancer (95% CI). In addition, *CHEK2* 1100delC was found in 13.5% of individuals with breast cancer from families known to be negative for *BRCA1* or *BRCA2* mutations with at least one male breast cancer case (102). Thus, this mutation is associated with an RR of 10 for male breast cancer.

MLH1 and *MSH2*

Muir-Torre syndrome, a variant of hereditary nonpolyposis colon cancer (HNPCC, also called *Lynch syndrome type II*), is the eponym given to the association between multiple skin tumors and multiple benign and malignant tumors of the upper and lower gastrointestinal and genitourinary tracts (103). Many of the manifestations of Muir-Torre syndrome are common lesions (basal cell carcinomas, keratoacanthomas, and colonic diverticula) in distributions similar to that in the general population but with earlier age at onset in affected individuals. Women with the syndrome reportedly have an increased tendency to develop breast cancer, particularly after menopause, although lifetime risk has not been calculated (104). Multiple genes responsible for HNPCC have been described, including *MLH1* and *MSH2* (104). Mutations in these genes are thought to lead to the development of HNPCC through accumulation of DNA replication errors and associated subsequent genome instability (104).

PALB2

PALB2 was originally identified as a protein which interacts with the N-terminal region of *BRCA2* (105). This association is essential for *BRCA2* function and *PALB2* deficient cells are defective in double-strand break repair HR and sensitive to DNA cross-linking agents. These properties resemble genes involved in the Fanconi Anemia network and in fact biallelic mutations in *PALB2* cause Fanconi Anemia type N (106). A role for *PALB2* mutations in breast cancer susceptibility was established in two studies. Rahman et al. (107) identified five different monoallelic *PALB2* truncating mutations in 10 individuals with familial breast cancer; it was estimated that these mutations conferred a 2.3-fold elevated risk of breast cancer. In a separate study, a founder *PALB2* mutation in Finland was identified which appears to be associated with an approximately fourfold risk (108).

BRIP1

BRIP1 is a nuclear *BRCA1* interacting protein originally referred to as *BACH1* (109). This protein is a helicase and interacts with *BRCA1* via the BRCT-motif and contributes to its DNA repair functions. Like *PALB2, BRIP1* is implicated in Fanconi anaemia; *BRIP1* is the *FANCJ* gene. Seal et al. (110) identified constitutional truncating mutations of the *BRIP1* gene in individuals with breast cancer from *BRCA1 and BRCA2* mutation-negative families. These were significantly more common in this group than in a control population. It was estimated that *BRIP1* mutations confer a relative risk of breast cancer of about 2.

Low-Penetrance Breast Cancer Susceptibility Genes

Large collaborative studies using genome-wide association studies in thousands of breast cancer patients have led to the discovery of multiple genetic variants (SNPs) conferring relatively small risks of breast cancer on individuals. Some of these are within or near known genes such as *FGFR2, TOX3, MAP3K1,* and *RAD51L1* whereas others are present in regions of the genome distant from the nearest gene such as the SNPs on 2q35 and 8q24 (111) (Table 16-1). All of the SNPs so far identified confer small increases in risk of no less than 1.5-fold. Together, the variants so far identified explain around 10% of the overall familial risk suggesting that many more risk variants are to be found. Interestingly, some variants such as those in *FGFR2* confer elevated risk of ER-positive but not ER-negative breast cancers. Currently, the clinical utility of typing individuals for these variants is limited but may increase as more risk SNPs are identified and technology to analyze genomes becomes simpler and cheaper (111).

FUTURE DIRECTIONS IN BREAST CANCER GENETICS

Following the identification of *BRCA1* and *BRCA2,* there is an improved understanding of cancer risks associated with these genes, and management strategies to reduce cancer risks based on clinical evidence have been developed. Further elucidation of the basic mechanisms involved in the pathogenesis of *BRCA1*- and *BRCA2*-related breast cancers may allow more targeted interventions to eliminate risks in individuals with germline mutations and may provide critical information regarding the development of sporadic tumors. The influence of modifying factors, both genetic and environmental, is being addressed as families with identical mutations can have marked variation in cancer phenotype. However, known breast cancer susceptibility genes account for less than 25% of the familial aggregation of breast cancer. Many other variants with moderate or low penetrance, some of them common, will be discovered by utilization of new rapid and cheap methods of DNA sequencing. This will have considerable implications for risk assessment. The hope is that these advancements will improve the diagnosis and treatment of breast cancer in women affected with both inherited and sporadic forms of the disease.

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CHAPTER 17

Genetic Testing and Management of Patients with Hereditary Breast Cancer

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CHAPTER CONTENTS

Genetic counseling and testing are increasingly an integral component of the management of women with newly diagnosed breast cancer, particularly if they have a family history of breast and/or ovarian cancer. Because breast cancer is such a common disease in North America and northern Europe, it is not uncommon to encounter families in which two or three women have had this disease. Such clusters may be typical of *familial* breast cancer, particularly when the ages of onset are postmenopausal. In the majority of such familial clusters there is no clear single genetic etiology. *Hereditary* breast cancer, which is much less common, is usually characterized by two or more generations affected with breast and related cancers (e.g., ovarian cancer), often with a predisposition to early ages of onset. As discussed in this chapter, specific features of an individual's personal and family history can provide substantial clues about potential etiology. When family histories are suggestive of hereditary risk, women and their family members may benefit from genetic counseling and testing. Women at high risk can reduce their risk of cancer-related morbidity and mortality through increased surveillance and adoption of risk-reducing strategies. Noncarriers of known familial risk-conferring mutations may be relieved of persistent worry and avoid unnecessary interventions. Pre- and posttest genetic counseling ensure that individuals have appropriate information about the risks, benefits, and limitations of genetic testing, as well as how to use results for clinical management.

Although genetic counseling and testing for breast cancer, particularly with regard to *BRCA1* and *BRCA2* mutations, have diffused into mainstream oncologic care, questions regarding individualized cancer risks, the long term impact of management options, and how best to use this information to treat breast cancer patients remain. While risk reduction and early detection strategies have been extensively studied in individuals with *BRCA1* and *BRCA2* mutations, much less is known regarding management of individuals with mutations in rare high penetrance cancer susceptibility alleles (e.g., *PTEN, TP53, STK11, CDH1*). An additional layer of complexity stems from the discovery of a host of moderate penetrance genes (e.g., *CHEK2, BRIP, BARD*) for which there are particular concerns regarding clinical utility. These limitations in our knowledge create challenges for providers who must counsel patients about clinical management and for the patients who face the decisions to undergo genetic testing. This chapter provides an overview of the medical and psychosocial issues that are relevant to this process. The focus of this chapter is on patients at high risk who have family histories consistent with inherited susceptibility to breast cancer.

CLINICAL CHARACTERISTICS OF HEREDITARY BREAST CANCER

Approximately 5% to 10% of breast cancers arise as a result of an inherited susceptibility owing to alterations in a single highly penetrant gene. Most cases of hereditary breast cancer, and particularly hereditary breast and ovarian cancer, are attributable to mutations in *BRCA1* and *BRCA2 (BRCA1/2)* (1). Other hereditary breast cancer syndromes,

caused by mutations in highly penetrant genes (noted in parentheses), account for less than 1% of all cases of breast cancer each and include Li-Fraumeni syndrome (*TP53*) (2), Cowden syndrome or *PTEN* hamartoma syndrome (*PTEN*) (3), Peutz-Jeghers syndrome (*STK11*) (4), and hereditary diffuse gastric cancer syndrome (*CDH1/E-cadherin*) (5) (see Table 17-1 for details on these as well as associated cancer risks). Recently it has been demonstrated that women with Lynch Syndrome (Hereditary Non-Polyposis Colorectal Cancer Syndrome, HNPCC) also have an elevated risk of breast cancer (6). However, in contrast to the very elevated risk of colon cancer associated with mutations in *MLH1, MSH2*, and *MSH6*, the risk of breast cancer is only modestly elevated. Thus, mutations in these genes are highly penetrant for colon cancer, but only moderately penetrant for breast cancer (6). Multiple other moderate penetrance genes for breast cancer are also known, for example *CHEK2, ATM, BRIP, BARD*, and *PALB2* (7). These genes are associated with increased risk of breast cancer of 2–5 fold. Mutations in some of these genes have been clearly associated with other cancer risks, such as the association of *PALB2* mutations and pancreatic cancer risk (8). For most of the others, associated cancer risks are uncertain.

For most women with or at increased risk for breast cancer, genetic testing for *BRCA1/2* mutations is the most clinically useful and informative strategy. The reasons for this are that i) mutations in these genes are the most common of the highly penetrant genes, ii) the associated, significantly increased risk of ovarian cancer has major implications for clinical management, and iii) data exist to guide clinical management for mutation carriers and their family members. Mutation testing for the other high penetrance susceptibility genes is generally reserved for families in which there is suspicion for these distinct clinical syndromes (see Table 17-1). However, the landscape of genetic testing for cancer susceptibility is rapidly changing. Next generation sequencing (also known as massively parallel sequencing) allows for rapid genetic testing of multiple genes. Several multiplex panels incorporating moderate and high penetrance genes are now commercially available with more expected in the near future (see Table 17-2). In addition, panels of low penetrance single nucleotide polymorphisms (SNPs) are also commercially available. In addition to all of this, the costs of whole exome and whole genome sequencing have rapidly decreased. These rapid technical advances in germline sequencing currently exceed our ability to apply results to clinical practice and will be discussed further later.

In this chapter, we will focus on cancer risks and management strategies associated with mutations in *BRCA1/2*, but we will also discuss issues related to genetic counseling and management issues related to other genes.

BRCA1 and *BRCA2* Cancer Risks

Breast and Ovarian Cancer Risks

The literature addressing cancer risks in *BRCA1* and *BRCA2* mutation carriers reveals a wide range of potential risks for breast and ovarian cancer which are considerably elevated over the U.S. general population risks of 7% and less than 1%, respectively, to age 70. When reviewing these studies, it is important to consider various sources of ascertainment (e.g., through linkage testing versus direct genotyping, clinic-based versus unselected or population-based series, and selection through affected or unaffected cases or probands) and the relative advantages and limitations of specific study designs. Most of these studies are retrospective in nature, therefore yielding less robust estimates of cancer risk than prospective cohorts. In consideration of these factors, it is appropriate to inform patients about a range of reported risks in mutation carriers that is based on analysis of several studies. For example, the largest meta-analysis of studies published by Antoniou et al (9). combined data from 22 international studies comprising more than 8,000 index cases affected with female (86%) or male (2%) breast cancer or epithelial ovarian cancer (12%). To be included, index cases were

TABLE 17-1

High Penetrance Breast Cancer Susceptibility Genes

Gene	*Syndrome*	*Risk of breast cancer*	*Risk of epithelial ovarian cancer*	*Other cancer risks*	*Associated finding*
BRCA1	HBOC	50–70%	20–45%	Incompletely defined	
BRCA2	HBOC	50–70%	10–20%	Prostate, pancreatic, male breast cancer	
TP53	LFS	50–90%		Multiple: sarcoma, brain tumor, leukemia, adrenocortical tumors, colon cancer	Childhood malignancies
PTEN	Cowden	50–85%		Endometrial, thyroid, renal, colon, melanoma	Macrocephaly, skin findings, benign thyroid and uterine findings, developmental delay
STK11	PJS	55%		Colorectal, small bowel, pancreatic cancer; ovarian sex cord tumors	Lip freckling
CDH1	HDGC	40%		Gastric cancer	Lobular breast cancers

HBOC, hereditary breast and ovarian cancer; LFS, Li-Fraumeni Syndrome; PJS, Peutz-Jeghers Syndrome; HDGC, hereditary diffuse gastric cancer.

TABLE 17-2

Genes Analyzed in Commercially Available Multiplex Panels for Breast Cancer*

Gene	*Ambry Genetics (Aliso Viejo, CA)*			*University of Washington (Seattle, WA)*	*Syndrome (Major Cancer Risk)*
	CancerNext™	*BreastNext™*	*OvaNext™*	*BROCA™*	
APC	•			•	FAP[1](Colon)
ATM	•	•	•	•	
ATR				•	
BABAM1				•	
BAP1				•	
BARD1	•	•	•	•	
BMPR1A				•	Juvenile polyposis
BRIP1	•	•	•	•	
CDH1	•	•	•	•	HDGC[2] (Gastric cancer)
CDK4				•	
CDKN2A				•	FAMMMPC[3]
CHEK1				•	
CHEK2	•	•	•	•	
FAM175A/Abraxas				•	
MLH1	•		•	•	Lynch/HNPCC[4](Colon, uterine, ovary)
MRE11A	•	•	•	•	
MSH2+ EPCAM	•		•	•	Lynch/HNPCC (Colon, uterine, ovary)
MSH6	•		•	•	Lynch/HNPCC (Colon, uterine, ovary)
MUTYH	•	•	•	•	Recessive, colon cancer
NBN	•	•	•	•	
PALB2	•	•	•	•	
PMS2	•		•	•	Lynch/HNPCC (Colon, uterine, ovary)
PRSS1				•	
PTEN	•	•	•	•	Cowden Syndrome (Table 1)
RAD50	•	•	•	•	
RAD51				•	
RAD51B				•	
RAD51C	•	•	•	•	
RAD51D				•	
RBBP8				•	
RET				•	MEN2[5](Medullary thyroid cancer)
SMAD4	•			•	Juvenile polyposis
STK11	•	•	•	•	PJS[6](Table 1)
TP53	•	•	•	•	LFS[7](Table 1)
TP53BP1				•	
UIMC1				•	
VHL				•	VHL[8]
XRCC2				•	
XRCC3				•	

*As of May 2013
Shaded: Gene associated with a high penetrance of cancer (although not necessarily breast cancer).
[1]FAP, familial adenomatous Polyposis; [2]HDGC, hereditary diffuse gastric cancer; [3]FAMMMPC, familial atypical multiple mole melanoma syndrome; [4]HNPCC, hereditary non-polyposis colorectal cancer; [5]MEN, Multiple endocrine neoplasia; [6]PJS, Peutz-Jeghers syndrome; [7]LFS, Li-Fraumeni Syndrome; [8]VHL, von Hippel Lindau.

sampled independently of family history. The average cumulative breast cancer risk to age 70 years in *BRCA1* carriers was 65% (95% CI, 51%–75%), versus 45% (95% CI, 33%–54%) in *BRCA2* carriers. Interestingly, when families were ascertained through an index case diagnosed with breast cancer at an early age, especially before age 35 years, cumulative cancer risks were about 20% higher for *BRCA1* carriers (i.e., 87% risk of breast cancer [95% CI, 67%–95%] and 51% risk of ovarian cancer [95% CI, 9.1%–73%] versus 61% risk of breast cancer [41%–74%] and 32% for ovarian cancer [11%–49%] for families containing an older proband with breast cancer). When the index case was older, the *BRCA1*-associated breast cancer risks were similar to those identified through ovarian cancer probands. Similarly, in *BRCA2* families, the breast cancer risks were higher in families with breast cancer index cases versus ovarian cancer probands. Although breast cancer incidence was not impacted by the age of the index patient, *BRCA2*-associated ovarian cancer risks were higher when the proband had breast cancer before age 35. Another notable finding from these analyses was that the breast cancer incidence in *BRCA1* carriers increased with age, but starting at 50 years the incidence remained somewhat constant. In *BRCA2* carriers, however, the incidence of breast cancer continued to rise. These data also confirmed that ovarian cancer rates in women younger than 30 years are very low, but after that, risk rises more dramatically, especially for *BRCA1* carriers. Specifically, Antoniou et al. reported the lifetime risk of ovarian cancer in *BRCA1* carriers to be 39% (95% CI, 22%–51%) and 11% (95% CI, 4.1%–18%) in *BRCA2* carriers but for both *BRCA1* and *BRCA2* mutation carriers the risk of ovarian cancer prior to age 40 was less than 3% (9).

Chen et al. (10) performed a meta-analysis of ten international mixed-ascertainment studies that included data from families at high risk as well as population-based series. The cumulative risks to age 70 for breast cancer were 57% (95% CI, 47%–66%) for *BRCA1* and 49% (95% CI, 40%–57%) for *BRCA2* and ovarian cancer risks of 40% (95% CI, 35%–46%) for *BRCA1* and 18% (95% CI, 13%–23%) for *BRCA2* mutation carriers. These data are roughly consistent with the findings of Antoniou et al. (9) and provide reasonable parameters for clinical use. In addition, Chen and Parmigiani derived age-specific predicted mean breast and ovarian cancer risks for currently unaffected *BRCA1/2* mutation carriers based on their current age (20–60 years) (10). These data, published in tabular form, may be useful in clinical counseling. For example, based on the table, it is estimated that a 30-year-old, unaffected *BRCA1* carrier has a cumulative risk of breast cancer to age 40 of 10%; to age 50 it is 28%; to age 60 is 44%; and to age 70 it is 54%. In addition, her cumulative risk of ovarian cancer to age 40 is 2.2%; 8.7% to age 50; 22% to age 60; and 39% to age 70. Age-specific risks may be one important component to guide decisions about the timing of risk management procedures, such as prophylactic surgery.

Finally, investigators associated with the EMBRACE (Epidemiological study of *BRCA1* and *BRCA2* mutation carriers) consortium recently published one of the largest prospective studies of cancer risk in 978 *BRCA1* and 909 *BRCA2* mutation carriers from the United Kingdom (11). Using Kaplan-Meier estimates, they reported that the average cumulative breast cancer risk to age 70 in *BRCA1* and *BRCA2* carriers was 60% (95% CI, 44%–75%) and 55% (95% CI, 41% –70%), respectively. The average ovarian cancer risk to age 70 in *BRCA1* and *BRCA2* carriers was 59% (95% CI, 43%–76%) and 16.5% (95% CI, 7.5%–34%), respectively.

Considering these three studies together, the average cumulative risk of breast cancer in *BRCA1* and *BRCA2* carriers to age 70 is between 57% and 65% and 45% and 59%, respectively. The average cumulative risk of ovarian cancer to age 70 in *BRCA1* and *BRCA2* carriers is between 39% and 55% and 11% and 18%, respectively. In several instances, these average ranges encompass confidence intervals from different studies. It is also important to bear in mind that the life expectancy for most mutation carriers without cancer is greater than age 70, so these risks need to be extrapolated to older ages.

Importantly, primary fallopian tube cancer and primary peritoneal cancer are part of the tumor spectrum associated with *BRCA1* and *BRCA2* mutations (12) and are often included under the category of "ovarian cancer." A related question that arises, particularly for surgical treatment, is whether carriers face an elevated risk of uterine cancer. Overall, it does not appear that *BRCA1/2* mutation carriers have an excess risk of this malignancy unless they have used tamoxifen either as treatment or primary prevention (13).

These data underscore the complexity in providing an individualized risk assessment for *BRCA1/2* carriers. It is important, however, to counsel individuals about features of the pedigree that may hamper risk assessment, such as small family size, few women in the family, limited or unverifiable cancer history data, and so forth. Recent studies also suggest that more recent birth cohorts have an increased risk of breast cancer (14) In addition, variation in risk is likely to be attributable in part to genetic and nongenetic risk factors, as addressed later in this chapter. Validated comprehensive risk models to provide more individualized risk assessment are needed.

Second Malignancies after Breast Cancer

A hallmark of hereditary cancer is the predisposition toward multiple primary cancers. For example, *BRCA1/2* carriers who are affected with breast cancer have a 40% to 65% cumulative risk of contralateral breast cancer (12,15,16). These risks appear to differ depending on the age at first breast cancer diagnosis and mutation type (i.e. *BRCA1* vs. *BRCA2)* (15). For example, the 10 year risk of contralateral breast cancer is estimated to be 31% for *BRCA1* carriers whose first breast cancer was diagnosed at age less than 40, as compared with 8% for those who were initially diagnosed at age greater than 50 (15). The overall risk of contralateral disease in women diagnosed with breast cancer prior to age 40 at 25 years is estimated to be approximately 63% in *BRCA1* and *BRCA2* carriers (15). The risk of contralateral breast cancer may be reduced substantially with the use of tamoxifen, oophorectomy, or both (oophorectomy in premenopausal women) (17). This is discussed in greater detail in the section on management of mutation carriers with breast cancer. Of note, women with sporadic breast cancer have a 0.5% to 1.0% annual risk of contralateral breast cancer, leveling off at 20% at 20 years of follow-up. Although specific risks are difficult to quantify, it does appear that, over the long term, mutation carriers are at elevated risk of developing metachronous ipsilateral breast cancer (18).

A significant concern for *BRCA1/2* breast cancer survivors is the threat of developing ovarian cancer. Metcalfe et al. (19) reported that the 10-year actuarial risk of ovarian cancer in such patients was 12.7% and 6.8% for *BRCA1* and *BRCA2* carriers, respectively. Similar findings were seen by Domchek et al. with a risk of ovarian cancer following breast cancer of 7.8% in *BRCA1* carriers and 3.3% in *BRCA2* carriers with a median follow up of approximately 4 years (20). Of note, the development of ovarian cancer was the cause of death in one-fourth of the patients with stage I breast cancer in the Metcalfe study, underscoring the importance of considering the impact of mutation status in individuals who present with a malignancy.

Second Malignancies after Ovarian Cancer

An additional clinical concern is the risk of breast cancer following a diagnosis of ovarian cancer in *BRCA1/2* mutation carriers. Two studies have examined this issue and have found a low risk of breast cancer within 5 years of the diagnosis of ovarian cancer, which may be due in part to the impact of ovarian cancer treatment. At the same time, the risk of developing recurrent ovarian cancer was quite high. Specifically, Vencken et al. reported that women with *BRCA*-associated ovarian cancer had lower 5-year and 10-year risks of primary breast cancer (6%, and 11%, respectively) compared with unaffected mutation carriers (16%, and 28%, respectively); in addition, those with ovarian cancer had significantly higher mortality rates. The risk of death in those with ovarian cancer at 2, 5, and 10 years were 13%, 33%, and 61%. In comparison, the corresponding risks of death in carriers unaffected at the start of follow up were 1%, 2%, and 2%, respectively; $p < .001$). Similar findings were seen in Domchek et al. in which the 5- and 10-year breast cancer free survivals for *BRCA1/2* mutation carriers following ovarian cancer were 97% (95% CI = 0.92, 0.99) and 91% (95% CI = 0.82, 0.95), respectively. The 5- and 10-year overall survival rates were 85% (95% confidence interval [CI] = 0.78, 0.90) and 68% (95% CI = 0.59, 0.76), respectively. This information can help guide women making decisions about breast cancer management, but suggests that particularly in the first 5 years after diagnosis, conservative (non-surgical) management is reasonable (21,22).

Other Cancers

Several studies have reported an association between pancreatic cancer and *BRCA2* and *BRCA1* mutations (23,24), although the risk is more elevated in the former. The overall number of carriers with pancreatic cancer in these studies is low, but with this limitation, relative risks (RR) have been estimated at 2 to 3 for *BRCA1* and 2 to 6 for *BRCA2*. Despite the clear elevation in RR, the risk of pancreatic cancer in the general population is relatively low and thus even in *BRCA2* mutation carriers the lifetime risk estimates for pancreatic cancer appears to be 5% or less. There is concern that individuals in *BRCA*-families with multiple cases of pancreatic cancer have higher risks but these are difficult to quantify.

With respect to colon cancer risk in mutation carriers, some studies have identified elevated risks (12,25) and others have not (26). Thus, it is likely that if an elevation in risk exists, it appears to be small. In addition, increased risks of other cancers such as melanoma, uveal melanoma, and gastric cancer (particularly in *BRCA2* carriers) (12,25,27,28), have been seen but additional studies are needed to better quantify such risks. There may be a modest global risk in cancer in general.

Cancers Affecting Males

Multiple studies have demonstrated that prostate cancer risks are elevated in *BRCA2* mutation carriers with RR as high as 8 (28,29) with cancers often occurring younger than age 65 (25,27). The lifetime risk to age 65 is approximately 15% (29). *BRCA2*-associated prostate cancer appears to be more aggressive with higher risk disease and poorer survival. Male mutation carriers also have a substantially elevated risk of developing breast cancer. For example, a retrospective study utilizing data from 1,939 families, including 97 men with breast cancer, revealed that the cumulative risk of breast cancer at age 70 was 1.2% (95% CI, 0.22%–2.8%) and 6.8% (95% CI, 3.2%–12%) in *BRCA1* and *BRCA2* carriers, respectively (30). Although these absolute risks are low, the relative risks, particularly up to age 50, are sizable.

Summary: BRCA1/2-Associated Cancer Risks

In summary, given the wide confidence intervals reported in most studies and the range of risks found in different populations, it is difficult to define the precise cancer risks for individual mutation carriers. While it is known that genotype–phenotype correlations, genetic modifiers, and family history impact the risk of breast cancer it is uncertain how to translate these factors into clinical risk assessment (see Cancer Risk Modifiers). Nonetheless, although exact cancer risks for an individual are not known, it is clear that women with *BRCA1* and *BRCA2* mutations face a substantially elevated risk of early onset breast and ovarian cancer, with increased risks that persist throughout their lifetime.

Breast and Ovarian Cancer Risks in *BRCA1/2*-Negative Families

When an individual tests negative for *BRCA1/2* mutations, the first question that should be asked is whether there is a known mutation in the family. Several studies have demonstrated that individuals who test negative for a known mutation in the family (a "true negative") are at approximately the same risk for developing breast and ovarian cancer as women in the general population (in the absence of independent risk factors) (31–34).

In individuals with negative *BRCA1/2* testing and no known mutation in the family, testing is uninformative. Cancer risks in these families are dependent on the strength of the family history. In clinical practice, uninformative results from *BRCA1/2* testing are the most commonly encountered outcome and it is important to provide cancer risk assessments that factor in these results. Not surprisingly, relatives of *BRCA1/2* negative probands with early onset breast cancer or a strong family history of breast cancer still face increased risks of breast cancer, perhaps as much as three- to fourfold (34). However, of significant importance is that studies have also shown that there is no excess risk of invasive ovarian cancer in high risk *BRCA1/2* negative families ascertained through a breast cancer proband. (35,36) For example, a large study of 8,005 women from 895 families in the United Kingdom found the RR of ovarian cancer to be 0.37 (95% CI, 0.01–2.03) in uninformative *BRCA1/2* families (35). However, Lee et al. (37) found that if a family is ascertained through a woman who has *ovarian cancer*, her close relatives have an elevated risk of ovarian cancer, with a standardized incidence ratio of 1.9. Together, these studies suggest that members of *BRCA*-negative families, especially those with many cases of breast cancer, have an increased incidence of breast cancer, but are likely not at a significantly increased risk for ovarian cancer. Several computer models (e.g., BRCAPRO, BOADICEA, and IBIS—models which will be discussed shortly—allow the clinician to impute *BRCA1/2* test results (in this case, negative or uninformative) and obtain an estimate of breast and ovarian cancer risks in consideration of such test results and the individual's personal and family history. For families with at least one documented case of ovarian cancer, the possibility must be considered that an undetected mutation in *BRCA1/2* exists, there is a mutation in a different gene, or less likely, that the proband tested may be a phenocopy, as discussed later in this chapter.

Cancer Risk Modifiers

Genotype–Phenotype Correlations Within BRCA1 *and* BRCA2

Patients frequently ask whether mutation-specific data are available that may help individualize *BRCA1* or *BRCA2* risks. Although studies have suggested that genotype–phenotype correlations may exist, these data are not yet sufficiently

substantiated to integrate into clinical counseling. For example, a study of 164 families found that mutations occurring within the central region of the *BRCA2* gene, called the ovarian cancer cluster region (OCCR), was associated with a lower risk of breast cancer (RR = 0.63, 95% CI, 0.46–0.84) and a higher risk of ovarian cancer (RR = 1.88, 95% CI, 1.08–3.33) (38). Interestingly, in another study of unselected *BRCA2* carriers with ovarian cancer, first-degree relatives had ovarian, colon, stomach, pancreatic, or prostate cancer only when the proband's mutation was within the OCCR of exon 11, and an excess of breast cancers was observed when the mutation was outside of the OCCR (39). These findings suggest that mutations within the OCCR in *BRCA2* may confer a diminished risk of breast cancer (i.e., not necessarily a higher risk of ovarian cancer) and that mutations within the region may be associated with a broader tumor spectrum altogether.

Further studies in *BRCA1* and *BRCA2* carriers are needed before these data can be used to refine risk estimates in the clinic. In addition, an understanding of putative molecular mechanisms for differential risks will further contribute to our understanding of genotype–phenotype correlations.

Modifier Genes

As discussed earlier, it is possible that specific mutations in the *BRCA1/2* genes are associated with variable cancer risks. An increasing body of research is focusing on how polymorphisms in other genes impact *BRCA1/2* cancer risks. To generate sample sizes with sufficient statistical power to detect effects of modifier genes, an international consortium of more than 60 groups has been formed, known as CIMBA (Consortium of Investigators of Modifiers of *BRCA1* and *BRCA2*). By pooling data from approximately 30,000 mutation carriers, this group has found multiple genetic modifiers which impact breast risk in *BRCA1* and *BRCA2* mutation carriers. Interestingly, and importantly, it appears possible that the addition of single nucleotide polymorphism (SNP) panels could aid in individual risk prediction for *BRCA1/2* mutation carriers. In one study examining 7 risk-associated SNPs in *BRCA2* mutation carriers, the 5% of *BRCA2* carriers at highest risk were predicted to have a probability between 80% and 96% of developing breast cancer by age 80, compared with 42% to 50% for the 5% of carriers at lowest risk (40). Although as yet unknown, it is possible that these risk differences might be sufficient to influence the clinical management of mutation carriers.

In the future, it is very possible that individuals seeking information about their cancer risk may undergo a series of genetic tests that could help better personalize their risks. Thus, information about penetrance may be derived from data specific to an identified *BRCA1* or *BRCA2* mutation as well as SNPs or variants in other genes. In addition, other factors, such as a woman's reproductive history, hormone use, environmental risk factors, and utilization of risk-reducing measures, may be integrated into estimates of lifetime cancer risk. Integrative models are needed.

Reproductive Factors

A central question has been whether reproductive factors that affect risk in the general population are applicable to *BRCA1/2* carriers. Although data are limited, several studies have suggested that early menarche may confer slightly elevated risks for breast cancer among *BRCA1/BRCA2* carriers (41,42). Data on parity and breast cancer risk are less consistent. Some studies have demonstrated an increased risk of breast cancer with increased pregnancies among *BRCA1* carriers (41) and *BRCA2* carriers (42); with others showing a protective effect (43). Several studies have demonstrated a protective effect of breast-feeding among *BRCA1* carriers (41,44). However, other studies have failed to detect such an effect (43).

The impact of parity on risk of ovarian cancer is inconsistent and controversial. Contrary to studies of the general population, several studies have suggested that increased parity might be a risk factor for ovarian cancer among *BRCA1/2* carriers. For example, in a matched case-control study with 794 cases and 2,424 controls, parity was associated with a 33% reduction in the odds of ovarian cancer among *BRCA1* carriers, but an increase of the odds of ovarian cancer among *BRCA2* carriers (45). However, consistent with literature in the general population, there have also been studies reporting a protective effect of increasing parity among mutation carriers (46).

Oral contraceptive use has been shown to significantly reduce the risk of ovarian cancer, and some studies have shown that use may be associated with a modest increased risk of breast cancer (45,47) although others have not. Tubal ligation may also reduce the risk of ovarian cancer in mutation carriers (48).

In summary, despite a growing literature on reproductive risk factors, the limited research to date and the inconsistent nature of the results preclude definitive conclusions or concrete integration into risk assessments. Thus, clinical recommendations may not be affected by these factors.

GENETIC COUNSELING AND RISK ASSESSMENT

Criteria for Genetic Counseling Referral

In general, it is recommended that individuals with a suggestive personal and/or family history of breast cancer be referred for genetic counseling, which includes a detailed risk assessment and discussion about the potential likelihood that genetic testing will provide informative results for medical management or for clarifying relatives' cancer risks. A 10% *BRCA1/2* carrier probability has been suggested as a possible threshold for recommending genetic testing (49). However, quantitative estimates combined with clinical judgment form the optimal basis for referral and risk assessment in clinical practice. Indeed, many organizations have published statements about the importance of genetic counseling for individuals at elevated cancer risk, and some contain specific criteria for genetic counseling referral. These groups include the American Society of Clinical Oncology (ASCO), the National Society of Genetic Counselors (NSGC), the National Comprehensive Cancer Network (NCCN), the United States Preventive Services Task Force (USPSTF), the National Institute for Health and Clinical Excellence (NICE), and others (49,50). In the United States, some third-party payers have established their own criteria for genetic counseling and testing which are used in decisions regarding insurance coverage for testing. We provide sample criteria for referral for consideration of *BRCA1/2* testing in Table 17-3. Notably, the criteria for who is considered a "good" candidate for genetic testing has expanded significantly since genetic testing became commercially available in the late 1990s. This is due, in part, to the understanding that in certain clinical situations individuals have a high enough pre-test chance ("prior probability") of having a gene mutation that there is no need to also have a strong family history. These situations include women diagnosed with breast cancer under 40, women with triple negative breast cancer, women with high grade serous ovarian cancer, men with breast cancer,

TABLE 17-3

Criteria for Referral for Genetic Counseling of Individuals at Increased Risk for *BRCA1/2*-Associated Hereditary Breast Cancer[a,b]

- Personal history of breast cancer diagnosed ≤45
- Personal history of breast cancer and Ashkenazi Jewish ancestry
- Personal history of breast cancer diagnosed ≤50 and at least one first- or second-degree relative with breast cancer ≤50 and/or epithelial ovarian cancer
- Personal history of breast cancer and two or more relatives on the same side of the family with breast cancer
- Personal history of breast cancer and one or more relatives with epithelial ovarian cancer
- Personal history of epithelial ovarian cancer, diagnosed at any age, particularly if Ashkenazi Jewish
- Personal history of male breast cancer, particularly if at least one first- or second-degree relative with breast cancer and/or epithelial ovarian cancer
- Personal history of triple negative breast cancer ≤60
- Relatives of individuals with a deleterious *BRCA1/2* mutation

[a]Close relatives of individuals with the history mentioned in the table are appropriate candidates for genetic counseling. It is optimal to initiate testing in an individual with breast or ovarian cancer prior to testing at-risk relatives.
[b]Criteria modified from NCCN Version 2.2013 (50).

and Ashkenazi Jewish individuals with breast or ovarian cancer. More liberal application of genetic testing has also been aided by a significant decrease in the rate of detection of variants of uncertain significance (discussed in more detail in the next section).

The Genetic Counseling Process

Genetic counseling is an important component of the risk assessment and genetic testing process. In the latter, pre- and posttest counseling is important because of complexities in test result interpretation and discussion of medical management options, as well as the potential implications for family members. The process of genetic counseling, which encompasses everything from initial history taking to a review of the potential benefits, limitations, and risks of testing, is comprehensive in nature and is designed to facilitate informed decision-making (51).

Initial or pretest genetic counseling sessions involve a detailed review of the patient's family and medical history. The family history may be conveniently recorded in the form of a pedigree and should be updated periodically. Pedigrees should include information about maternal and paternal relatives encompassing at least three generations, if possible. It is important to record all cancer or precancerous diagnoses, ages at diagnosis, laterality, treatment, and history of prophylactic or other related surgery. Review of pathology reports is important, not only to verify diagnoses but also to confirm whether certain histologies are present. For example, nonepithelial ovarian cancers, such as germ cell cancers, are not part of the tumor spectrum observed in *BRCA1/2* mutation carriers. Relevant environmental and exposure history is also important to note, as well as ethnic ancestry. It is important to document specifically whether individuals are of Ashkenazi (Eastern or Central European) Jewish ancestry. In addition, current ages, or ages at and causes of death, as well as other chronic medical conditions in unaffected and affected individuals, should also be indicated on the pedigree. For example, women who undergo oophorectomy at an early age who also have a positive family history of heart disease or osteoporosis may consider a more in-depth assessment of their own personal risk factors for these conditions so that they can discuss appropriate management options.

Analysis of the pedigree for hallmark features of hereditary cancer provides the basis for an accurate risk assessment. The two approaches to pedigree analysis are (a) a qualitative impression and (b) a quantitative estimate of carrier probability. A qualitative analysis is helpful to determine if a family history contains features suggestive of hereditary breast cancer, especially syndromes not attributable to *BRCA1/2* mutations. For example, early onset breast cancer in the presence of a sarcoma, adrenocortical cancer, or childhood cancer is suggestive of Li-Fraumeni syndrome (see Table 17-1) (2). In addition, it can be determined if factors in the family history may make it difficult to discern a pattern of hereditary cancer, thus limiting the utility of some quantitative models of risk assessment. Small family size, few women in the family, premature deaths, and lack of knowledge regarding medical history, are all potential limitations of pedigree analysis. For example, Weitzel et al. (52) found that in families containing a proband with breast cancer before age 50 and a limited family structure, three commonly used risk assessment models did not accurately predict *BRCA1/2* carrier probability.

Assessing *BRCA1/2* Carrier Probability

Cancer risk assessment encompasses several factors, including the likelihood that an individual or family harbors a gene mutation, the chance that an individual is a gene carrier based on Mendelian analysis, and the cancer risks derived from estimates of gene penetrance. As discussed in the section The Genetic Counseling Process, qualitative impressions of the pedigree are invaluable, particularly for identifying rare syndromes associated with hereditary breast cancer. However, for most women at moderate to high risk presenting for genetic counseling, consideration of *BRCA1/2* testing will be most appropriate. In this section, quantitative models for estimates of *BRCA1/2* carrier probability will be reviewed.

Several models are available to provide estimates for gene carrier probability. Most of the models discussed here are available to run on the internet or are downloadable at no cost. Probabilities generated by many models vary based on which person is chosen for the analysis, so for some patients it might be more appropriate to run the model on the person most likely to harbor a mutation (or who has the most affected relatives who will be captured within the model) and then Mendelian probabilities can be calculated for other relatives.

Two of the most widely validated models are BRCAPRO and BOADICEA (53–55). BRCAPRO was developed in the United Sates and uses Bayesian theory and family history information (e.g., affected status for breast or ovarian cancer, ages of affected and unaffected first- and second-degree relatives) to estimate *BRCA1/2* carrier probabilities as well as breast cancer risk (53). The model, which is included in CancerGene (54) and is frequently updated, also incorporates data about *BRCA1/2* mutation frequency and a range of *BRCA1/2* mutation penetrance figures based on published estimates. In addition to providing *BRCA1/2*

probability estimates, this model also generates a pedigree, and age-specific risks for breast cancer (primary and contralateral) and ovarian cancer based on positive and uninformative negative test results. Breast cancer risks are also calculated using Gail model parameters and breast density. Other strengths of the model include the ability to integrate multiple pieces of additional information into *BRCA1/2* carrier probability estimates, such as Jewish ancestry, race, age at oophorectomy and/or bilateral prophylactic mastectomy, genetic testing results (for residual probability in the person tested or to account for the possibility of a phenocopy or uninformative result in an unaffected person), and breast tumor marker status, including estrogen and progesterone receptors, HER-2/neu, and cytokines CK14 and CK5/6. Tumor markers indicating the triple negative or basaloid phenotype are predictors of *BRCA1* positivity. Of note, however, despite the establishment of ductal carcinoma *in situ* (DCIS) as part of the *BRCA1/2* tumor spectrum (56), at present, the program does not count DCIS as breast cancer (i.e., it factors in cases of invasive breast cancer only); therefore, carrier probability may be underestimated. Users may therefore wish to enter DCIS cases as invasive.

The BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm) model was originally developed using segregation analysis of breast and ovarian cancer in families identified through population-based series of breast cancer cases and multiple case families in the United Kingdom, and has since been extensively updated to include data from over 2,700 families (57). Unique strengths are that risk estimates computed by the model take into account the polygenic nature of hereditary breast cancer (i.e., implicating genes other than *BRCA1* and *BRCA2*), other cancers associated with *BRCA1/2* mutations (i.e., prostate and pancreatic), and the effect of birth cohort on cancer risk (58). Although the online model allows for imputation of any family size and pedigrees may be imported, data input for each family member can be time consuming as, for example, year of birth must be entered. The program will generate a full pedigree. Like BRCAPRO, *BRCA1/2* test results are considered; however, oophorectomy status and breast pathology is not included and the model was not developed with *in situ* cancers in mind. BOADICEA also can be used to predict mutation carrier probabilities as well as cancer risks. This model is widely used in the United Kingdom, and is one of the models suggested for use by the NICE guidelines (49).

Researchers at the University of Pennsylvania developed a model known as Penn II, which is based on 966 *BRCA1/2* tested families with at least two cases of breast or ovarian cancer from four high-risk breast cancer screening clinics, and uses logistic regression analysis to determine the likelihood of finding a *BRCA1* or *BRCA2* mutation in an individual and family (59). Data input consists of answers to 11 short questions (e.g., providing the answers yes/no, the number of affected relatives, and the age of the youngest breast cancer case). Strengths of the model include the incorporation of third-degree relatives in the risk assessment (e.g., first cousins) as well as other *BRCA*-associated cancers (e.g., pancreatic, prostate, and male breast). If the proband is not affected, carrier probability can be determined by Mendelian calculations. As expected, predictors of finding a mutation include the presence of breast cancer before age 50, male breast cancer, breast–ovarian double primaries, ovarian cancer, and Ashkenazi Jewish ancestry. This model is easy to use in clinical practice and appears to perform well (60). It does not calculate cancer risks.

The Myriad model uses data derived from empirical rates of *BRCA1/2* mutation prevalence in over 180,000 consecutive gene analyses performed in their commercial laboratory (61,62). Mutation carrier probability is calculated based on the age at diagnosis of breast cancer (<50 or ≥50 years), the presence of ovarian cancer or male breast cancer, and the presence or absence of Ashkenazi Jewish ancestry. Like other models, these data also underscore that the presence of ovarian cancer in the family increases the probability of testing positive and, in many cases, as other models substantiate, with comparable family history, Jewish individuals are more likely to harbor a *BRCA1/2* mutation than non-Jewish individuals. In families with multiple cases of breast and ovarian cancer, however, the impact of Jewish ancestry has a less significant effect on the likelihood of detecting a mutation. Of note, family history used for inclusion in these data was limited and often not verified. This model is included in the CancerGene package and online (62), and is very easy to use.

The Manchester scoring system was developed based on empiric data from 921 non-Jewish British families, and has been updated to include extensive breast pathology from 2,156 samples (63). This model was developed to ascertain families with at least a 10% prior probability of having a *BRCA1* or *BRCA2* mutation for the purposes of clinical triage. The model assigns a score for *BRCA1* and *BRCA2* based on the presence of various cancers (e.g., female and male breast cancer, ovarian, prostate, and pancreatic), the age range in which cancer was diagnosed, and breast pathology and receptor status information (63). No information about unaffected relatives is considered, nor are data about race or Jewish ancestry. Families with a combined score of at least 16 can be used as a 10% threshold, and 20 points as a 20% threshold (63). Limitations of the model include its lack of applicability to Ashkenazi Jewish individuals and that it may underestimate risk in small families or single affected breast cancer probands diagnosed at a young age. This tool is widely used in the U.K. and is incorporated into the NICE guidelines as a tool for selecting candidates for genetic testing (20% or higher) and various management strategies (49). This model, along with others, performs reasonably well in discriminating mutation carriers from noncarriers in validation studies (49).

Finally, a model based on the International Breast Cancer Intervention Study is referred to as IBIS or Tyrer-Cuzick (64). Of importance, this model is applicable only to unaffected women. It considers a family history of breast or ovarian cancer in first-, second-, and third-degree relatives, including a father or brother with breast cancer, and uses Bayesian calculations, *BRCA1/2* penetrance data from the Breast Cancer Linkage Consortium, and assumptions about the existence of a dominantly inherited, low penetrance gene in calculating gene carrier probability. The model is also used frequently to calculate breast cancer risk, and in addition to family history it also incorporates personal risk factors, such as age at menarche and menopause, age at first live childbirth, parity, height, and body mass index, use of hormone replacement therapy, and history of breast conditions that may elevate risk (e.g., atypical hyperplasia and lobular carcinoma *in situ* [LCIS]). The model has been shown to accurately predict breast cancer risk in some populations, but significantly overestimates it in women with atypical hyperplasia (65). Genetic test results can be entered, but the model assumes that sensitivity for *BRCA1/2* mutation detection is 100% because the residual probabilities after testing are always zero. Table 17-4 summarizes the *BRCA1/2* mutation probabilities for probands in three

TABLE 17-4

BRCA1/2 Mutation Probabilities for Select Pedigrees

	Pedigree 1 (Fig. 17-1)		*Pedigree 2 (Fig. 17-2)*		*Pedigree 3 (Fig. 17-3)*	
	Jewish (%)	*Non-Jewish (%)*	*Jewish (%)*	*Non-Jewish (%)*	*Jewish (%)*	*Non-Jewish (%)*
Penn II[a]	54	26	41	19	27	13
Myriad[b]	33	27	27	21	8	5
BRCAPRO[c]	72	50	74	36	17	2

Combined probabilities of finding a *BRCA1* or *BRCA2* mutation for the proband indicated by an arrow in each pedigree (see Figures 17.1, 17.2, and 17.3). See text for model descriptions and references.
[a]http://www.afcri.upenn.edu/itacc/penn2 (59).
[b]Data from Myriad Genetic Laboratories, Mutation Prevalence Tables (62).
[c]Data from CancerGene, copyright University of Texas, 1998–2010 (54) Version 6.

different pedigrees as determined by commonly used probability models.

Pedigree 1 (Fig. 17-1) is an example of a high-risk family, in that it contains four cases of breast cancer (one bilateral and two under the age of 50 years) in three generations and one case of ovarian cancer. Regardless of ancestry, BRCAPRO gives the highest carrier probability estimate (50% or 72% if non-Jewish or Jewish, respectively). If the ovarian cancer patient is used as the proband for BRCAPRO, the prior probabilities increase further.

Pedigree 2 (Fig. 17-2) is also a highly suggestive family, with four cases of breast cancer, three under age 50 years, in three generations.

Finally, Pedigree 3 (Fig. 17-3) is an example of a moderately suggestive family history of the type commonly encountered in clinical practice. If the family is non-Jewish, all models yield a relatively low probability that the proband (III-1) will test positive, whereas, as expected, the probabilities are higher if the family is Jewish. Interestingly, if breast cancer tumor markers indicative of the basaloid phenotype are entered for the proband (e.g., estrogen and progesterone receptor negative, HER-2 negative), the probability of testing positive is substantially increased based on the BRCAPRO model. This finding underscores the importance of considering breast cancer pathology in addition to family history, especially because this is a small family with few females in it.

These examples demonstrate several important concepts. First, quantitative probability estimates of *BRCA1/2* status may be highly variable, so it is important to understand the features of each model that could account for some of these differences, as well as the strengths and limitations of each model. Thus, carrier probability estimates must be interpreted in addition to a qualitative impression of the pedigree. In some cases, it might make more sense to calculate carrier probability for someone in the family other than the proband. Such an approach might be useful if the proband is unaffected with breast or ovarian cancer (i.e., by calculating carrier probability for an affected individual, Mendelian analysis can then be used to derive risks), or if there is a "higher risk" proband in the family (e.g., a woman with ovarian cancer, or who was diagnosed with breast cancer at a younger age). Finally, Jewish ancestry significantly impacts carrier probability, so it is critical to ascertain ethnic background when taking the pedigree. As pedigrees 1 and 2 underscore, paternal family history is also critical to ascertain.

Another critical aspect of pretest counseling is a psychosocial assessment, along with a discussion about the review of the possible benefits, risks, and limitations of genetic testing. Although no individual can imagine fully how he or she might react on learning a test result, having this discussion beforehand can at least begin to prepare individuals for different responses and enable them to mobilize coping, support, and informational resources ahead of time. It is also helpful to clarify expectations about what the patient hopes to learn from genetic testing, and how he or she may handle uncertainties associated with test result interpretation.

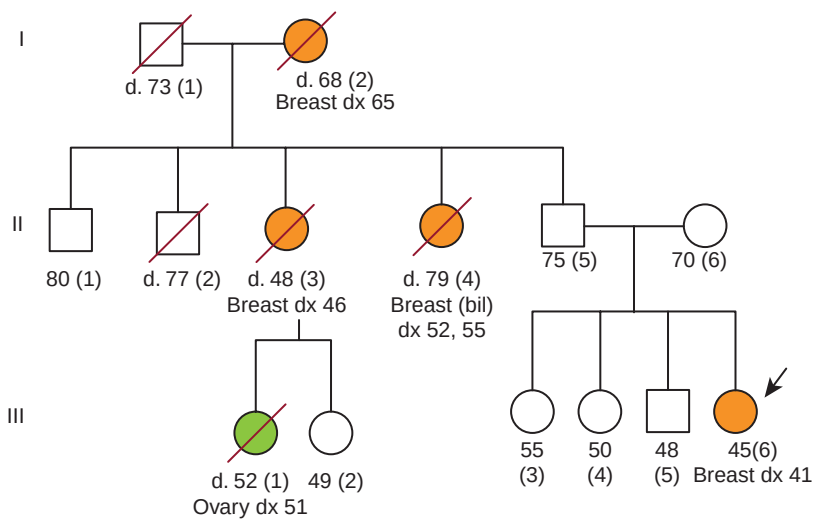

FIGURE 17-1 Pedigree 1, high risk breast/ovarian cancer family.

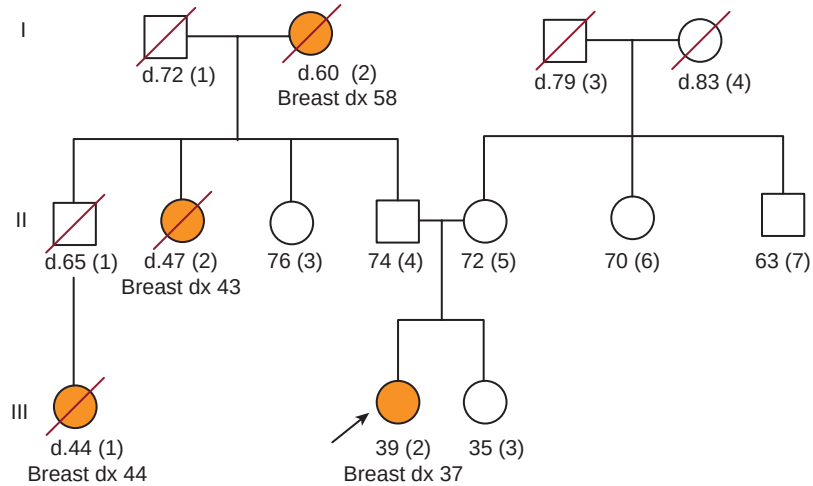

FIGURE 17-2 Pedigree 2, high risk site-specific breast cancer family.

Discussing risk perception, attitudes toward cancer screening and risk reduction, past health behaviors, impact of relatives' diagnosis, and current and past psychiatric history can help frame discussions about goals, coping strategies, and decision-making.

Potential benefits of testing include the reduction of uncertainty because of increased knowledge. In addition, results may help facilitate more informed decision-making about medical options, including risk reducing surgery or definitive surgery in newly diagnosed breast cancer patients.

Frequently, the choice to be tested may also be motivated by a desire to obtain information for other family members. For patients with cancer who are very ill or actively in treatment, this reason may be their main motivation for pursuing genetic testing, because the medical implications for them may be very limited. Among individuals of childbearing age, concern about transmitting their mutation to future children may also exist. It is important to address reproductive concerns in the context of genetic counseling, especially as options such as prenatal and preimplantation genetic testing are available, although requests for these types of testing are uncommon. Decision-making around these issues can be very complex and fraught with ethical dilemmas; thus, genetic counseling can be instrumental in helping patients clarify their own values and preferences.

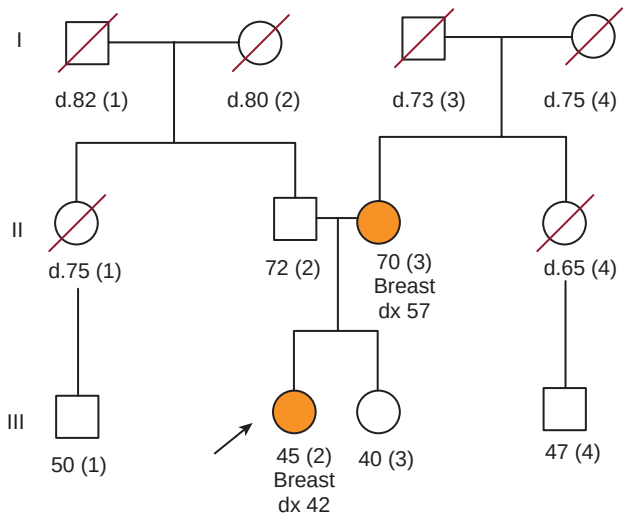

FIGURE 17-3 Pedigree 3, moderate risk site-specific breast cancer family.

A limitation of testing is the possibility that results may not be informative. Although no significant physical risks are associated with genetic testing, psychosocial risks must be taken into consideration. Although few cases of genetic discrimination have been documented, it is important to inform individuals considering genetic testing about current national and state laws that address this concern. In May 2008, the Genetic Information Nondiscrimination Act (GINA) was signed into law in the United States, which provides many protections against discrimination based on genetic information for those with individual and group health insurance plans, and in employment settings (66). For some individuals and depending on the status of their insurance plan, genetic counseling and testing for *BRCA1/2* mutations is also a covered service under the Affordable Care Act (67). It is also encouraging that *BRCA1/2* testing, which can cost up to approximately $4,000, is often a covered expense by many insurance companies in the United States.

Although studies have not demonstrated significant adverse emotional effects of testing, as described in the section on psychosocial outcomes, it is not uncommon for mutation carriers to experience some feelings of distress, anxiety, or sadness, which is usually manageable without clinical intervention and which dissipates over time. Although many individuals pursue testing for the sake of obtaining information for family members, the decision to disseminate one's test results and the ensuing ramifications can cause strain among relatives. It is not uncommon for those with true negative results to feel a combination of relief and survivor guilt for being spared a burden that other relatives may experience. In addition, the role of information gatekeeper may be overwhelming for some individuals as they try to attend also to their own needs for support. Through the process of genetic counseling, at-risk individuals can be identified from the pedigree, and the process of family communication may be facilitated with the provision of educational material and, for example, sample letters that can be modified and sent to relatives, for those wishing to use that means of notification.

Thus, in considering the complexities involved in genetic counseling and testing, and the potential for testing to have a significant impact on an individual and his or her family, an integral part of the informed consent process involves discussion of these issues before genetic testing. Posttest genetic counseling provides an opportunity to review pertinent information and may serve to help individuals begin to assimilate their results.

Genetic Testing Process and Results Interpretation

Regardless of which hereditary breast cancer syndrome is suspected within a family, the degree to which testing will be informative is always maximized by first testing an individual in the family who is most likely to carry a mutation (e.g., a woman diagnosed with breast cancer before age 50 or with ovarian cancer). The sensitivity and specificity of testing are important considerations when selecting a laboratory. *BRCA1/2* testing is the most frequently ordered test for hereditary breast or ovarian cancer susceptibility, with more than 1 million tested altogether (68). Of note, other variants may also be identified and may be classified as follows: *suspected deleterious*, which are likely but not definitively proven to be risk conferring; *favor polymorphism*, which are likely but not definitively proven to be of no clinical consequence; and those of *uncertain significance* where insufficient data exist for classification (69). Although unclassified variants are relatively uncommon, occurring in 5% to 10% of clinical samples, and the rates of such variants have been falling, they may occur with increased frequency in specific ethnic groups (e.g., 14% in African American or Caribbean probands) (70). It is critical that providers counsel patients appropriately about these results and retain the ability to recontact them if the variant becomes reclassified.

In addition to sequencing, testing for other large rearrangements in *BRCA1* and *BRCA2* is available, which further increases the sensitivity of testing. The National Comprehensive Cancer Center Network recommends that large genomic rearrangements be part of routine comprehensive *BRCA1/2* testing (50). Large rearrangements in general account for up to 10% of mutations identified, and while they are more prevalent in patients of Latin American/Caribbean ancestry relative to other ethnicities, they are very rare in the Ashkenazi Jewish population (71).

When a deleterious mutation is not identified in the proband after full testing, such results are considered to be indeterminate or uninformative. If an affected individual at high risk is the first to be tested in the family, a negative result could arise owing to a number of possibilities, such as

1. A mutation could be present in the gene/s analyzed, but was not detectable by the method/s used.
2. A rare mutation in another gene or mutations in multiple genes could be implicated, for which testing may or may not be available.
3. The individual tested developed sporadic cancer.

With respect to the latter possibility, it is important to bear in mind that phenocopies can occur within families as breast cancer is a common disease. That is, a proband with breast cancer who tests negative for *BRCA1/2* mutations may represent a sporadic occurrence within a hereditary breast cancer family particularly when the breast cancer is at a later age. However, ovarian cancer is less likely to be a phenocopy given that it occurs much less frequently than breast cancer and is a significant predictor of finding a deleterious mutation. Whenever possible, testing should begin in affected individuals who have the highest chance of testing positive for a *BRCA1/2* mutation. For example, it is preferable to test a 32-year-old with bilateral breast cancer, or her mother with ovarian cancer, not the grandmother with breast cancer at 70, as the latter could be a phenocopy.

Founder Mutations in Ashkenazi Jews and Other Ethnic Groups

Targeted testing for specific mutations may also be appropriate based on a patient's ethnicity. The occurrence of recurrent or "founder" mutations is pronounced in individuals of Ashkenazi (central or eastern European) Jewish descent. In this population, three mutations occur with increased frequency: 187delAG and 5385insC in *BRCA1* and 6174delT in *BRCA2*. Whereas the general population frequency of *BRCA1/2* mutations in the United States is estimated at 1/500, in Ashkenazi Jews, the incidence of these founder mutations is 1/40 (10). Not surprisingly, the incidence of these founder mutations is substantially higher when selected Jewish populations are studied, such as patients with breast or ovarian cancer (72). Although double heterozygotes are rare, owing to this possibility individuals with a relative who carries one of these mutations should still be tested for all three mutations if they have Ashkenazi Jewish ancestry on both sides of their family (73). Of note, these three founder mutations do not occur exclusively in Ashkenazi Jews, and nonfounder mutations have been reported in this ethnic group, although they are rare. For example, Myriad reported that among 926 Ashkenazi Jewish individuals who underwent comprehensive *BRCA1/2* analysis, 110 had a nonfounder mutation (12%) and 4 had a large rearrangement (<1%, all of whom were high risk) (71). At this time, it is not possible to predict which features of the family history will make it more likely that a nonfounder mutation will be identified. However, individuals who have a high prior probability of testing positive based on models such as BRCAPRO (e.g., if calculated as though the family was non-Jewish), or who have qualitative features within the family history that are highly suggestive of a mutation (e.g., more than one case of ovarian cancer, male breast cancer, or pancreatic cancer) should consider pursuing comprehensive testing after three founder mutations are ruled out. Myriad Genetics offers an Ashkenazi Jewish panel with the three common mutations which is significantly cheaper than comprehensive analysis. Therefore, it is suggested testing in individuals start with this panel prior to comprehensive analysis. Founder mutations have also been described in other European and non-European populations, such as those with Icelandic, Norwegian, Dutch, or French Canadian ancestry. It is important for clinicians to determine whether targeted testing is appropriate. For most non-Ashkenazi Jewish individuals in the United States, targeted testing is not indicated.

Testing for a Familial Mutation

Finally, once a mutation in a cancer susceptibility gene is identified, relatives may be offered testing for only the single mutation. As mentioned, one exception to this is for Ashkenazi Jewish individuals, who should generally be tested for all three founder mutations regardless of which one is segregating in the family. In general, testing for a familial mutation yields definitive information: A deleterious (positive) test result is obtained, with the attendant cancer risks, or the result is classified as a true negative, in which the patient can be reassured that cancer risks are thought to be close to those observed in the general population. It is critical, however, to assess other potential risk factors, such as environmental factors and the history on the side of the family in which the mutation is not segregating (i.e., the family history of the other parent). If cases of cancer are present, and especially if these are suggestive of an inherited predisposition, the patient may still have an elevated risk of cancer and his or her medical management plan may need to take this into account.

Examples of Results Interpretation

To illustrate concepts in result interpretation, consider Pedigree 2 (Fig. 17.2). If the proband (III.2) underwent full *BRCA1/2* testing, including testing for large rearrangements, and no mutation was identified, this finding is considered to be uninformative given that this family history is strongly consistent with hereditary breast cancer. Although the

likelihood is low that the proband's cancer is a phenocopy (given her young age at diagnosis), this possibility could be further discounted if her affected cousin had also tested negative for *BRCA1/2* mutations.

If the affected proband (III.2) in Figure 17.2 was found to carry a variant of uncertain significance, and it was subsequently not identified in her father, this finding suggests that the mutation is not likely to be associated with heightened cancer risks as it is not segregating on the side of the family with multiple cases of breast cancer. If this observation can be replicated in numerous families, the accumulation of such data in conjunction with statistical approaches, would add further credence to this assumption. Except to assist in the determination of a variant's significance, at-risk relatives should not be offered testing for a variant because it provides no further information about their risk of developing cancer.

If individual III.2 is found to harbor a *BRCA2* mutation, and her sister (III.3) subsequently tests negative for this mutation (true negative), the sister's chance of developing breast or ovarian cancer is reduced to that observed in the general population. This example underscores the importance of offering genetic testing to an affected individual first. If, however, the proband's sister (III.3) was the first person in the family to undergo *BRCA1/2* testing and tested negative, at that point, it would not be clear whether this result would be attributable to the fact that she did not inherit a mutation segregating in her family or whether a *BRCA1* or *BRCA2* mutation does not exist in this family. In this scenario, rather than a test result providing reassurance, the patient would have to be counseled that she is still considered to be at high risk for breast cancer.

In summary, there are several possible outcomes of genetic testing. There are two types of definitive test results: (a) a *positive* result refers to the identification of a deleterious mutation associated with increased cancer risks; and (b) a *true negative* result means that a mutation previously identified in a blood relative has been ruled out. Even among highly selected probands the most commonly obtained result is one that is *indeterminate* or *uninformative*. These classifications mean that a deleterious mutation has not been identified in the family and the possibility of an inherited susceptibility cannot be definitively ruled out. Given the complexities in test result interpretation, it is important that it be done in the context of an individual's medical and family history, especially given that critical medical management may hinge on an accurate risk assessment.

Psychosocial Outcomes of *BRCA1/2* Genetic Testing

The advent of *BRCA1/2* testing was accompanied by considerable concern about the potential for adverse psychosocial outcomes in this already distressed population. Many women have now undergone genetic testing for *BRCA1/2*. A growing literature has begun to evaluate both the immediate and long-term psychosocial impact of learning one's *BRCA1/2* mutation status.

Studies evaluating the short-term impact of genetic testing demonstrate substantial decreases in distress and anxiety among women who learn that they do not carry a *BRCA1/2* mutation (74). The short-term impact on women who receive positive test results is less consistent. Although many studies suggest increased distress and anxiety in the months immediately following receipt of a positive *BRCA1/2* test result (74,75), others demonstrate stable levels of distress and anxiety (76). This combination of decreased distress among those receiving negative test results and stable or increased distress among those who receive positive results yields significant short-term differences in distress between these groups. These differences typically remain stable or even dissipate during the year following testing (77,78).

There have now been several cross-sectional and prospective studies that have evaluated the long-term psychosocial outcomes of *BRCA1/2* testing. Two small studies that focused on individuals unaffected with cancer found no differences on psychosocial outcomes between carriers and noncarriers at three years or five years posttesting (78). In contrast, a more recent small study found that distress increased in the two years following receipt of a positive *BRCA1/2* test result (79). A recent cross-sectional study reported statistically significant, but not clinically significant, genetic testing distress in *BRCA1/2* carriers compared with noncarriers at 7 years posttest (80). Similarly, in a prospective study with an average follow-up of over five years posttesting, Graves and colleagues found modest but significantly increased distress among *BRCA1/2* carriers compared to women who received negative or uninformative test results (81). These long-term studies suggest that, while a positive *BRCA1/2* result may remain salient over the long term, distress related to testing rarely reaches a clinical level. These studies also highlight the potential modifying role of risk reducing surgery on psychosocial outcomes. Specifically, *BRCA1/2* carriers who opted for risk reducing mastectomy or risk reducing oophorectomy reported lower levels of distress and perceived risk over the long term (79,81).

Although these studies are reassuring, need for caution exists in interpreting these results owing to the wide variability in emotional responses to testing and the select nature of research samples to date. For example, a number of studies have shown that individuals who report high levels of distress, poor quality of life, or who have inaccurate perceptions of their likelihood for carrying a mutation before testing are more likely to report ongoing distress following a positive test result (82,83). Further, more research is needed to determine whether the largely positive outcomes associated with genetic testing in controlled research programs can be replicated in community settings in which extensive genetic counseling may not always be provided or where genetic counseling is provided via telephone or the internet (84). Finally, the participants in most of these studies have been overwhelmingly white, well-educated, and of high socioeconomic status. However, limited reports that have focused on the impact of *BRCA1*/2 among black patients suggest comparable outcomes to previous studies (85).

Ethical Issues in Genetic Counseling and Testing for Hereditary Breast Cancer

Genetic counseling and testing for hereditary cancer risk often raises many complex issues because of the uncertain but often predictive nature of information obtained; potential risks and limitations of testing; and because genetic test results, especially positive results, have implications, not just for the persons tested, but for their family members as well. In this section, the following major themes will be highlighted: (a) the importance of informed consent; (b) predictive testing in children; (c) duty to warn; and (d) duty to recontact.

First, to maximize the likelihood that patients make fully autonomous decisions about genetic testing, including a full appreciation of the potential benefits, limitations, risks, and implications of testing, it is imperative that informed consent is obtained before testing. The process of genetic counseling affords patients with an opportunity to make informed decisions and to actively consent to genetic testing. It is comprehensive in nature, not only encompassing information,

potential implications, and options, but it also includes a discussion of the psychosocial and familial aspects of testing (86). Documentation of this discussion should be made, and, if required, patients should sign a written consent form prior to genetic testing.

An issue that continues to garner a significant amount of attention is the issue of testing children for susceptibility to adult onset cancers. Most professional societies agree that, in general, genetic testing for minors should occur when medical benefits accrue in childhood (87). However, individual circumstances, including the maturity of the minor and his or her ability to provide assent/consent, and the family concerns should all be explored during the process of genetic counseling and with the involvement of other providers such as the pediatrician and a psychologist. With respect to hereditary breast cancer syndromes, childhood cancers are a feature of Li-Fraumeni syndrome and, although no approach for screening of the associated cancers has proven efficacy, a case for *TP53* testing could be made to relieve parental worry and unnecessary medical procedures in an at-risk child. With respect to *BRCA1/2* testing, however, other factors may play into testing decisions, such as the child's motivation, readiness for, and interest in genetic testing, particularly for "mature minors"; the impact on the family unit and relationships with parents and siblings; the desire to obtain relief from true negative test results (which of course must be balanced against the possibility of testing positive for a familial mutation); and the impact on autonomous decision-making for the child once he or she reaches adulthood. *BRCA1/2* testing in minors remains controversial and, to date, is a rare event. However, it is important for clinicians to explore the issue of family communication about genetic testing and to be sensitive to concerns that parents and adolescents may have about future cancer risk and the associated implications.

Another matter related to family communication concerns what responsibilities individuals have to inform their relatives about genetic risk and the ethical obligations of clinicians to ensure that relatives of the tested patient are informed about this risk (i.e., the "duty to warn"). Studies have shown that the rate of *BRCA1/2* test result disclosure to adult relatives, especially first-degree relatives, is generally high, although underserved, minority, and older patients may have lower rates of disclosure (88). However, the clinician's role in informing at-risk relatives when the tested individual does or will not is unclear. On one hand, patient autonomy and respect for privacy are critically important, but there are circumstances when it might be argued that providing benefit (e.g., the potential to reduce worry and distress and to provide information for medical management) and avoiding harm (e.g., avoidance of unnecessary screening or risk-reducing surgery) may be compelling ethical arguments for overriding patient autonomy. From a legal standpoint, the well-known Tarasoff case set the precedent for a breach of confidentiality between health care provider and patient when imminent harm is foreseeable and preventable (89). In this case from 1976, a patient discussed with his psychotherapist his intention to kill a woman, which he ultimately did. The therapist in this case did not warn the woman of impending danger, but this ruling allows for patient confidentiality to be overridden to avoid harm. However, subsequent case law in the United States has not been consistent with respect to whether a clinician's obligation is fulfilled by informing patients about potential risks to relatives or whether relatives need to be informed directly (89). Indeed, the logistics of identifying and directly contacting relatives often prove to be prohibitive. In the United States, another legal consideration is raised by the HIPAA Privacy rule, which prohibits disclosure of "individually identifiable health information," which would include genetic testing results (89). It is not clear how this regulation impacts public health mandates to override confidentiality in the setting of a serious health threat (90). If it becomes necessary to override a patient's wishes about disclosure, consultation with an ethics committee or legal counsel should be considered.

Although several organizations worldwide have developed guidelines that outline the exceptional circumstances in which it may be permissible to override patient confidentiality to disclose genetic test results, guidance from organizations such as the American Medical Association and the American Society of Clinical Oncologists is very practical (91,92). These guidelines stress the importance of pre- and posttest counseling as an opportunity for providers to explain risks to relatives and their expectations about family disclosure, and to offer assistance to patients to accomplish this goal. In addition, consent forms can include language about the role that the provider and patient will play in identifying and notifying at-risk relatives, including circumstances, if any, under which patient confidentiality may be breached. It is helpful to reiterate implications to relatives in a summary letter to the patient, as well as facilitating the process of disclosure by giving patients resources to help accomplish this goal (e.g., educational material, sample letters, or text for e-mails) and contact information for genetic counselors convenient to relatives.

Finally, given the many developments in cancer genetics, the issue of whether or when to recontact patients has been raised. For example, many women were tested prior to the availability of commercially available large rearrangement testing and received "negative" or uninformative *BRCA1/2* genetic testing. Or, more recently, providers are grappling with whether high risk patients who received uninformative results should be recontacted about the availability of multi-gene panel testing. Changes in management recommendations may also prompt questions about whether and which patients to recontact. These questions raise the issues of whether and when there is a requirement to recontact patients when technology changes, and how to determine whether patients want to be informed about ongoing developments. At a minimum, patients need to be recontacted if the interpretation of their result changes (for example, a variant of uncertain significance that is reclassified to a deleterious mutation). Thus, it is important that clinicians encourage patients to maintain up-to-date contact information with their office. In addition, summary letters to patients can specify that patients check in with the clinic at defined time intervals or that they should check reliable resources for important updates.

In summary, genetic counseling and testing for hereditary cancer risk may yield many potential benefits to individuals and their families. In some instances, however, patient values and preferences and the possibility of adverse outcomes need to be balanced carefully when considering ethically challenging issues.

MANAGEMENT OF HEREDITARY BREAST CANCER

Over the past few years, significant data have emerged regarding the benefit of various screening and prevention options in those with a known inherited susceptibility to cancer and other women at high risk. This section summarizes current knowledge regarding the benefits and limitations of these interventions. The management options for unaffected *BRCA1/2* mutation carriers will be discussed first, followed

by a review of the impact of *BRCA1/2* status on treatment of patients with breast cancer, and finally we will summarize management options for those with other hereditary breast cancer syndromes. It is important to note that most of the recommendations for screening or risk reduction in this group of women at high risk are based on nonrandomized data or expert opinion (50).

Management of Unaffected *BRCA1/2* Carriers

In general, management options for women at increased risk for hereditary breast cancer include screening, prevention interventions, or both.

Breast Cancer

Screening Options: The current breast cancer screening guidelines for women with a known inherited susceptibility to cancer include education about monthly breast self-examinations beginning at age 18, semiannual clinician-performed breast examinations beginning at age 25, and annual mammograms and MRI beginning at age 25 or individualized based on earliest age of onset in the family (49,50) Studies from a number of different countries in Europe and North America demonstrated the benefit of MRI in women at increased risk for breast cancer, and specifically in *BRCA1/2* mutation carriers. MRI had a sensitivity of 71% to 100% and specificity of 81% to 97%, whereas mammography had sensitivity of 33% to 59% and specificity of 93% to 99.8% (Table 17-5). However, these studies also noted that false-positive MRI results were quite frequent, with MRI having a positive predictive value that ranged from 7% to 63%. Optimal breast MRI requires a dedicated breast coil, a well-established imaging technique, radiologic expertise in the interpretation of these studies, and the ability to perform MRI-guided biopsies. Additionally, to further minimize the likelihood of false-positive findings in studies, breast MRI in premenopausal women should be performed on days 7 to 14 of the menstrual cycle. Screening breast MRI in combination with mammogram has shown to be cost effective in *BRCA1/2* mutation carriers (93).

A number of outstanding issues remain. Although studies have demonstrated that breast cancers detected by MRI tend to be small and frequently node negative (94–97), no randomized data exist on the impact of this screening modality on breast cancer mortality. Breast MRI has been shown to be associated with a decreased risk of advanced stage breast cancer (98). In addition, data from 1,275 *BRCA1/2* mutation carriers in a combined analysis of several studies were used to develop natural history models. These models predicted a 50% to 62% decrease in breast cancer mortality with the use of combined mammogram and MRI (99). Therefore, it is felt likely that breast MRI will decrease breast cancer specific mortality despite an absence of randomized data. Although initial studies in women at high risk suggested that MRI was not as sensitive for the detection of DCIS as is mammography (94–96); a subsequent single institution study of more than 7,000 women not selected for family history referred for breast MRI found that MRI detected 92% of the cases of pure DCIS, whereas mammography diagnosed only 53% ($p < .0001$) (100). Whether mammogram and MRI should be staggered every 6 months or be performed simultaneously is also not clear (101).

An additional unresolved issue is the concern that radiation exposure, either in the form of prior chest x-ray or mammograms, may increase the risk of breast cancer in mutation carriers (102–104). Several studies specifically examining mammograms do not support this association (105,106), while others have demonstrated a non-statistically significantly elevated risk (103). In contrast, several studies have demonstrated that radiation exposure prior to age 20 (not mammography) appears to be particularly associated with risk, with the role of mammography between ages 25 and 30 less certain (102,103). It is worth noting that the benefit of mammograms in women 25 to 30 may also be limited due to significant breast density; therefore, while mammograms in women 25 to 30 may not be associated with significant risk, they also may not be associated with significant benefit. Consistent with this, the current NCCN guidelines contain a footnote that states: "The best screening strategy for women 25 to 30 is uncertain with some data suggesting that mammogram be added to MRI only after age 30" (50).

Risk Reduction Options: Many women at increased risk for hereditary breast cancer choose prevention interventions as an alternative to screening or in addition to screening. Options for unaffected women include risk-reducing or prophylactic surgery and chemoprevention. The two surgical options for risk reduction are bilateral mastectomy and risk-reducing salpingo-oophorectomy.

Risk-Reducing Mastectomy Studies have examined the role of risk-reducing mastectomy (RRM) in mutation carriers and demonstrated that this is a very effective means of breast cancer prevention. The Prevention and Observation of Surgical End Points (PROSE) study group has examined the impact of prophylactic mastectomy in a prospective cohort. *BRCA1/2* mutation carriers with breast tissue intact at the time of ascertainment were prospectively followed. With a mean follow-up of 3.1 years, 0 of 172 carriers who underwent risk-reducing mastectomy developed breast cancer (4 incidental cancers were detected at the time of prophylactic surgery). In contrast, breast cancer was diagnosed in 64 of

TABLE 17-5

Results from Prospective Studies of Mammography and Breast MRI for High Risk Women

			Breast MRI		*Mammography*	
Study (year)	*No. Subjects (% BRCA1/2 carrier)*	*No. of Cancers*	*Sensitivity (%)*	*Specificity (%)*	*Sensitivity (%)*	*Specificity (%)*
Kriege, 2004 (94)	1909 (18.5)	51	71	90	40	95
Leach, 2005 (96)	649 (18)	35	77	81	40	93
Kuhl, 2005 (100)	529 (8.1)	43	91	97	33	97
Sardanelli, 2007 (97)	278 (60)	18	94	NR	59	NR

787 (8.1%) who did not undergo prophylactic mastectomy with median followup of more than 3 years (20). The group at the Rotterdam Family Cancer Clinic has reported their experience with risk-reducing bilateral or contralateral mastectomy in 358 women with either known *BRCA1/2* mutations (N = 236) or at risk for hereditary breast cancer (N = 122) (107). The women in this study underwent skin-sparing mastectomy often accompanied by immediate reconstruction. With a median follow-up of 4.5 years, 1 case of metastatic breast cancer developed in a previously unaffected woman who had undergone risk-reducing mastectomy. The mastectomy specimens were carefully examined for the presence of occult malignancy, which was identified in 10 of the 358 women (2.8%). Invasive cancer was detected in three, whereas DCIS was seen in five and LCIS in two. These cases were equally distributed among women with known *BRCA1/2* mutations and those at increased risk with no known heritable condition, and in women previously affected and unaffected with breast cancer.

Given the risk of occult malignancy, it has been suggested that mutation carriers planning RRM undergo the sentinel node procedure. Studies examining the rate of occult invasive malignancy in prophylactic mastectomy specimens (108) and modeling studies, suggest that routine the sentinel node procedure in this setting is neither cost-effective nor would it minimize the risk of complications. Thus, at present, the routine sentinel node procedure is not recommended in those undergoing RRM.

A number of surgical techniques are available, including total or simple mastectomy which involves removal of both breasts and the overlying skin; skin-sparing mastectomy in which both breasts are removed but the overlying skin is preserved; nipple sparing mastectomy entailing removal of both breasts with preservation of overlying skin and nipple and areolar complexes. Although long-term outcomes on nipple sparing prophylactic mastectomy are not yet available, data have suggested low rates of early local recurrence in those undergoing nipple sparing mastectomy for cancer treatment or prophylaxis (109,110).

Risk Reducing Bilateral Salpingo-Oophorectomy A number of studies have evaluated the impact of risk-reducing salpingo-oophorectomy (RRSO) on subsequent risk of breast cancer and demonstrated that *BRCA1/2* carriers who underwent this procedure had a significant reduction in their breast cancer risk (111–114). In 2002, two important papers were published simultaneously. A prospective study from Memorial Sloan-Kettering Cancer Center of 170 *BRCA1/2* carriers followed for a median of 2 years found that 3 of the 98 carriers who underwent salpingo-oophorectomy developed breast cancer as compared with 8 of the 72 women who chose surveillance (p = .07) (113). Similarly, a multi-institution study of 241 *BRCA1/2* carriers from the PROSE study followed for about 8 years observed that breast cancer developed in 21% of those who had undergone bilateral salpingo-oophorectomy as compared with 42% of those who had not undergone this procedure (HR = 0.47, 95%, CI, 0.29–0.77) (111).

An important question is whether there is a differential protective effect of this procedure on breast cancer risk in *BRCA1* versus *BRCA2* carriers. A prospective study of 368 *BRCA1* and 229 *BRCA2* carriers found that RRSO resulted in a 72% reduction in risk of breast cancer in *BRCA2* carriers (HR = 0.28, 95% CI, 0.08–0.92, p = .036) as compared with a non-significant 39% reduction in *BRCA1* carriers (HR = 0.61, 95% CI, 0.30–1.12, p = .16) (17). However, a retrospective, international case-control study of 1,439 *BRCA1/2* carriers with breast cancer and 1,866 *BRCA1/2* unaffected *BRCA1/2* carriers, found that prior history of oophorectomy conferred greater protection against breast cancer for *BRCA1* carriers than *BRCA2* carriers (56% reduction in *BRCA1* carriers [OR = 0.44, 95% CI, 0.29–0.66] vs. 46% reduction in *BRCA2* carriers [OR = 0.57, 95% CI, 0.28–1.15]) (112). More recently, the PROSE study examined the impact of RRSO on breast cancer risk by *BRCA1* and *BRCA2* mutation status in a large prospective cohort. RRSO was associated with a reduction in breast cancer risk both in previously unaffected *BRCA1* (N = 869; HR 0.63 [0.41–0.96]) and *BRCA2* (N = 501; HR 0.36 [0.16–0.82]) (20). Therefore, there does appear to be breast cancer risk reduction for both *BRCA1* and *BRCA2* mutation carriers following RRSO. Further work is required to determine whether the magnitude of risk reduction is truly different between those with *BRCA1* versus *BRCA*2 mutations. Importantly, RRSO was also shown to be associated with a significant reduction in breast cancer–specific mortality (HR, 0.44 [95% CI, 0.26–0.76]) (20).

BRCA1/2 carriers who choose to undergo prophylactic oophorectomy at a young age frequently consider taking hormone replacement therapy (HRT) to deal with the consequences of premature menopause. Data from the PROSE study group suggest that short-term use of HRT did not alter the protective effect of RRSO on breast cancer risk. Of the 155 carriers who underwent RRSO, 60% reported use of HRT, most of whom were under age 50, and these women had a 63% reduction in their risk of breast cancer as compared with a 62% reduction for the group as a whole (114). In addition, the Hereditary Breast Cancer Clinical Study Group conducted a matched case-control study of 472 postmenopausal women with a *BRCA1* mutation to examine HRT use and subsequent breast cancer risk. The risk of breast cancer with ever use of HRT compared with never use was 0.58 (95% CI, 0.35–0.96; p = .03) (115). Thus, mutation carriers who undergo RRSO before the age of natural menopause can consider short term HRT after an appropriate discussion of the potential risks and benefits, but such therapy should not extend beyond age 50, the age after which it has been shown to increase breast cancer risk in the general population (116). Additionally, nonhormonal interventions to reduce menopausal symptoms and the management of other medical issues, such as bone health, should be considered.

Chemoprevention Data from the national surgical adjuvant breast and bowel project (NSABP) P1 Breast Cancer Prevention Trial, the International Breast Cancer Intervention Study (IBIS-I), and the Study of Tamoxifen and Raloxifene (STAR) demonstrate that 5 years of the selective estrogen receptor modulators (SERM) tamoxifen and raloxifene reduce the risk of breast cancer by 30% to 50% in healthy women at increased risk for this disease based on a family history, age, and certain high-risk conditions, such as LCIS or atypical hyperplasia (104,117–119). Similarly, exemestane has also been demonstrated to decrease the risk of breast cancer in women with LCIS or a Gail 5 year risk of breast cancer of more than 1.66% (120). However, limited information exists regarding the role of such agents in reducing the risk of breast cancer in *BRCA1/2* mutation carriers. Given that SERM have only been demonstrated to decrease the risk of hormone receptor positive breast cancer in these studies, it has been postulated that these agents may be more effective in *BRCA2* carriers who tend to develop hormone receptor positive breast cancer as opposed to *BRCA1* carriers who more frequently have hormone receptor negative disease. This hypothesis was supported by a study in which genetic analysis was performed on 288 of the NSABP P1 participants who developed breast cancer (121). Only 19 (6.6%) were found to carry disease-conferring mutations. Tamoxifen was associated with

a decrease in risk of breast cancer among *BRCA2* carriers (RR = 0.32, 95% CI, 0.06–1.56), but no reduction in risk among *BRCA1* carriers (RR = 1.67, 95% CI, 0.32–10.7). Of note, the study included only small numbers of carriers (8 *BRCA1* and 11 *BRCA2* carriers) and, thus, was not powered to address adequately the impact of tamoxifen in *BRCA1/2* carriers.

In contradistinction, other studies support the notion that endocrine interventions that reduce estrogen levels result in a lower risk of breast cancer in both *BRCA1* and *BRCA2* carriers. As previously described, bilateral salpingo-oophorectomy significantly reduces the risk of breast cancer in both *BRCA1* and *BRCA2* carriers (17,20,111–113). Additionally, a number of studies have found that tamoxifen significantly reduced the risk of contralateral and ipsilateral breast cancer in *BRCA1* and *BRCA2* carriers. A case-control study by Gronwald et al. (122) matched 285 *BRCA1/2* carriers with bilateral breast cancer with 751 carriers affected with unilateral breast cancer, and demonstrated that the use of tamoxifen was associated with a 55% reduction in the odds of contralateral breast cancer (OR = 0.45, 95% CI, 0.29–0.70). This protective effect of tamoxifen was noted both for *BRCA1* carriers (OR = 0.48, 95% CI, 0.29–0.79) and *BRCA2* carriers (OR = 0.39, 95% CI, 0.16–0.94). Additionally, a retrospective cohort study of mutation carriers undergoing breast-conserving therapy performed by Pierce et al. (18) also noted that tamoxifen use resulted in a significant reduction in the rate of contralateral breast cancer (HR = 0.31, p = .05).

In summary, when counseling mutation carriers about the use of tamoxifen as a risk-reducing agent, it is important that they be informed that insufficient data currently exist to define clearly the benefit of such therapy. At present, no data exist regarding the potential benefit of raloxifene or aromatase inhibitors in mutation carriers.

Ovarian Cancer

Screening Options: It is recommended that mutation carriers who have not had prophylactic oophorectomy undergo concurrent semiannual transvaginal ultrasound (TVUS) and CA-125 beginning at age 30 or 5 to 10 years younger than the earliest age of onset of ovarian cancer in the family. For premenopausal women, it is recommended these studies be performed between days 1 and 10 of the menstrual cycle (49,50). It is important to note, however, that the benefit of such interventions is currently unclear. A number of completed and ongoing trials are addressing the utility of screening with CA-125 and TVUS, both in the general population and in women at high risk. CA-125 has typically been considered abnormal if over 35 U/mL. It has also been suggested that the change over time of CA-125 compared with the patient's baseline (the risk of ovarian cancer algorithm or ROCA) may be a more accurate indicator of risk. In the United States, the Prostate, Lung, Colorectal, and Ovarian (PLCO) screening trial performed a randomized controlled trial of 78,216 women aged 55 to 74 years assigned to undergo either annual screening with CA-125 and TVUS (for varying numbers of years) or usual care. There was no difference in ovarian cancer mortality and there were serious complications seen following false positives (123). On the basis of this information, routine ovarian cancer screening in the general population is not recommended. More recently, a study of 3,563 women with an estimated lifetime risk of ovarian cancer of more than 10% underwent frequent screening with some evidence suggesting early stage tumors were detected using this approach (123,124). Several other studies have completed accrual and results are pending. Further data from these large prospective trials are needed to shed light on the utility of CA-125 screening in this high-risk group of women. In the absence of these data, however, it is still recommended that mutation carriers who have not undergone salpingo-oophorectomy perform the screening outlined above. Additionally, studies are evaluating the utility of novel serum markers and several trials have prospectively collected serum for such analyses.

Risk Reduction Options

Risk-Reducing Bilateral Salpingo-Oophorectomy Risk-reducing bilateral salpingo-oophorectomy is strongly recommended for mutation carriers between ages 35 and 40 and once childbearing is complete. Two pivotal studies published in 2002 demonstrated the strong protective effect of this intervention. Among 551 *BRCA1* and *BRCA2* carriers followed for more than 8 years, fallopian tube or ovarian cancer, or primary peritoneal carcinomatosis developed in 8 of the 259 (3.1%) subjects who had undergone RRSO as compared with 58 of the 292 (19.9%) who had not undergone this procedure (HR = 0.04, 95% CI, 0.01–0.16) (14). Similarly, in a prospective study of 170 *BRCA1* and *BRCA2* carriers over the age of 35 followed for 2 years, cancer of the fallopian tubes or ovaries or primary peritoneal carcinomatosis was diagnosed in 5 of the 83 women choosing surveillance as opposed to 1 of the 98 women who underwent salpingo-oophorectomy (p = .04) (113). In a subsequent analysis with data from the above two studies, 498 *BRCA1* carriers and 294 *BRCA2* carriers were prospectively followed for a median of 38 months. An 88% reduction in risk of *BRCA*-associated gynecologic malignancies was noted in those electing RRSO (3 of 509) as compared with surveillance (12 of 283) (HR = 0.12, 95% CI, 0.03–0.41). In this study, no post-RRSO cancer was seen in *BRCA2* mutation carriers (17). Additionally, an international study of 1,828 *BRCA1/2* carriers demonstrated that, with a median follow-up of 3.5 years, RRSO was associated with an 80% reduction in risk of *BRCA*-associated gynecologic malignancies (HR = 0.20, 95% CI, 0.07–0.58; p = .003) (125). Of note, this study estimated a 4.3% cumulative incidence of peritoneal carcinomatosis at 20 years in those undergoing RRSO. Recently the PROSE study group examined the impact of RRSO on ovarian cancer risk with specific analysis not only by gene (*BRCA1* vs. *BRCA2*) but also by breast cancer status (prior breast cancer vs. none). No post-RRSO peritoneal cancers were seen in *BRCA2* mutation carriers either in those with or without prior breast cancer. For *BRCA1* mutation carriers, RRSO decreased the risk of ovarian cancer in both unaffected mutation carriers and those with prior breast cancer (20).

In addition to the residual risk of peritoneal carcinomatosis after RRSO, which appears to be higher in *BRCA1* compared to *BRCA2* mutation carriers, studies have demonstrated that occult malignancies, including cancer of the fallopian tubes, occur in 2% to 10% of women at the time of risk-reducing surgery (111,113,126). This finding underscores the importance of removal of the fallopian tubes at the time of risk-reducing surgery as well as the significance of careful examination of the specimen for occult malignancy.

Studies have also demonstrated that RRSO is associated not only with a reduction in breast and ovarian cancer incidence but also a reduction in disease related mortality. Following an initial small study in 2006, the PROSE study group reported on 2,482 prospectively followed *BRCA1* and *BRCA2* mutation carriers. RRSO was associated with a significant decrease in breast cancer specific (HR 0.44 [95% CI, 0.26–0.76]), ovarian cancer specific (HR 0.21 [95% CI, 0.06–0.80]), and overall mortality (HR 0.40 [95% CI, 0.26–0.61]) (20). These data confirm the critical importance of RRSO in

the management of *BRCA1/2* mutation carriers. Further data are needed on the optimal timing of oophorectomy.

Commonly questioned is the role of hysterectomy in mutation carriers at the time of RRSO. Given the risk of fallopian tube cancer, concern has been raised that a small portion of the proximal fallopian tube remains if hysterectomy is not performed, thus resulting in a residual increased risk of fallopian tube cancer. However, two studies examining fallopian tube cancers indicate that more than 90% occur in the distal or mid-portion of the tube (127), suggesting that the occurrence of a proximal fallopian tube cancer would be a very unlikely event. Some reports have suggested an increased incidence of uterine carcinoma in mutation carriers, whereas others have not confirmed an elevated risk of serous uterine cancer. A case-control study suggested that any increased incidence of uterine cancer among mutation carriers was related to the use of tamoxifen (13); this was confirmed in a more recent study by the same group of 4,456 *BRCA1/2* mutation carriers. Even with tamoxifen use the excess risk of endometrial cancer was small, with a 10 year cumulative risk of 2% (13). In addition, the use of tamoxifen can be minimized at this time given the options of raloxifene for breast cancer prevention (which does not increase the risk of uterine cancer) (128) and aromatase inhibitors for treatment of postmenopausal breast cancer. Therefore, based on our current understanding risk of uterine cancer is not a singularly compelling reason to consider hysterectomy at the time of RRSO.

A final issue to be considered centers on the type of HRT after RRSO. Findings from the Women's Health Initiative have shown an increased risk of breast cancer with combination hormone replacement therapy (estrogen plus progesterone) but not estrogen alone (129). In carriers undergoing hysterectomy, estrogen alone could be used; however it is unclear if the findings from the Women's Health Initiative apply to mutation carriers undergoing premature menopause for whom a brief duration of HRT is being considered. Thus, carriers should consider this information at the time they are undergoing RRSO, but at present, hysterectomy is not routinely recommended.

It has been proposed that the majority of ovarian cancers arise in the fallopian tube (130). Therefore, the concept of salpingectomy only (with delayed oophorectomy—potentially as late as the time of natural menopause) has been proposed as an option for *BRCA1/2* mutation carriers in an effort to avoid premature menopause. However, given the substantial data demonstrating benefit of RRSO, this approach should be viewed as experimental (131,132).

Chemoprevention Oral contraceptives are known to decrease the risk of ovarian cancer in the general population. As discussed previously in the section on cancer risk modifiers, a large case-control study demonstrated that oral contraceptive use reduced the risk of ovarian cancer in *BRCA1* and *BRCA2* carriers (45). However, data from The International *BRCA1/2* Carrier Cohort Study, a retrospective study of 1,593 mutation carriers, indicate that both current and past use of oral contraceptives was associated with an increased risk of breast cancer (HR = 1.47, 95% CI, 1.16–1.87) (47). Other studies have not shown this association (133). Therefore, women and their physicians should consider both the benefits (ovarian cancer risk reduction, prevention of unintended pregnancy, and others) and the risks (potential increased risk of breast cancer, deep venous thrombosis, and others). On the basis of the current data, there is no recommendation specifically for or against the use of oral contraceptives.

Male Breast Cancer

It is recommended (based on expert opinion rather than direct evidence) that male *BRCA1/2* carriers consider monthly breast self-examination, undergo semiannual clinical breast examination starting at age 35, and consider undergoing baseline mammogram at age 40 followed by annual mammogram if gynecomastia is present or baseline study reveals parenchymal or glandular breast density (50). Data regarding the optimal clinical management of male mutation carriers are lacking.

Prostate Cancer

The United States preventative services task force (USPSTF) now recommends against prostate cancer screening in the general population. Given the increased risk of prostate cancer in *BRCA2* mutation carriers, prostate specific antigen (PSA) screening can still be considered, and guidelines suggest that male mutation carriers should *consider* prostate cancer screening starting at age 40 (50). The IMPACT study, a multicenter prostate cancer screening study in *BRCA1* and *BRCA2* mutation carriers and controls ("true negatives"—men who test negative for the known familial *BRCA1* or *BRCA2* mutation) will provide significant information on this issue (134).

Other Cancers

The management of pancreatic cancer risk is uncertain and evolving. Studies in familial pancreatic cancer patients (which generally have included *BRCA2* mutation carriers with at least one first- or second-degree relative with pancreatic cancer) have reported that screening with endoscopic ultrasound, abdominal MRI, or both can detect presumed precursor lesions, namely intraductal papillary mucinous neoplasm (IPMN) (135). However, it is uncertain whether this results in a decrease in pancreatic cancer mortality. A recent multicenter study has suggested that, if pancreatic cancer screening is considered, the earliest age of initiation should be 50 or 10 years prior to earliest pancreatic cancer in the family (136). Novel strategies are also being evaluated. Additionally, it is often recommended that *BRCA2* carriers undergo annual skin examination with a dermatologist for the increased risk of melanoma.

Management of *BRCA1/2*-Associated Breast Cancer

Breast Cancer

Phenotype: Histopathologically, *BRCA1*-associated breast cancers have been consistently noted to be both more frequently high grade and more frequently estrogen and progesterone receptor negative (137–139). In addition, these tumors exhibit more lymphocytic infiltration and continuous pushing margins than is typically seen in sporadic breast cancer (140) and more frequently have medullary or atypical medullary features. On molecular analyses, *BRCA1*-associated breast cancers showed an increased incidence of *p53* mutations (137), but a decreased incidence of overexpression of *erb*B-2 (137). Studies examining *BRCA2*-associated breast cancers have demonstrated that these appear to be similar to sporadic breast cancer with respect to hormone receptor status (139). In addition, in contrast to *BRCA1, BRCA2*-associated breast cancers did not exhibit any differences in expression of *p53* or *erb*B-2 (137).

More detailed molecular analyses from the Cancer Genome Atlas have demonstrated that *BRCA1*-associated breast cancers are often of the basal phenotype and have

confirmed a high rate of *p53* mutations (141). In addition, *BRCA1/2*-associated tumors appear to have a distinct profile of deletions as well as a characteristic signature of substitution mutations (142).

Breast Cancer Prognosis

Investigations have focused on whether the observed phenotypic differences between sporadic and *BRCA1/2*-associated breast cancers have prognostic implications. There has been variability in the findings of these studies, as well as the methodologies employed. Some studies have sought to overcome survival biases that could hinder the interpretability of the findings by genotyping tumor blocks from all Jewish women diagnosed over a specified timeframe and correlating the findings with clinical outcome. Rennert et al. (139) obtained data on all incident cases of invasive breast cancer diagnosed between January 1987 and December 1988 in the Israeli National Cancer Registry. DNA was extracted from available blocks and tested for the three founder mutations in those of Ashkenazi Jewish descent. A total of 1,545 subjects had tumor specimens available for analysis as well as clinical and pathologic records. *BRCA1* or *BRCA2* mutations were identified in 10% of the subjects. The 10-year survival rate was 49% for *BRCA1* carriers, 48% for *BRCA2* carriers, and 51% for noncarriers. The hazard ratio for death from breast cancer adjusted for age, tumor size, and nodal status, did not differ between *BRCA1* carriers (HR = 0.76, 95% CI, 0.45–1.30, p = .31), or *BRCA2* carriers (HR = 1.31, 95% CI, 0.8–2.15, p = .28) compared with noncarriers. Interestingly, among those receiving chemotherapy, a nonstatistically significant trend was seen for improved survival in *BRCA1* carriers (10-year survival of 71% in carriers vs. 46% in noncarriers; HR = 0.48, 95% CI, 0.19–1.21, p = 0.12) and the interaction term between *BRCA1* status and chemotherapy was significant for overall survival (p = .02). Additionally, a survival disadvantage was seen for *BRCA1* carriers with tumors less than 2 cm in size (p = .04). In a study by Robson et al. (143), tumor blocks of 496 Jewish women diagnosed between 1980 and 1995 who underwent breast-conserving surgery were analyzed. Founder mutations were identified in 11% of the women and 10-year breast cancer specific survival was significantly worse in *BRCA1* carriers than noncarriers (62% vs. 86%, p < .001), but not in those with *BRCA2* mutations (84% vs. 86%, p = .76). However, *BRCA1* status predicted for a worse outcome only in those not receiving chemotherapy. Other studies have also demonstrated no differences in breast cancer specific survival in *BRCA1/2* carriers versus noncarriers. Based on these data, mutation status should currently not be viewed as an independent predictor of clinical outcome.

Local Treatment

Although the increased risk of contralateral breast cancer in *BRCA1/2* mutation carriers with breast cancer is well-established, it is less clear whether *BRCA1/2* carriers incur greater risks for ipsilateral cancer if treated with breast-conserving therapy. Additionally, concerns regarding increased radiation sensitivity and potential impact on cosmesis in mutation carriers have been raised. A comprehensive review article noted that among 17 studies examining the risk of in-breast tumor recurrence in genetic cohorts as opposed to those with sporadic disease, 5 noted an increased risk, whereas 12 did not (145). Many of these studies however, did not factor in the impact of either tamoxifen or oophorectomy on subsequent risk of breast cancer. In a study by Pierce et al. (18), which compared 160 *BRCA1/2* carriers with breast cancer who underwent breast-conserving therapy with 445 matched controls with sporadic breast cancer, no overall difference in rate of ipsilateral recurrence at 10 years was noted. However, when women who had undergone prophylactic oophorectomy were excluded from the analysis, mutation carriers had significantly higher rates of ipsilateral recurrence (p = .03). The metachronous ipsilateral breast cancers in carriers were more commonly located in a quadrant other than that of the primary lesion and tended to be associated with longer time to recurrence, suggesting that these represented second primary cancer rather than an in-breast tumor recurrence. Additionally, in this study no negative impact on cosmesis was observed.

A second study by Pierce et al. examined 655 women with known *BRCA1/2* mutations diagnosed with breast cancer who underwent either breast conservation (N = 302) or mastectomy (N = 353) and were followed. There were no differences seen in regional or systemic recurrences between the breast conversation therapy and mastectomy groups, and no difference in overall survival. However, women undergoing breast conservation therapy had an elevated risk of a second in-breast event (largely felt to be second primary tumors) that was significantly reduced by chemotherapy (144).

Thus, breast-conserving therapy is an appropriate local treatment option for mutation carriers with newly diagnosed breast cancer. Nonetheless, it is important that these women understand that they face increased risks for both contralateral and ipsilateral new breast cancers. Thus, some mutation carriers with a newly diagnosed breast cancer may wish to consider bilateral mastectomy to minimize their risk of developing a new primary.

Systemic Treatment

As discussed, current data regarding the impact of *BRCA1*/2 status on breast cancer related prognosis suggest that the details of the breast tumor (stage and hormone receptor status) and not *BRCA1/2* status should remain the main determinants regarding systemic therapy. It is possible that, in the future, choice of systemic therapy may be influenced by genetic information because preclinical and early clinical data suggest that *BRCA*-associated breast cancers may have enhanced sensitivity to certain chemotherapeutic agents such as platinum (146). The increased efficacy of platinum agents is thought to be a possible explanation for the improved survival seen in *BRCA*-associated ovarian cancers as compared with sporadic disease (147). Small, single arm studies of cisplatin chemotherapy in *BRCA1* mutation carriers have demonstrated high response rates in both the metastatic and neoadjuvant settings (148). However, it has also been demonstrated that *BRCA*-mutation associated breast cancers appear sensitive to chemotherapy in general (not just to cisplatin) with improved responses compared with sporadic breast cancers in both the metastatic and neoadjuvant (149,150) setting. Studies are underway to compare platinum-based chemotherapy to standard chemotherapy in *BRCA*-associated breast cancer to directly address whether there is difference in outcome. In addition, hope is that a novel class of drugs Poly(ADP-ribose) polymerase-1 (PARP-1) inhibitors, may be particularly effective in *BRCA* mutation-associated breast cancer. PARP-1 is an enzyme involved in the repair of single-strand DNA (ssDNA) breaks through base excision repair. In PARP-1 deficient states, ssDNA breaks may go on to become double strand DNA (dsDNA) breaks. The repair of dsDNA breaks is dependent on *BRCA1*- and *BRCA2*-mediated processes. Thus, in *BRCA*-deficient cells, it is hypothesized that PARP-1 inhibition will

result in accumulation of dsDNA breaks, ultimately leading to apoptosis (151,152). Clinical trials of PARP inhibitors in *BRCA*-associated breast and ovarian cancers have demonstrated encouraging results and multiple studies are ongoing (153,154).

Screening and Risk Reduction Options for Second Malignancies

Mutation carriers with a breast cancer diagnosis are at increased risk of developing a second breast cancer and ovarian cancer (see section on Clinical Characteristics). As previously noted, up to 25% of mutation carriers with stage I breast cancer will subsequently succumb to ovarian cancer. Thus, it is recommended that the screening and prevention guidelines for breast and ovarian cancer as described in the prior section on management of unaffected mutation carrier, be utilized. It is important to note that these must be individualized and balanced, incorporating information on the underlying prognosis related to the breast cancer. Two separate studies have examined the risk of breast cancer following the diagnosis of ovarian cancer. In both of these studies, the risk of developing breast cancer within five years of an ovarian cancer diagnosis was quite low (while unfortunately the risk of relapse and death due to ovarian cancer was not). Thus, conservative management of breast cancer risk following the diagnosis of ovarian cancer in *BRCA1/2* mutation carriers is suggested (18,19).

Management of Individuals with Other Hereditary Breast Cancer Syndromes

Li-Fraumeni Syndrome

Li-Fraumeni syndrome (LFS) is a rare, highly penetrant autosomal-dominant condition characterized primarily by soft tissue sarcomas, osteosarcomas, leukemias, brain tumors, adrenocortical malignancies, and early onset breast cancer (Table 17-1) (2). Specific testing criteria based on these features have been published which include women diagnosed with breast cancer at age 35 or younger with a negative *BRCA1/2* test result (50). Mutations in the tumor suppressor gene *TP53* occur in at least 70% of families with LFS (2). It is estimated that 50% of carriers will develop a LFS-associated cancer by age 30 years and the lifetime risk of cancer exceeds 90% (2). Individuals are also at high risk for developing multiple primary cancers (2). In particular, the occurrence of breast cancer in these families is remarkable in that the median age of diagnosis in women is in the early 30s; male breast cancer, however, is rarely reported. Owing to concerns about increased risks for cancer in the field of radiation treatment, mastectomy is recommended over lumpectomy; alternatively bilateral mastectomy may be the treatment of choice. Management guidelines from the National Comprehensive Cancer Network indicate that, for women, the recommended surveillance for breast cancer consists of consideration of monthly breast self-examination beginning at age 18; semiannual clinical breast examinations beginning at age 20 to 25 or 5 to 10 years before the age of occurrence of the first breast cancer in the family; and annual breast MRI starting at age 20 to 25 (46). Mammography can be added at the start of MRI screening or at age 30 as MRI only may be sufficient between ages 20 and 30. Risk-reducing mastectomy should also be discussed on an individual basis. Beginning at age 20 to 25 years, an annual comprehensive physical examination is recommended with particular focus on rare cancers (50). Early studies have suggested that intensive surveillance may aid in the early detection of malignancy. Recent data on an intensive screening regimen including full body MRI and brain MRI, which has the advantage of avoiding radiation, have been encouraging. Participation in clinical trials with novel imaging is encouraged. Colonoscopy should be considered by age 25, and be repeated every 2 to 5 years (50). Pretest counseling is imperative in testing for *TP53* mutations given the significant implications of a positive result, including for children.

Cowden Syndrome

Cowden syndrome is a rare, although potentially underrecognized, autosomal-dominant condition characterized by macrocephaly; multiple hamartomatous lesions; characteristic skin findings; benign lesions of the breast, uterus, and thyroid; and an increased risk of early onset breast cancer, as well as cancers of the thyroid (usually follicular), endometrium, kidney (renal cell), colorectum, and skin (melanoma) (Table 17-1) (3). Specific criteria for testing are available, in which up to 85% of individuals who meet these criteria have a mutation in the *PTEN* gene. The lifetime risk of breast cancer is between 25% and 50%, with most cases diagnosed before age 50 (3). Recent data have suggested a lifetime risk of breast cancer as high as 85%; however, this penetrance estimate may have been high due to the study design and ascertainment bias (155). In addition, up to 75% of women with Cowden syndrome have been observed to have a variety of benign breast conditions, including ductal hyperplasia, intraductal papillomatosis, adenosis, lobular atrophy, fibroadenomas, and fibrocystic changes (3). Management guidelines from the National Comprehensive Cancer Network indicate that, for women, the recommended surveillance for breast cancer consists of consideration of monthly breast self-examination beginning at age 18; semiannual clinical breast examination beginning at age 25 or 5 to 10 years before the age of occurrence of the first breast cancer in the family; and annual mammogram and breast MRI starting at age 30 to 35 or 5 to 10 years younger than the earliest known breast cancer in the family. Risk-reducing mastectomy and hysterectomy should also be discussed on an individual basis. Additional screening should include annual comprehensive physical examination beginning at age 18, with particular focus on breast and thyroid examinations, colonoscopy beginning at age 35, baseline thyroid ultrasound at age 18 with consideration of annual examination, and annual dermatologic examination. Screening strategies for endometrial cancer and renal cell cancer are not clearly defined at this time.

Peutz-Jeghers Syndrome

Peutz-Jeghers syndrome (PJS), arising predominantly from mutations in the *STK11* (*LKB1*) gene, is an autosomal-dominant condition characterized by hamartomatous polyps in the gastrointestinal tract and by mucocutaneous melanin deposits in the buccal mucosa, lips, fingers, and toes (Table 17-1) (4). With respect to extraintestinal cancers, the most significant risk is for breast cancer, with a lifetime risk estimated to be 45% to 50%. Although overall few cases have been reported, onset before age 50 years and bilateral disease is not uncommon. The risk of ovarian cancer, estimated at about 20%, is significant, but many of these are nonepithelial sex cord tumors (4). Women also face elevated risks for colon, stomach, pancreatic, small intestine, cervical, uterine, and lung cancers. Management guidelines from the National Comprehensive Cancer Network indicate that women with PJS should be managed by a specialized team and consider participation in clinical trials (50). They recommend that women undergo annual mammography and breast MRI

starting at about age 25, colonoscopy and upper endoscopy every 2 to 3 years starting in the late teens, as well as consideration of other gastrointestinal and gynecologic screening. Many of these guidelines are provisional, and may be modified based on an individual's family history.

Hereditary Diffuse Gastric Cancer

Hereditary diffuse gastric cancer is an autosomal-dominant cancer predisposition syndrome associated with diffuse gastric cancer (signet ring carcinoma or isolated cell-type carcinoma) and female lobular breast cancer. Up to 50% of affected individuals harbor a mutation in the *CDH1* gene; in other cases, the causative gene mutations remain unidentified. Based on multi-case families, it is estimated that the lifetime risk of gastric cancer is 80%, and the average age of onset is before age 40 (range 14 to 69 years). The lifetime risk of breast cancer in women is between 39% and 52%, and the average age of onset is 53 years; however, this risk estimate assumes that women do not develop gastric cancer or that they survive it long term (5). It is important to note that lobular breast cancers are typically difficult to detect on mammography and MRI may be more accurate in this setting. Thus, annual mammography and breast MRI from the age of 35 years is recommended for women (156). Given that lobular carcinomas are frequently hormone receptor positive, chemoprevention with tamoxifen or raloxifene is a very reasonable option. Additionally, risk-reducing mastectomy can be considered.

Moderate Penetrance Genes

A number of "moderate" penetrance genes have been identified, mutations in which are associated with a relative risk of breast cancer of 2 to 5. Multiplex panels (described in Table 17-2) are increasingly commercially available and may be appropriate to consider for women with breast cancer or a family history of breast cancer who have tested negative for *BRCA1/2* mutations. Despite the availability of these panels, it remains uncertain how the presence of a moderate penetrance breast cancer susceptibility allele should change clinical management. Multiple studies are ongoing to attempt to address this issue. In addition, as demonstrated in Table 17-2, these commercial multiplex panels contain both high penetrance and moderate penetrance genes. The mix of moderate and high penetrance alleles in a single panel raises concerns about appropriate counseling and consent. For many of the moderate penetrance genes on these panels, very limited information is available on breast cancer risk estimates and associated risks of other cancers. In addition, because many genes are being analyzed, it is very likely that variants of uncertain significance will be detected, further complicating the interpretation of results. Finally, significant caution should be taken prior to counseling family members as "true negatives" of moderate penetrance gene mutations. Different counseling models are needed prior to wide use of these panels (7). Here, we discuss two of the moderate penetrance genes for which the most information is available, *CHEK2* and *PALB2*.

CHEK2: CHEK2 (cell cycle checkpoint kinase 2) plays a role in cell-cycle arrest and DNA repair. One of the most commonly identified variants in the *CHEK2* gene is a small deletion (1100delC), which is found predominantly in individuals of northern and eastern European descent (157). A recent meta-analysis of breast cancer risk associated with this specific mutation reported that, among pedigrees with "familial breast cancer" (i.e., one case of female breast cancer with one or more relatives with breast cancer, including male breast cancer, or ovarian cancer), the cumulative risk of breast cancer to age 70 was 37% (95% CI, 26%–56%) (157). Although this risk roughly compares with those reported in lower end of the range for *BRCA1* and *BRCA2* carriers, it is important to bear in mind that the studies used in the analysis used a variety of ascertainment methods, which may have biased estimates of penetrance (157,158). Mutation type and type of cancer in the proband may impact the cancer risks in relatives (159); and the full spectrum of cancers associated with this and other specific variants in *CHEK2* is not fully defined (157,158). Moreover, it is unclear whether other low penetrance genes could contribute to familial breast cancer risks in *BRCA1/2*-negative families in addition to potential *CHEK2* mutations and what management strategies are optimal. Given that most *CHEK2*-related breast cancers are hormone receptor positive (160), chemoprevention with the selective estrogen receptor modulators (SERM) tamoxifen or raloxifene could be considered; however, whether such testing information impacts uptake of SERM use is unknown. Recent data have suggested a worse outcome of breast cancer associated with germline *CHEK2* mutations, but it is not clear if this is independent of other tumor features (such as gene expression profiles from Oncotype testing in ER positive, node negative breast cancer patients) (161). In summary, *CHEK2* is a known, although uncommon, moderate penetrance breast cancer susceptibility allele, but how to best use knowledge of mutation status in clinical practice is evolving.

PALB2: Truncating mutations in the *PALB2* gene on chromosome 16p12.2 have been described in individuals with familial breast cancer. Such mutations have not been seen in controls and thus the relative risk of breast cancer is estimated to be 2–3. Heterozygous *PALB2* mutations have also been associated with pancreatic cancer (8). In this study, 3 of 96 familial pancreatic cancer patients had truncating *PALB2* mutations, and no mutations were found in control subjects. However, *PALB2* are not frequently found, even in families with both breast and pancreatic cancer. Further work is needed on penetrance estimates for pancreatic cancer and to better understand the utility of pancreatic cancer screening.

SUMMARY

Most individuals with a family history of breast cancer have a familial rather than hereditary basis to their disease. For women with hereditary breast cancer, *BRCA1* and *BRCA2* mutations account for most cases. Mutations in these genes are associated with a significantly elevated risk of early onset breast and ovarian cancer. In addition, other cancers may be seen with an increased frequency in mutation carriers. Models based on cancer history, family history, and ethnic background are available to guide clinicians in estimating the likelihood that an individual harbors a risk-conferring mutation. Data from prospective studies have emerged demonstrating a strong protective effect of bilateral salpingo-oophorectomy and bilateral mastectomy on cancer incidence. Additionally, it is now recommended that women with a hereditary predisposition to breast cancer alternate annual breast MRI with mammogram. Because of the complexities involved in decision-making about genetic testing and medical management, genetic counseling is recommended before and after undergoing testing. Further studies on genetic and environmental cancer risk modifiers, genotype–phenotype correlations, and the impact of cancer screening and prevention options are underway and will continue to provide greater insight into the features and management of individuals at high risk.

MANAGEMENT SUMMARY

- *BRCA1/2* carriers face significantly elevated risks of early onset breast and ovarian cancer as well as increased risk of pancreatic, prostate, and male breast cancer.
- Decisions regarding more intensive screening versus prevention (particularly risk reducing surgery) are often personal, based on a careful balancing of the relative risks and benefits of the various options.
- Breast cancer screening recommendations include annual mammogram alternating with annual breast MRI.
- Breast cancer prevention options can be combined with more intensive screening and include RRSO, risk reducing mastectomy, and chemoprevention (with tamoxifen, raloxifene, or exemestane).
- For management of ovarian cancer risk, bilateral salpingo-oophorectomy between ages 35 and 40 and once childbearing is complete is strongly recommended. Short-term HRT before age 50 can be considered.
- For women who have not undergone salpingo-oophorectomy, semiannual CA-125 and TVUS are recommended, beginning at age 30 or 5 to 10 years younger than the earliest age of onset of ovarian cancer in the family. However, few data support a benefit of screening for ovarian cancer.
- Male mutation carriers should perform monthly breast self-examination, have semiannual clinical breast examination, and consider annual mammography. Prostate cancer screening can be considered, particularly in *BRCA2* mutation carriers.
- *BRCA2* mutation carriers may consider annual skin examination, on an individualized basis, and consider participating in studies on pancreatic cancer screening.
- Mutation status does not impact early stage breast cancer systemic management in *BRCA1/2* carriers at this time, but mutation carriers need to consider their risks of second malignancy and should follow similar guidelines to those outlined previously for unaffected carriers.
- Recommendations for management of members of hereditary breast cancer families who have undergone genetic testing and tested negative for *BRCA1/2* mutations need to be individualized based on their personal and family history.

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CHAPTER 18

Nongenetic Factors in the Causation of Breast Cancer

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CHAPTER CONTENTS

Breast cancer has an enormous impact on the health of women. Approximately 227,000 women are diagnosed with invasive breast cancer annually in the United States, accounting for approximately 29% of all incident cancers among women (1). Each year, 40,000 women die of breast cancer, making it the second leading cause of cancer deaths among U.S. women, after lung cancer, and the leading cause of death among women aged 40 to 55 years. Breast cancer is rare among men, with only 2,190 incident cases and 410 deaths estimated for the United States in 2012 (1). The lifetime risk of being diagnosed with breast cancer through age 85 years for an American woman is approximately 1 in 8, or 12.15%, whereas the lifetime risk of dying from breast cancer is approximately 3.4% (2).

This chapter begins with a description of the marked variations in breast cancer rates among populations and over time. Decades of research have led to a substantial understanding of the factors involved in the development of breast cancer; known and suspected risk factors are reviewed and considered in relation to etiologic mechanisms leading to breast cancer. The contribution that known risk factors make to the existing variations in rates is considered; this contribution is central to the question of whether unidentified pollutants or dietary factors explain the current high rates in the United States. Because of the major investments in breast cancer research, the means for preventing a substantial fraction of breast cancer now exists; strategies that can be adopted by individual women, their healthcare providers, and societies and governments as a whole are examined.

DESCRIPTIVE EPIDEMIOLOGY OF BREAST CANCER

High- and Low-Risk Populations

The incidence of female breast cancer varies markedly between countries, being highest in the United States, western and northern Europe, intermediate in southern and eastern Europe and South America, and lowest in Asia and Africa (3). In 2008, the age-adjusted incidence rate of breast cancer varied by about a factor of five across countries worldwide (Fig. 18-1) (3). However, incidence rates have been rising in traditionally low-incidence Asian countries, particularly in Japan, Singapore, and urban areas of China as these regions are making the transition toward a Western style of economy and pattern of reproductive behavior (4,5). As a result of unfavorable trends in these countries, the international gap in breast cancer incidence has narrowed since 1970 (6).

Age–Incidence Curve of Breast Cancer Risk

Breast cancer is extremely rare among women younger than 20 years and is uncommon among women younger than 30 years. Incidence rates increase sharply with advancing age, however, and become substantial before age 50 years. From 2000 to 2009, the incidence of breast cancer among American women aged 30 to 34 years was 26 per 100,000 and increased to 188 per 100,000 among women aged 45 to 49 years (1). The rate of increase in breast cancer incidence continues throughout life but slows somewhat around ages 45 to 50 years, strongly suggesting the involvement of reproductive hormones in breast cancer etiology because non–hormone-dependent cancers do not exhibit this change in slope of the incidence rate curve around the time of menopause (7). By age 70 to 74 years, the incidence of breast cancer among American women rises to 425 per 100,000 (8). The shape of the age–incidence curve in low- and intermediate-risk populations is similar to that of the United States, although the absolute rates are lower at each age (9) (Fig. 18-2).

Racial/Ethnic Groups within the United States and Studies of Migrants

According to recent data from the Surveillance, Epidemiology, and End Results (SEER) registries (1), the lifetime risk of breast cancer for white women in the United States is 12.8%, approximately 1 in 8, whereas that for black women is 10.1%, approximately 1 in 10. Between 2000 and 2009, the overall age-adjusted incidence rate of breast cancer among white women in the United States averaged 127 per 100,000 women, whereas the corresponding rate among black women averaged 121 per 100,000 women (1). However, these age-adjusted figures conceal a crossover pattern in which the risk of breast cancer at a young age is modestly higher among black women than white women. At older ages, incidence rates for white women are substantially higher than those among black women (Fig. 18-2).

Unlike that of most other illnesses, the lifetime risk of breast cancer is positively associated with higher socioeconomic status. This association is largely explained by the known reproductive risk factors (10); women in lower socioeconomic strata are more likely to have more children and to have them at younger ages than women in higher socioeconomic strata. It is likely that much, if not all, of black/white differences in breast cancer rates among older women reflect racial differences in social class distribution (11) and, thus, in the distribution of established reproductive risk factors. The modestly higher incidence rates of breast cancer among young black women relative to young white women are consistent with the hypothesis of a short-term increase in breast cancer risk immediately following pregnancy, although the overall lower lifetime risk of breast cancer among black women is consistent with the hypothesis of a long-term benefit of early and repeated pregnancy (12). The effect of these reproductive factors on breast cancer risk is described in greater detail in the following section on

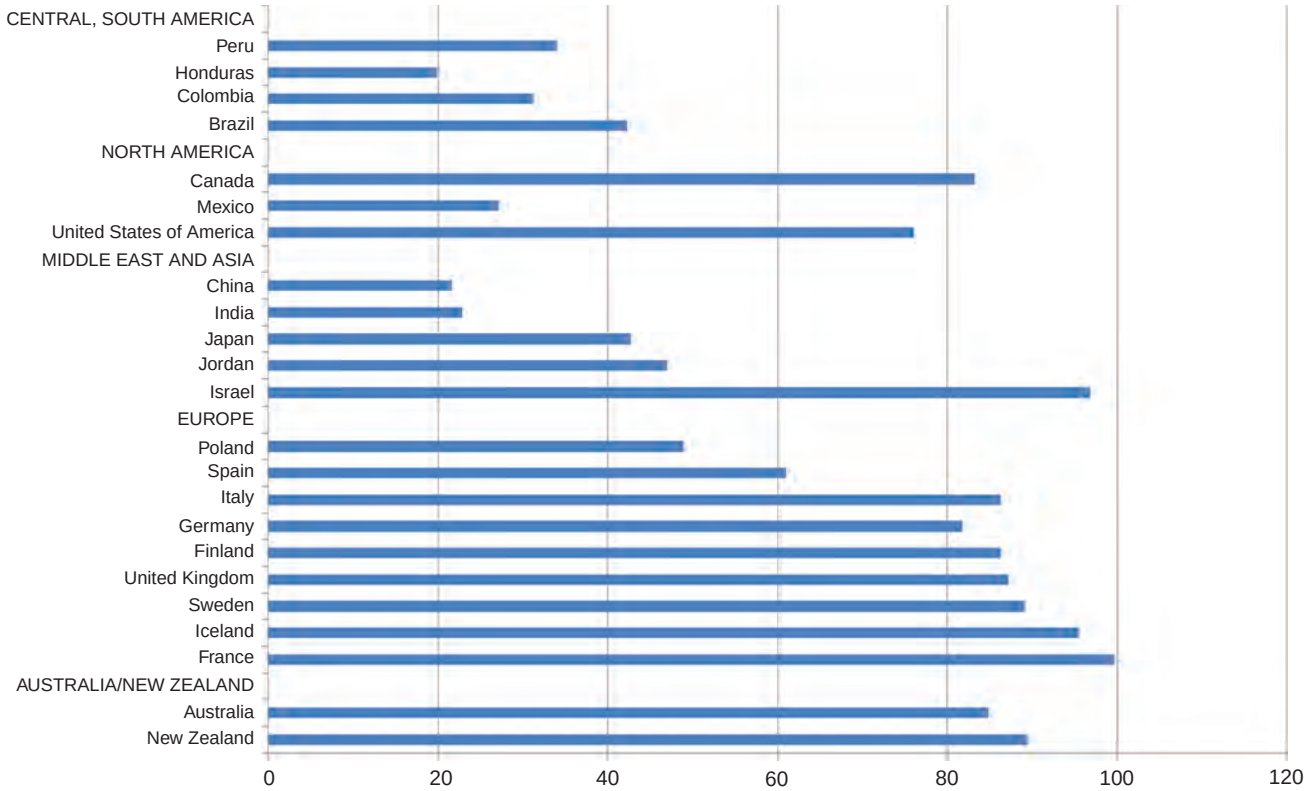


FIGURE 18-1 International variation in breast cancer incidence among women in 2008, per 100,000 women-years, age adjusted to the world standard. (Data from GLOBOCAN 2008. Ferlay J, Shin HR, Bray F, et al. *Cancer incidence, mortality and prevalence worldwide*. Lyon, France: IARC Press, 2010.)

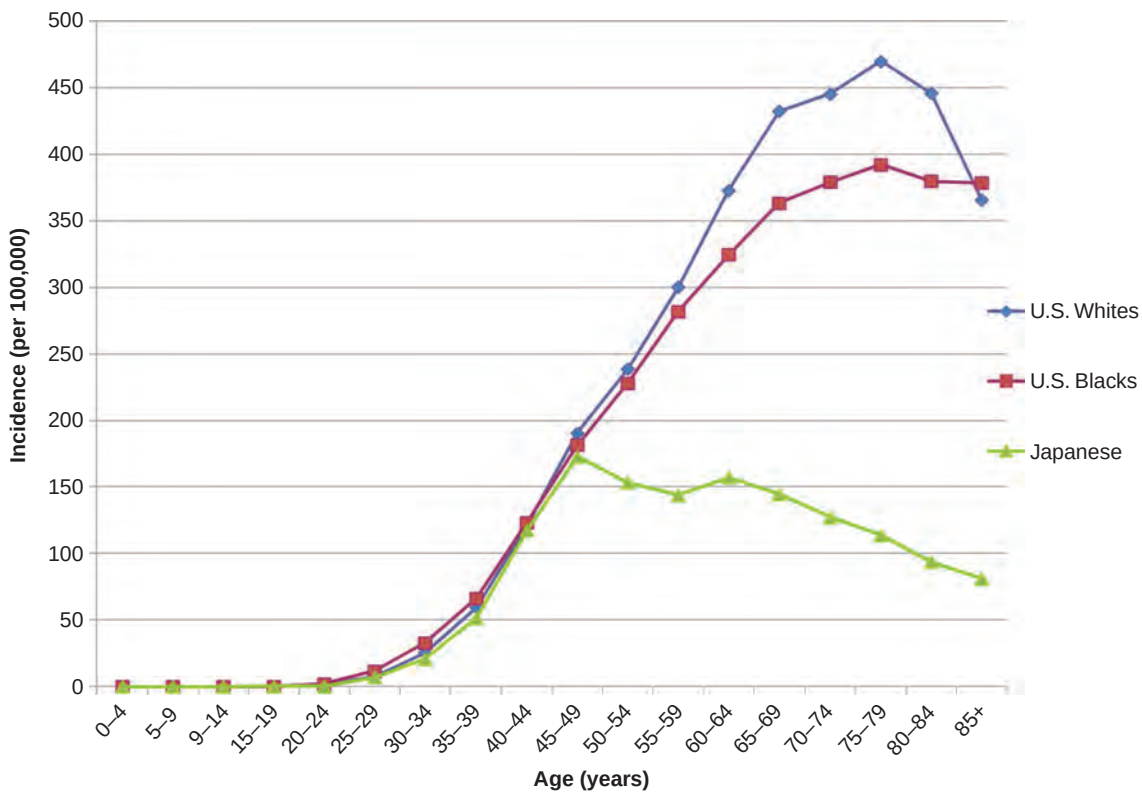


FIGURE 18-2 Age-specific breast cancer incidence rates, white and black U.S women (2000–2009) and Japanese women (2006). (Data from U.S. women from Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov), National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch; data for Japanese women from Cancer Statistics in Japan (http://www.ncc.go.jp.))

modeling. Although black women have a lower probability of developing breast cancer over their lifetime, their risk of dying from breast cancer is the same or perhaps even slightly higher than white women (3.26% compared to 2.86% for black and white women, respectively) (13). Black women have poorer 5-year survival rates from breast cancer at all ages of diagnosis compared to white women (2). This poorer survival can be attributed, in part, to the tendency of black women to be diagnosed at later stages of disease (2). In addition, there is evidence that molecularly defined subtypes of breast cancer associated with poor prognosis, specifically basal-like tumors, are more likely to occur among black women (2).

Breast cancer incidence rates among Asian, Hispanic, and American Indian women in the United States are considerably lower than those of (non-Hispanic) white women (2). The magnitude of the difference in incidence rates among various ethnic groups often depends on migrant status. For instance, breast cancer incidence for Chinese American and Japanese American women from 1973 to 1986 was about 50% lower for those born in Asia and about 25% lower for those born in the United States compared to U.S.-born white women (14). Among Filipino residents of the United States, the incidence rate of breast cancer was nearly identical between foreign-born and U.S.-born women, and both were less than half that of U.S.-born white women. Compared with Chinese women living in the mainland, Singapore, and Hong Kong, Asian-born Chinese women living in the United States had an almost twofold higher annual rate of breast cancer, and U.S.-born Chinese women had a higher rate still (14,15). The pattern for Japanese women was similar (14).

These findings are consistent with a large body of literature showing increases in breast cancer incidence following migration from a low-risk country to the United States (16–21). Ziegler et al. (21) noted a six-fold gradient in risk of breast cancer among Asian women, depending on recency of migration. Asian American women with three or four grandparents born in the West were at highest risk, whereas women who were born in rural areas of Asia and whose length of residence in the United States was a decade or less were at lowest risk. Although the studies of breast cancer risk among migrants have focused almost exclusively on migrants from low-risk to high-risk countries and have shown convergence of rates, there are also data suggesting that a convergence of rates similarly occurs when migrants move from high-risk to low-risk countries. For instance, Kliewer and Smith (22), reporting on immigrants to Australia and Canada, note that immigrant groups coming from countries where breast cancer mortality rates were higher than those of native-born women often showed a decrease in mortality. Such findings strongly suggest that factors associated with the lifestyle or environment of the destination country influence breast cancer risk and are consistent with a positive relationship between length of time in the destination country and adoption of that country's lifestyle. For example, among immigrants, the fertility rate and the average number of children born tend to converge to the rates of the destination country (23,24).

Geographic Variation in the United States

Breast cancer incidence and mortality rates vary within the United States, although to a much smaller degree than among countries. During the 1980s, the incidence of breast cancer in the San Francisco Bay Area was somewhat higher than that for the rest of the United States, and international comparisons based on data from this decade led to an often-quoted statement that white women in the San Francisco Bay Area had the highest incidence of breast cancer in the world (15,25). Based on the most recent SEER data (1) and the National Cancer Institute (Fig. 18-3A), incidence of breast cancer is above the national average among women in the Pacific Northwest and the northeastern United States (age-adjusted incidence rate for Connecticut is 137 per 100,000 and for Washington is 132 per 100,000) (1). Previous reports have concluded that the high incidence of breast cancer in the San Francisco area and in the Northeast can likely be accounted for by regional differences in the prevalence of known risk factors, including parity, age at first full-term pregnancy, age at menarche, and age at menopause (25–29). Among the 17 SEER registry sites, the lowest age-adjusted incidence rates among women are found in Arkansas (109 per 100,000), Utah (108 per 100,000), and New Mexico (110 per 100,000) (1,9). Again, regional differences in reproductive risk factors largely explain these lower rates.

Geographic differences in breast cancer mortality across the United States vary by approximately 1.5 comparing areas of highest versus lowest mortality (1). Figure 18-3B illustrates these regional differences from 2005 to 2009. Although incidence rates are highest in the Pacific Northwest and Northeast, these regions tend to have lower breast cancer mortality rates than the national average. These differences may be due to regional differences in breast cancer risk factors, mammographic screening, and treatment. Geographic differences in the prevalence of established risk factors explain much of the geographic differences in mortality. In 1987, age-adjusted mortality ratios among women 50 years and older were 1.15, 1.18, and 1.30 in the West, Midwest, and Northeast, respectively, compared with the South. After adjustment for established breast cancer risk factors, these mortality ratios fell to 1.13, 1.08, and 1.13, respectively (29).

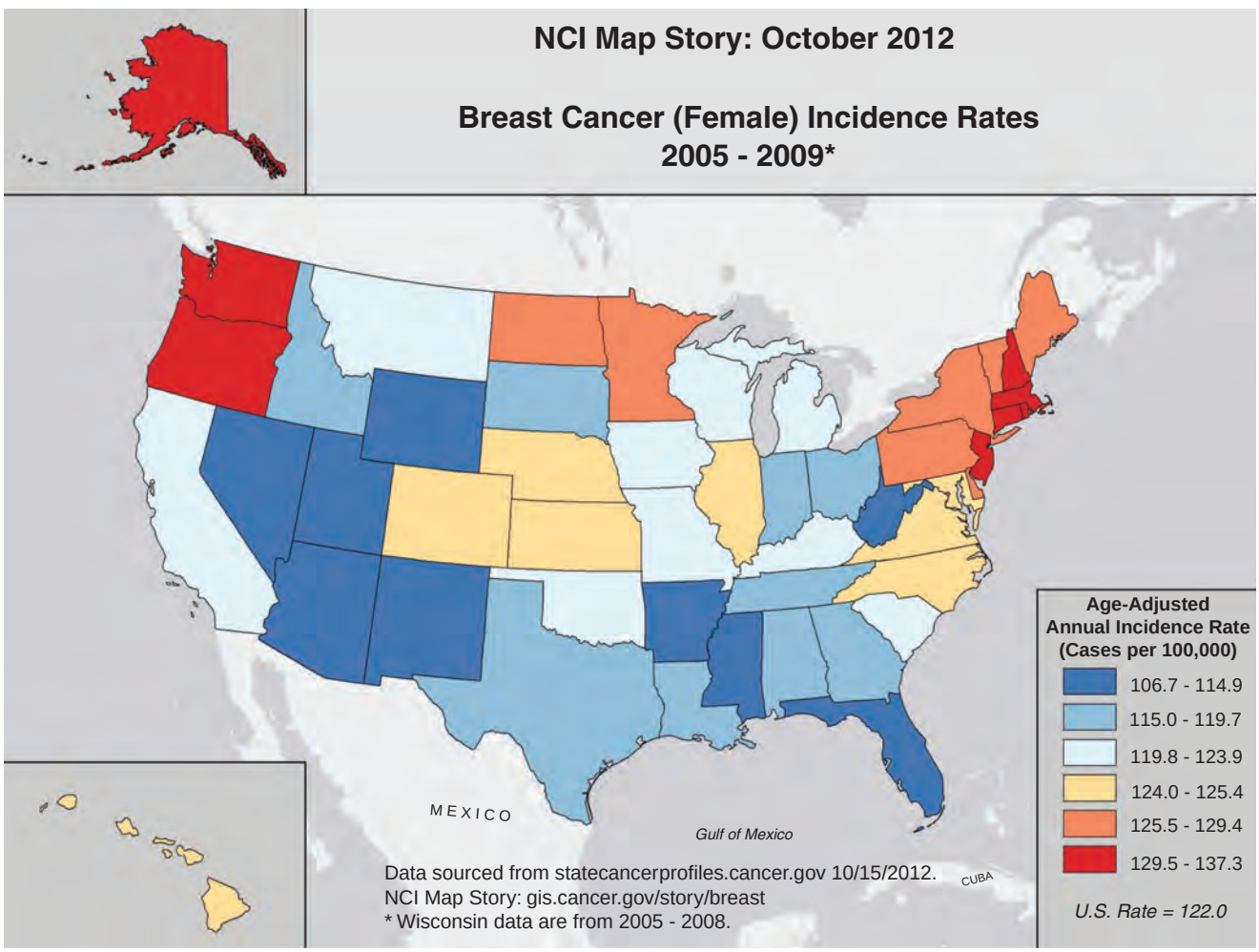
Trends in Incidence and Mortality

Incidence rates of breast cancer have steadily increased in the United States since the 1930s, when formal record keeping began in Connecticut, until 2000. Between 1950 and 2000, the age-adjusted incidence rate rose by an average of 1.4% per year in this state (30), which has the oldest cancer registry in continuous operation. This represents a cumulative increase of about 70% over the 50 years. During the 1980s, incidence rates rose more sharply. Data from the SEER program, which began collecting data from different registries across the country in 1973, confirm the trends in incidence portrayed in the Connecticut registry since that time (Fig. 18-4). Increases have occurred in all age groups since 1935, although the magnitude of increase has been greater for older women. Between 1975 and 2000, incidence rates among black women younger than 50 years increased by 22% compared to a cumulative increase of 10% for white women younger than 50 years (8). Among women 50 years and older, the cumulative increase was 40% for both black and white women. Between 2001 and 2004, incidence rates of breast cancer decreased by approximately 3.5% per year. Between 2005 and 2009, incidence rates among white women have remained relatively constant; while among black women incidence rates have increased.

Several studies have examined whether the increase in breast cancer incidence in the United States has been due to the increasing use of screening mammography (31–36). Because screening causes at most a transient increase in incidence, and because its use was limited before the 1980s, it can explain little of the long-term increase between the 1930s and the 1980s. However, during the 1980s, the

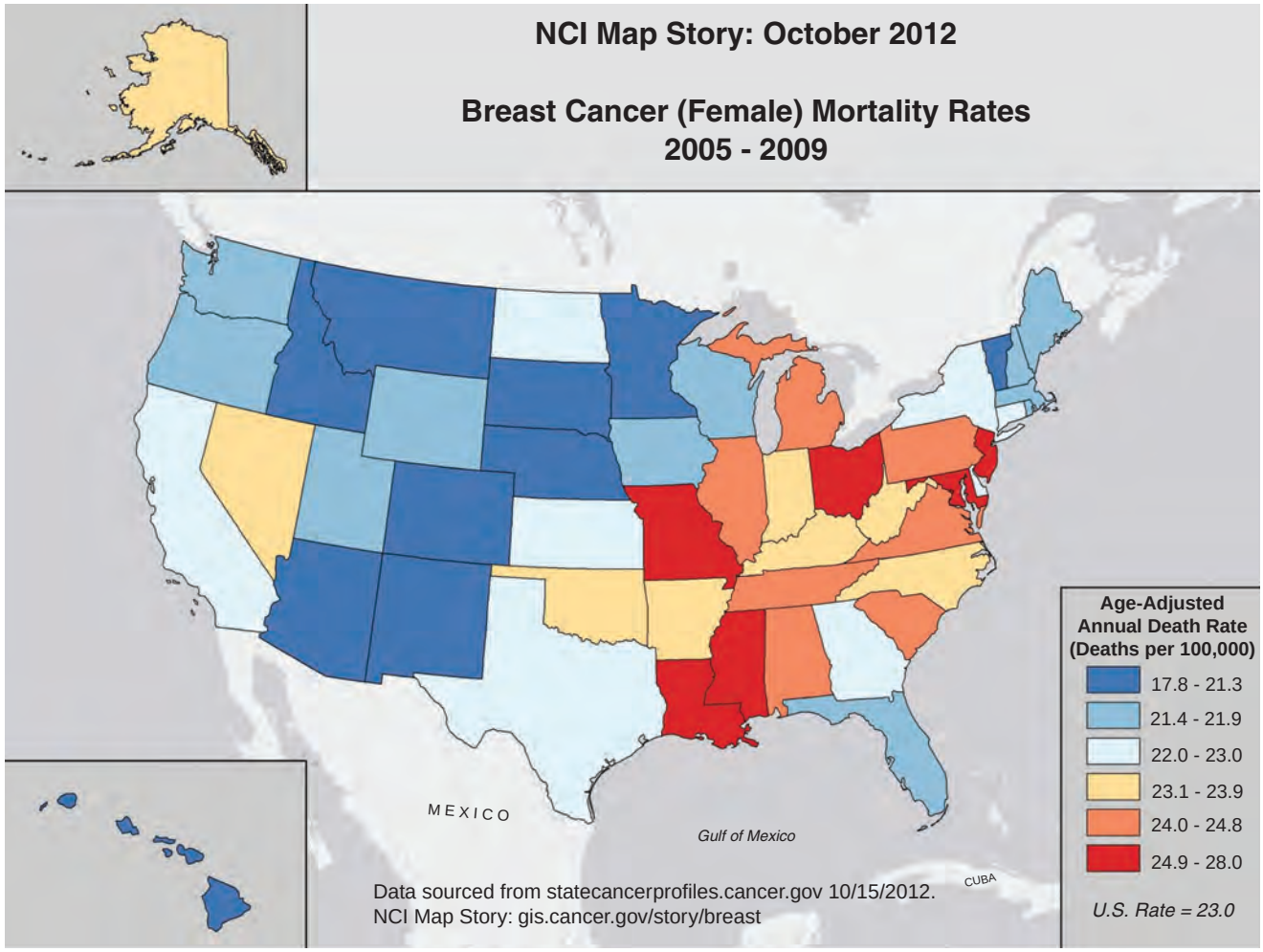
increased incidence was almost entirely due to an increase in localized disease and in tumors measuring less than 2 cm in diameter; the incidence of tumors 2 cm or larger remained stable. These findings suggest that the increase in use of screening mammography accounts for part of the recent increase in breast cancer incidence (34,37). A recent analysis of SEER data suggests that 31% of breast cancers diagnosed in 2008 are due to overdiagnosis and in the absence of mammographic screening would have never been clinically detected (38). Although this study was limited by making a number of assumptions, including that the underlying incidence was constant over this time and was unable to distinguish between DCIS and regional disease, the results are in line with other studies suggesting that a substantial amount of breast cancers are overdiagnosed with mammographic screening (39). The continued increase in breast cancer rates during the 1990s may be due in part to increased use of hormone replacement therapy, obesity, and mammography screening. The decline in rates observed between 2001 and 2004 likely reflect decreases in both mammographic screening and postmenopausal hormone use after publication of results from the Women's Health Initiative (WHI) randomized trial in 2002 (30,40). Since 2005, breast cancer rates have plateaued in the United States, Canada, Australia, and parts of Europe (3).

Trends in breast cancer mortality are of major public health interest, but their interpretation is complex because they reflect the combined effects of trends in underlying risk of breast cancer, changes in screening practices, and effectiveness of treatment. Also, the divergence between breast cancer incidence and mortality rates began in the United States even before the use of mammography or chemotherapy (Fig. 18-5), suggesting that awareness of breast cancer and earlier use of simple surgical treatment have also influenced mortality rates (41). Further, mortality rates lag behind changes in breast cancer incidence, screening, and treatment by at least 5 to 10 years (42). Age-adjusted mortality rates in the United States were relatively stable between the 1950s and the mid-1980s, when an overall decline was first noted (37). Mortality rates in the late 1980s began to decline slightly (about 1% per year). Rates through the 1990s declined somewhat more (3% decline per year) (8,43), perhaps because of enhanced treatment and screening. These overall trends obscure important variation by age and race, however. Since the 1970s, mortality rates have fallen for younger white women, and this decline has accelerated since



A

FIGURE 18-3 Age-adjusted breast cancer **(A)** incidence and **(B)** mortality rates for women by state from 2005 to 2009. (Data sourced from http://statecancerprofiles.cancer.gov 10/15/012. NCI Map Story:gis.cancer.gov/story/breast.)



B

FIGURE 18-3 *(Continued)*

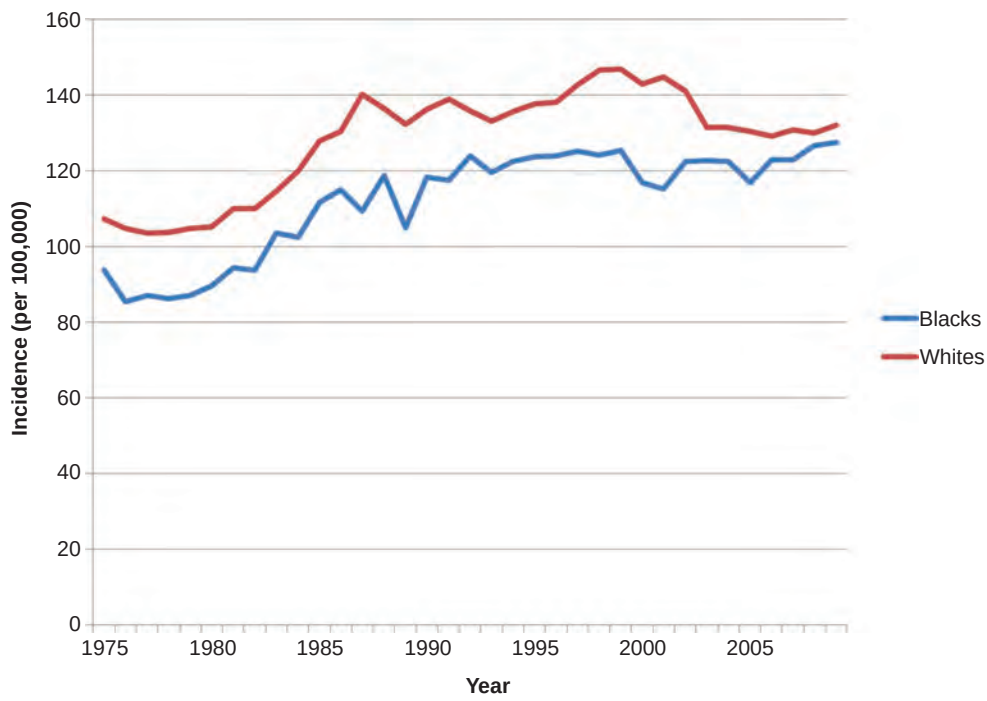


FIGURE 18-4 Age-standardized incidence of breast cancer in the United States. (Data from Surveillance Epidemiology, and End Results Program, Cancer Incidence, and Mortality Rates.)

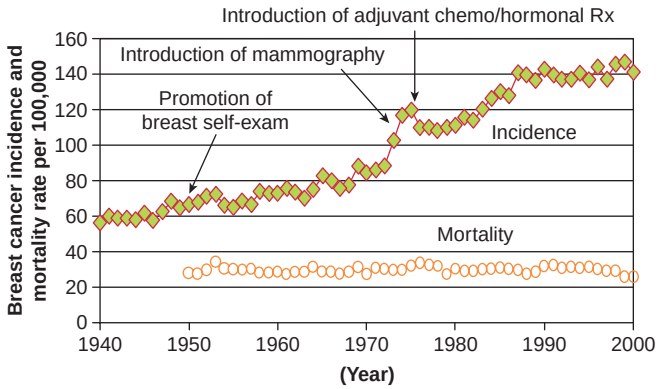


FIGURE 18-5 Breast cancer incidence and mortality in the United States, based on the Connecticut SEER database, 1940-2000. (From Shulman LN, Willett W, Sievers A, Knaul FM. Breast cancer in developing countries: Opportunities for improved survival. *J Oncol* 2010; 2010:595167, with permission.)

the late 1980s. From 1973 to 1995, the cumulative decline in mortality rates for white women younger than 60 years has been more than 20%, with much of this decline occurring since 1988. In contrast to these trends among younger white women, mortality rates for white women 60 years and older increased slowly during the 1970s and 1980s, although since the late 1980s, mortality has also begun to decline in this group (37,42). The trends in breast cancer mortality among black women have been unfavorable; between the 1970s and 1990, mortality rates increased for black women in all age groups (42), and only recently is there evidence of a decline, but to a lesser extent than what is observed in white women (Fig. 18-6). From 1992 to 2009, breast cancer death rates have declined by 1.8% per year in whites compared with 1.0% in black women (1).

Trends in Incidence and Mortality around the World

Since the 1950s, breast cancer incidence has been increasing in many of the lower risk countries and in high-risk Western countries. Some of the recent increases in incidence in high-risk populations may be due to greater use of mammography, as in the United States. This appears to be the case in Sweden (44) and in England and Wales (45). Breast cancer incidence rates have nearly doubled in recent decades in traditionally low-risk countries such as Japan (4,9) and Singapore (5) and in the urban areas of China (46). Dramatic changes in lifestyle in such regions brought about by growing economies, increasing affluence, and increases in the proportion of women in the industrial workforce have had an impact on the population distribution of established breast cancer risk factors, including age at menarche and fertility, as well as nutritional status (47). These changes have resulted in a convergence toward the risk factor profile of Western countries (47).

Trends in breast cancer mortality around the world have largely paralleled the trends in incidence. Between the 1970s and 1990s mortality increased in both high-risk and lower risk populations, although since the 1990s mortality has declined moderately in the United Kingdom, the Netherlands, and Sweden, similar to the decline observed in the United States (3,48,49). As in the United States, some of the downturn in mortality in these countries may be due to more widespread use of screening mammography, adjuvant chemotherapy during the 1980s (48,50), and more recently targeted therapies (51). Countries with mortality rates that are still increasing tend to be those with the lowest mortality (48). For instance, Russian Federation, Republic of Korea, and Japan all have breast cancer mortality rates that are continuing to increase (3). Thus, a convergence of breast cancer mortality rates may be occurring internationally, in part reflecting an international convergence of reproductive and behavioral risk factors (48).

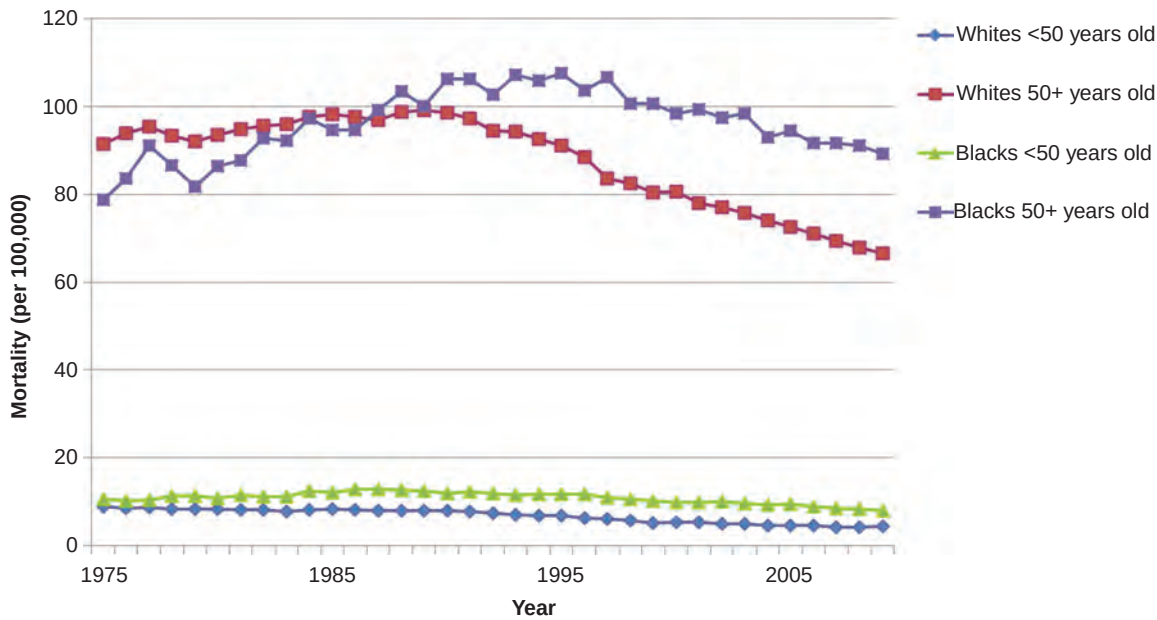


FIGURE 18-6 Trends in breast cancer mortality for white and African American women in the United States by age-group. (Data from National Cancer Institute. Surveillance Epidemiology, and End Results Program, Cancer Incidence and Mortality Statistics. National Cancer Institute, DCCPS, Surveillance Research Program, Cancer Statistics Branch, Accessed December 2012.)

REPRODUCTIVE FACTORS

This section addresses reproductive factors during the course of a woman's life in relation to the risk of breast cancer. An underlying concept is that ovarian hormones initiate breast development and that subsequent monthly menstrual cycles induce regular breast cell proliferation. Puberty is a critical period during breast development. The onset of puberty is marked by a surge of hormones that induce regular breast cell proliferation. This pattern of cell division terminates with menopause, as indicated by cessation of ovulation and menstrual periods.

Menarche

Menarche represents the development of the mature hormonal environment for a young woman and the onset of monthly cycling of hormones that induce ovulation, menstruation, and cell proliferation within the breast and endometrium. Earlier age at menarche has been consistently associated with increased risk of breast cancer (52). Most studies suggest that age at menarche is related to both premenopausal and postmenopausal breast cancer, although the magnitude of effect appears to be greater for premenopausal than postmenopausal women (53). In a pooled analysis of 7,764 premenopausal women and 16,467 postmenopausal women, each additional year in delay of menarche was associated with a 9% decrease in premenopausal breast cancer and a 4% decrease in postmenopausal breast cancer (54). In addition, age at menarche is inversely associated with both estrogen receptor positive (ER+)/progesterone receptor positive (PR+) and estrogen receptor negative (ER-)/progesterone receptor negative (PR-) breast tumors, although the protective effect of late age at menarche is greater for hormone receptor positive tumors (55). More recently, studies have evaluated the association between reproductive factors and molecular subtypes of breast cancer. At least four major categories of invasive breast cancer have been reproducibly identified by gene expression profiling: luminal A, luminal B, HER2-type, and basal-like (56). Large-scale epidemiologic studies have used immunohistochemical markers as proxies to characterize tumors into these subtypes. These studies have tended to show an association with increasing age at menarche and reduced risk of luminal A tumors (57,58).

Although menarche is most clearly related to the onset of ovulation, some studies suggest that hormone levels may be higher through the reproductive years among women who have early menarche (59). In addition, early menarche may be associated with earlier onset of regular ovulatory menstrual cycles and hence greater lifetime exposure to endogenous hormones (60). Whether the levels of ovarian hormones or their cyclic characteristics are the underlying influence on breast cancer risk is unsettled (7); both likely play a role.

Menstrual Cycle Characteristics

Shorter cycle length has been quite consistently related to greater risk of breast cancer (52), although not all studies support this relation (61). Shorter cycle length during ages 20 to 39 years may be associated with higher risk of breast cancer, perhaps because the shorter cycle length is associated with a greater number of cycles and more time spent in the luteal phase when both estrogen and progesterone levels are high. Long and irregular cycles may also be related to reduced risk of breast cancer (61).

Ovulatory infertility, an indicator of infertility due to hormonal causes, has not been consistently related to risk of breast cancer, although one cohort study suggested a substantially lower risk among women with this condition (relative risk [RR] = 0.4 compared to women with no infertility history) (61). The significant inverse association seen in this study may be related to the young age of the cohort and thoroughness of investigation of the cause of infertility in this group of health professionals.

Pregnancy and Age at First Full-term Pregnancy

Nulliparous women are at increased risk of breast cancer compared to parous women. This risk is evident after age 40 to 45 years, but not for breast cancer diagnosed at younger ages. In the majority of epidemiologic studies, a younger age at first full-term pregnancy predicts a lower lifetime risk of breast cancer (52). The reduction in risk following pregnancy compared to nulliparous women is not immediate but takes approximately 10 to 15 years to manifest (62). In fact, risk of breast cancer is increased for the first decade following first pregnancy (12,63,64). The proliferation of breast cells during the first pregnancy results in differentiation into mature breast cells prepared for lactation; this may also lead to growth of mutated cells and excess risk over the next decade. Epidemiologic evidence for the transient excess risk after the first pregnancy is consistent. Less clear is the presence of a transient increase in risk after subsequent pregnancies; some studies suggest an adverse effect (65) but others do not (64).

The first pregnancy is associated with permanent changes in the glandular epithelium and with changes in the biologic properties of the mammary cells. After the differentiation of pregnancy, epithelial cells have a longer cell cycle and spend more time in the G_1 phase, the phase that allows for DNA repair (66). The longer the interval from menarche to first pregnancy, the greater the adverse effect of the first pregnancy (12). The later the age at first full-term pregnancy, the more likely that DNA mistakes have occurred that will be propagated with the proliferation of mammary cells during pregnancy. The susceptibility of mammary tissue to carcinogens decreases after the first pregnancy, reflecting the differentiation of the mammary gland. This is also seen in the age-dependent susceptibility of the breast to radiation, reviewed later in this chapter.

Number and Spacing of Births

A higher number of births is consistently related to lower risk of breast cancer; each additional birth beyond the first reduces long-term risk of breast cancer. Although in some analyses, this has not been independent of earlier age at first birth, the overall evidence indicates an independent effect of greater parity (67). In addition to a protective effect of higher parity, several studies now indicate that more closely spaced births are associated with lower lifetime risk of breast cancer (64,68). This may be due to the breast having less time to accumulate DNA damage before it attains maximal differentiation by repeated pregnancies.

Lactation

As early as 1926, it was proposed that a breast never used for lactation is more liable to become cancerous (69). There are two major biologic mechanisms proposed to induce the protective effect: Breast-feeding may result in further terminal differentiation of the breast epithelium, and lactation delays the resuming of ovulatory menstrual cycles after pregnancy. Ecological studies demonstrate a consistency with the patterns of international variation in breast cancer incidence: Rates are lower in populations where breast-feeding is both

common and of long duration. The overall evidence from case–control and cohort studies supports a reduction in risk with longer duration of breast-feeding, but the findings have varied substantially in the level of risk reduction. Some of the differences may relate to the pattern of breast-feeding, for example, whether feeding was exclusively from the breast or supplemented with other food; this needs to be evaluated further. A pooled analysis from almost 50 studies in 30 countries reported an overall 4% reduction in risk per 12 months of breast-feeding for all parous women (70). The authors estimate that if women in developed countries had the number of births and lifetime duration of breast-feeding of women in developing countries, cumulative incidence of breast cancer by age 70 years would be reduced by as much as 60%. About two-thirds of this reduction would be related to breast-feeding (70).

Recent studies have examined the association between lactation in relation to breast cancer subtype. In the Black Women's Health Study, ever breast-feeding was associated with a nonsignificant reduced risk of ER-/PR- breast cancer (Hazard ratio [HR]=0.78, 95% confidence Interval [CI], 0.60–1.03), but not ER+/PR+ breast cancer (HR=1.13; 95% CI, 0.91–1.42) (71). This study also found that higher parity was associated with an increased risk of ER-/PR- breast cancer and that breast-feeding appeared to ameliorate the increased risk. In addition, three recent studies have reported inverse associations between breast-feeding and reduced risk of basal-like breast cancers defined using immunohistochemical markers ranging from 20%–40% reduction comparing 4+ months of breast-feeding to never breast-feeding (57,72,73). In the Nurses' Health Study, 4+ months of breast-feeding relative to never breast-feeding was associated with a 40% reduced risk of basal-like tumors (RR = 0.6; 95% CI, 0.4–0.9) and a 20% reduced risk of luminal A tumors (RR = 0.8; 95% CI, 0.7–1.0) (57). Given that there are only a few studies that have assessed this relation and all three studies had less than 300 basal-like cases, additional studies are needed to better understand the association between lactation and tumor subtypes.

Spontaneous and Induced Abortion

Close to one-fourth of all clinically identified pregnancies in the United States end as induced abortions (74), and for women whose pregnancies continue for 8 to 28 weeks, the probability of spontaneous abortion ranges from 8% to 12% (75). It has been suggested that breast cells are the most vulnerable to mutation when breast tissue consists of rapidly growing and undifferentiated cells, such as during adolescence and pregnancy. In early pregnancy, the number of undifferentiated cells increases as rapid growth of the breast epithelium is taking place. If the pregnancy continues to term, these cells differentiate by the third trimester, thus, the number of cells susceptible to malignancy decreases. The interruption of the differentiation of breast cells that takes place as the result of spontaneous and induced abortions has been hypothesized to increase a woman's risk of developing breast cancer (76). This hypothesis appears to be supported by a meta-analysis that included data from 28 published reports on induced abortion and breast cancer incidence (77). However, this analysis, based largely on case-control studies, contains the underlying serious potential for bias in retrospective studies of the relation between abortion and breast cancer. Induced abortion can be an extremely sensitive topic, and reporting on abortion history by women with a life-threatening condition such as breast cancer may be more complete than reporting by women without breast cancer.

By far the largest study on the association between breast cancer and abortion was a population-based cohort study made up of 1.5 million Danish women born April 1, 1935, through March 31, 1978 (78). Of these women, 280,965 (18.4%) had one or more induced abortions. After adjusting for potential confounders of age, parity, age at delivery of first child, and calendar period, the risk of breast cancer for women with a history of induced abortion was not different from that of women who had not had an induced abortion (RR = 1.0; 95% CI, 0.94–1.06). In addition, there was no trend in risk with increasing number of induced abortions in a woman's history. Similarly, no association between induced abortion and breast cancer incidence was observed in four prospective cohort studies including the Iowa Women's Study (79), the Shanghai Textile Workers Study (80), the European Prospective Investigation into Cancer and Nutrition (81), and the Nurses' Health Study II (82). Taken as a whole and accounting for the limitations of the case-control study design, the available evidence does not support any important relation between induced abortion and risk of breast cancer. In 2003, the Early Reproductive Events and Breast Cancer Workshop, convened by the National Cancer Institute to assess the state of evidence between reproductive factors and breast cancer, recognized that spontaneous and induced abortions are not associated with breast cancer risk (83).

Age at Menopause

Early studies of age at menopause and risk of breast cancer focused on women who had undergone bilateral oophorectomy at a young age; these women have a greatly reduced risk of breast cancer (84,85). Women with bilateral oophorectomy before age 45 years have approximately half the risk of breast cancer compared to those with a natural menopause at 55 years or older. On average, the risk of breast cancer increases by some 3% per year of delay in age at menopause. Although some studies suggest the effect of age at menopause decreases with advancing age at breast cancer diagnosis (86), this may reflect greater error in recall of age at menopause as women are further removed from the event (87). Adjustment for error in recall removes this apparent decrease in the effect of menopause with advancing age.

The reduction in risk of breast cancer with early menopause is likely due to the reduction of breast cell division with the termination of menstrual cycles and the decline in endogenous hormone levels, which become substantially lower than during the premenopausal years.

Models of Reproductive Factors and Breast Cancer Incidence

Biomathematical models are derived by translating a series of hypotheses about the biologic process involved in carcinogenesis into mathematical terms. The classical models of carcinogenesis proposed by Armitage and Doll (88) and by Moolgavkar and Knudson (89) are the best known. Armitage and Doll noted that the gradient of 6 to 1 (i.e., 6 units increase in the logarithm of death rate per unit increase in logarithm of age) was more or less consistent across 17 cancer sites, but also noted a deficit in mortality from breast cancer among older women. They attributed this to a reduction during middle life in the rate of production of one of the later changes in the process of carcinogenesis (88). Pike et al. (63) reviewed the epidemiologic evidence in the early 1980s and proposed a model of tissue aging that accounted for the relation between reproductive risk factors and breast cancer incidence. Ultimately, models will ideally be developed that take into account all known risk factors.

The mathematical model proposed by Pike et al. (63) was based on the observed age-incidence curve and on the known relations of ages at menarche, first birth, and menopause to the risk of breast cancer. The model proposed by Pike et al. (63) is built on earlier work by Moolgavkar et al., who fitted mathematical parameters to breast cancer incidence data from several countries. The Pike et al. model related breast cancer rates to the growth of the breast. The model allowed a short-term increase in risk with first pregnancy followed by a subsequent decrease in risk accumulation. Finally, at menopause the breast begins an involutional process that is thought to reflect a decrease in cell turnover and eventual disappearance of epithelium. The original Pike et al. model, however, did not include terms for the second or subsequent births or for the spacing of pregnancies, nor did it easily accommodate pregnancies after age 40 years. Type of menopause was not considered either (bilateral oophorectomy vs. natural menopause). Although there has been controversy about whether the bearing of additional children beyond the first reduces the risk of breast cancer, substantial evidence reviewed earlier indicates that both the number of births and their spacing are associated with risk: The greater the number of births and the closer they are spaced, the lower a woman's risk of breast cancer.

An extension of the Pike et al. model of breast cancer incidence utilized prospective data from the Nurses' Health Study (12,64,90) and added a term to summarize the spacing of births. Nonlinear models produced parameters that were difficult to interpret (64), but a subsequent modification allowed ready estimation of RRs (12), thus making the results more accessible to epidemiologists and clinicians familiar with the RR as measure of the relation between an exposure and disease. Prior to menopause, the incidence of breast cancer increased 1.7% for a 1-year increase in age at first birth. Closer spacing of births was related to significantly reduced risk of breast cancer. For each additional year of delay between the first and second births, for example, the risk of breast cancer increased by 0.4%. The increase in risk with first pregnancy originally observed with this modified Pike model has since been documented in a prospective study from Sweden (65) and in an analysis from an international case-control study (91). The effect of age at first and subsequent births on breast cancer incidence was still greater after menopause (Fig. 18-7).

According to the extended Pike et al. model, a parous woman with a single birth at age 35 years has a 34% increase in breast cancer incidence at the time of the birth relative to a nulliparous woman. The excess risk goes down very slowly over time. Even at age 70 years such a woman has excess risk versus a nulliparous woman. In sum, the cumulative risk to age 70 is 16% greater than that of a nulliparous woman. Conversely, a parous woman with an early age at first birth (20 years of age) and multiple births conceived at a young age has a slight excess risk immediately after the first birth relative to the nulliparous woman (RR = 1.10), which slowly diminishes over time, reaching equality at age 32 years and continuing to decline until menopause (age 50 years), at which time the RR is 0.82. Since the relationship between breast cancer incidence and reproductive history changes with age, cumulative incidence, rather than age-specific incidence, is a useful summary (see Fig. 18-7). Compared to a nulliparous woman, a woman with one birth at age 35 years has a 16% excess risk over the age period 30–70 years, while the woman with births at ages 20, 23, and 26 years has a 27% decrease in risk over the similar age period (90).

In the original Pike et al. model (63), factors associated with reduced risk of breast cancer were each considered to slow the rate of breast tissue aging, which correlates with the accumulation of molecular damage in the pathway to breast cancer. In the Rosner and Colditz (12,90) extension of the Pike et al. model, the rate of tissue aging was highest between menarche and first birth, consistent with the hypothesis that this is the period when the breast is most vulnerable to mutagenesis. The transient increase in the risk of breast cancer associated with the first pregnancy is followed by a 20% decrease in the rate of breast tissue aging (12). This observation helps explain the cross-over effect in certain subgroups of women: Around menopause, rates of one subgroup that were initially higher drop below rates of a second subgroup. For instance, using data from New York State, Janerich and Hoff showed a cross-over in breast cancer incidence between single and married women at age 42, such that married women had a higher incidence before this age and lower mortality thereafter (92). A similar cross-over of incidence has been reported for black and white women in the United States (11,93), consistent with the distribution of age at first birth by race. Over many decades, pregnancy rates have been higher and age at first birth has been younger for black women than for white women (94).

The age-incidence curve from biomathematical models of reproductive events and breast cancer incidence also mirrors the observed patterns of breast cancer incidence across many countries. In China and many developing countries, the estimated number of births in the early 1960s was 6.5 births per woman (95), which is not associated with a late age at first birth. Also, the average age at menarche in China was about 17 years, even through the 1960s (96). Fitting the Rosner and Colditz model with menarche at age 16 years, first birth at age 19 years, six births spaced a year apart, and age at menopause 50 years, we estimate an annual rate of breast cancer incidence for 65-year-old Chinese women is 93.6 per 100,000. For the cohort of U.S. women born between 1921 and 1925, the average age at menarche was approximately 13.5 years, the median age at first birth was 23 years, the mean number of children was three, and the mean interval between births was 3 years (97). Considering these characteristics, and holding age at menopause constant at 50 years, the annual rate of breast cancer incidence predicted for 65-year-old U.S. women is 279 per 100,000—close to the observed SEER rate of 300 per 100,000 for women of

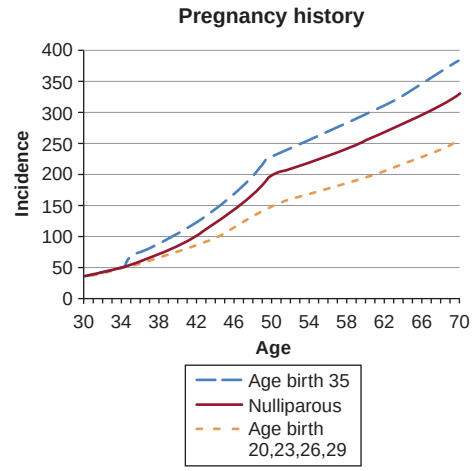


FIGURE 18-7 Age-specific incidence of breast cancer for three hypothetical women. (Data from Colditz G, Rosner B. Cumulative risk of breast cancer to age 70 years according to risk factor status: data from the Nurses' Health Study. *Am J Epidemiol* 2000;152:950–964.)

this age, and approximately three times the rate for Chinese women. Applying this model to typical reproductive patterns for women from low-incidence countries suggests that reproductive factors alone account for more than half of the international variation in the risk of breast cancer (98). These results were confirmed when the model was applied to data from a Chinese cohort (99).

The extension of the Rosner and Colditz model to include history of benign breast disease, height, weight, alcohol intake, and type of postmenopausal hormone used, in addition to reproductive factors and family history, gives a model that compares favorably to the Gail model for risk prediction (100). In a meta-analysis of breast risk prediction models that have been validated, the Gail model and the Rosner model have equivalent performance with area under the curve or c-statistic values of 0.63 (101). Furthermore, this extended Rosner model has been applied to the evaluation of risk factors for ER+ and ER- breast cancer. Incidence of ER+/PR+ tumors increases at 11.0% per year during premenopausal years and at 4.6% per year after natural menopause. In contrast, the incidence of ER-/PR- tumors increases at 5.0% per year during premenopausal years and 1.3% after natural menopause. The one-time adverse effect of first pregnancy is present for ER-/PR- breast cancer but not ER+/PR+ tumors. Parity shows a strong inverse association with ER+/PR+ tumors (RR = 0.6 for four births at 20, 23, 26, and 29 versus nulliparous), but not ER-/PR- tumors (RR = 1.1 for four births vs. nulliparous). Other risk factors, including benign breast disease, family history of breast cancer, alcohol use, and height, show consistent relations with both ER+/PR+ and ER-/PR- breast cancer, while body mass index after menopause is related to incidence of PR+ but not PR- tumors. The concordance statistic (indicating predictive ability of the model) adjusted for age was 0.64 (95% CI, 0.63–0.66) for ER+/PR+ tumors, and for ER-/PR- the concordance statistic was 0.61 (95% CI, 0.58–0.64) (102). Addition of circulating estrogen levels to the model adds further to the performance (103) as does refining benign breast disease (BBD) to consider atypical hyperplasia and proliferative disease without atypia (104).

Risk Prediction

Breast cancer incidence models have been applied to predict the risk of breast cancer over a defined time period, say 5 or 10 years. The larger the number of risk factors considered, the higher the likelihood the prediction model will separate those at risk of disease from those who are not as likely to develop disease. However, as Wald notes (105), to be useful as a screening test or an individual marker of risk or to identify those who will develop disease and those who will not, the magnitude of association for a predictor must be on the order of 10 or higher comparing extreme quintiles for a detection rate of 20%. No prediction models for breast cancer have achieved this level of discrimination to date. The Rosner model generates a relative risk of 6 or more comparing top versus bottom decile of risk among women in each 5-year age group.

Ottman et al. published a simple model in 1983 that calculates a probability of breast cancer diagnosis for mothers and sisters of breast cancer patients (106). They used life-table analysis to estimate the cumulative risks to various ages based upon two groups of patients from the Los Angeles County Cancer Surveillance Program, then derived a probability within each decade between ages 20 and 70 for mothers and sisters of the patients, according to the age of diagnosis of the patient and whether the disease was bilateral or unilateral.

Because risk factors may change over the life course (weight gain, change in alcohol intake, menopausal status, use of postmenopausal hormones for some years, etc.), it becomes more helpful to consider the impact of all these risk factors on breast cancer cumulative risk up to a given age, say 70 or 75. This approach has been developed for breast cancer risk according to family history (107), and the prediction of BRCA1 carrier status (108,109), but more general applications joining carrier status and lifestyle factors remain limited (110).

The complex nature of breast cancer incidence, with many possible time-dependent risk factors, requires prediction models that account for this variation over time. These are now shown to outperform traditional approaches that fit indicator variables with fixed effects across time (100). In addition, the log-incidence model of Rosner and Colditz performs significantly better than the commonly used Gail model for total breast cancer incidence that includes only five variables (age, age at menarche, age at first birth, number of benign breast biopsies, and family history). Growing emphasis is placed on mammographic breast density as a contributor to risk prediction (111,112), and while some models have incorporated this measure, none yet also include the details of reproductive risk factors, specific type of postmenopausal hormone therapy used, and breast cancer incidence.

The efficacy of chemoprevention for breast cancer is clearly shown for ER+ disease reducing risk by 50% (113). Given the need to balance risks and benefits when implementing a tamoxifen-based chemoprevention strategy (114), a model that successfully identifies women at increased risk of ER+ breast cancer will, therefore, improve the risk benefit ratio. Rosner and Colditz have applied their log-incidence model to breast cancers classified according to receptor status and reported that the area under the ROC curve adjusted for age was 0.630 (95% CI, 0.616–0.644) for ER+/PR+ tumors and was 0.601 (95% CI, 0.575–0.626) for ER-/PR- tumors, indicating adequate discriminatory accuracy. On the other hand, when we fit the Gail model to the same data set, it had performance characteristics that were somewhat lower than the Rosner and Colditz model with values of 0.578 for total cancer and 0.57 for ER+/PR+ tumors. The difference between the area under the ROC for the Rosner and Colditz model versus the Gail model for total breast cancer was statistically significant ($p < .0001$), indicating that the more complete modeling of risk factors across the life course could be more useful for discriminating among those women at high and low risk for breast cancer.

The clinical application of risk prediction models with performance evaluation showing improved patient satisfaction with decision-making, improved health outcomes, or cost-effectiveness of care remains the gold standard for evidence of clinical utility (115). To date, none of the breast risk prediction models have been evaluated in this routine use setting to show such benefits for women.

ENDOGENOUS SEX HORMONES AND RISK OF BREAST CANCER

Several lines of evidence have long suggested that sex hormones play a central role in the etiology of breast cancer. As noted earlier, rates of breast cancer increase rapidly in the premenopausal years, but the rate of increase slows sharply at the time of menopause, when estrogen levels decline rapidly. In addition, several reproductive variables that alter hormone status affect risk of breast cancer; for example, early age at menarche and late age at menopause

are associated with increased risk of breast cancer while parity is inversely associated with risk. After menopause, adipose tissue is the major source of estrogen, and obese postmenopausal women have both higher levels of endogenous estrogen and a higher risk of breast cancer (116). In animals, estrogens, progesterone, and prolactin all promote mammary tumors. Also, hormonal manipulations such as anti-estrogens (e.g., tamoxifen) are useful in the treatment of breast cancer and reduce breast cancer incidence in high-risk women (117–119).

Methodologic Issues in Studies of Endogenous Hormones and Breast Cancer Risk

In contrast to clinical needs where discerning grossly abnormal from normal hormone levels is the focus, epidemiologic studies are usually aimed at detecting modest differences within the normal range of levels. Considerable laboratory error has been reported in studies of assay reproducibility, with several hormones being measured quite poorly by some laboratories (120,121). Low reproducibility could result in true (and important) exposure/disease associations being missed. Varying sensitivities and specificities of different laboratory assays also have made comparison of results between studies difficult (122,123). For example, in studies of postmenopausal plasma estradiol, mean levels in control subjects have ranged from 9 (124) to 28 (125) pg/ml. Although these differences may result in part from differences in characteristics of study subjects (i.e., differences in adiposity), a substantial component is likely due to the use of varying laboratory methods. Increasing efforts by the CDC and several professional organizations are addressing these measurement issues (e.g., testosterone) (126).

Several hormones, particularly estrogens, fluctuate markedly over the menstrual cycle. In some early studies, hormone levels were measured in samples collected without regard to the menstrual cycle phase, thus adding considerable "noise" to the comparison of hormone levels between breast cancer cases and controls. This noise could mask true associations or, because of chance differences in the distribution of cycle phase between cases and controls, could result in associations that do not truly exist. More recent studies have tended to collect all samples at approximately the same time in the cycle, have matched on cycle day, or have carefully controlled for cycle day in the analysis—all appropriate strategies.

For both logistic and financial reasons, in most epidemiologic studies only a single blood sample can be collected per study subject. Whether a single sample can reflect long-term hormone levels (generally the exposure of greatest etiologic interest) is therefore an important issue. In several studies, repeated blood samples were collected over a 1- to 3-year period in postmenopausal women and the correlation between the samples calculated. Overall, steroid hormones were reasonably stable, with intra-class correlations ranging from 0.5 to 0.9 (127–130). This level of reproducibility is similar to that found for other biologic variables such as blood pressure and serum cholesterol measurements, all parameters that are considered reasonably measured and that are consistent predictors of disease in epidemiologic studies. Data on premenopausal women are more limited, although follicular or luteal estrogens were reasonably reproducible over a 3-year period (131), and androgens have been reasonably correlated over a several-year period (128,129,131). Data on circulating levels of insulin-like growth factors also indicates substantial stability over a several-year period (131,132).

Over the last decade a number of well-conducted prospective studies have assessed the role of circulating hormone levels and breast cancer risk; their findings are summarized below.

Estrogens

Estradiol, considered the most biologically active endogenous estrogen, circulates in blood either unbound ("free") or bound to sex hormone–binding globulin or albumin. Free or bioavailable (free plus albumin-bound) estradiol is thought to be readily available to breast tissue and thus may be more strongly related to risk than total estradiol. Postmenopausally, estrone is the source of most circulating estradiol, and estrone sulfate is the most abundant circulating estrogen (133). Both normal and malignant breast cells have sulfatase and 17-beta-dehydrogenase activity (134). Thus, estrone and estrone sulfate could serve as ready sources of intracellular estradiol.

In 2002, a pooled analysis was published consisting of all prospective studies of endogenous estrogens and androgens in postmenopausal women that had been available at that time (135). Data were from nine prospective studies with a total of 663 breast cancer cases and 1,765 healthy controls; none of the women were using exogenous hormones at blood collection. The risk of breast cancer increased with increasing estrogen levels. For example, the relative risks (95% CI) for increasing quintiles of estradiol level, all relative to the lowest quintile, were 1.4 (1.0–2.0), 1.2 (0.9–1.7), 1.8 (1.3–2.4), and 2.0 (1.5–2.7). Estrone, estrone sulfate, and free estradiol were similarly related to risk. No significant heterogeneity in results was noted between the studies. Subsequent to the pooled analysis, several additional prospective studies have been published and all have supported these findings (136–138). Further, urinary hormone levels have been assessed in relation to breast cancer in two prospective studies (139,140) and in each, positive associations were observed.

The association between circulating estrogens and breast cancer risk appears stronger for ER+ and PR+ tumors, with relative risks ranging from 2.0–2.6 comparing the extreme 20–25% of levels (141–143). Data are sparse and less consistent for ER- tumors. In the only two studies with more than 100 ER- cases, the association of estradiol with ER-/PR- tumors was similar to that observed for ER+/PR+ tumors in one (143) and considerably weaker than that observed in ER+ tumors in the second (142). The association with ER+ tumors is in line with findings from the tamoxifen and raloxifene trials, where risk of only ER+ tumors was reduced (118,144) and also from epidemiologic studies of obesity and breast cancer where stronger associations have been noted for ER+ tumors.

Whether the association between plasma estrogens and postmenopausal breast cancer is similar in women at varying levels of breast cancer risk has been addressed in two studies. The first was conducted in the high-risk population of the National Surgical Adjuvant Breast and Bowel Project Cancer Prevention Trial (P-1) with 89 cases and 141 non-cases enrolled in the placebo arm of the trial (145). In P-1, high risk was defined as having at least a 1.66% 5-year risk of breast cancer as estimated from the Gail model (146). No association was observed between estradiol levels and breast cancer risk: The relative risk for the top (vs. bottom) quartile of levels was 0.96 (95% CI, 0.47–1.95). In contrast, in the Nurses' Health Study cohort (with over 400 cases and 800 controls) (147), women were classified as high or low risk in several ways: according to family history of breast cancer, by their 5-year modified Gail risk score, and by their 5-year Rosner and Colditz risk score (90). Overall, the associations of plasma estrogens with breast cancer were robust across risk

categories regardless of which metric was used to define risk. Thus, the data from this larger cohort suggest that circulating estrogens are predictive of risk in women at low and at high risk of breast cancer; however, confirmation in other studies is needed.

Two prospective studies have addressed whether circulating estradiol levels are associated with breast cancer risk even in women using postmenopausal hormones (estrogen only or estrogen plus a progestin) (148,149). In the first and largest study, modest positive associations with estradiol and free estradiol were observed (top versus bottom quartile RR for estradiol = 1.3; 95% CI, 0.9–2.0, p-trend = 0.20 and RR for free estradiol = 1.7; 95% CI, 1.1–2.7, *p*-trend = 0.06) (148). In the second study, similar associations were observed between circulating estrogens and breast cancer, regardless of postmenopausal hormone use (149). Thus, although women using postmenopausal hormones have a different hormonal profile than non-users, plasma estradiol concentrations appear to be associated, albeit possibly more modestly, with breast cancer in this group of women.

Data on premenopausal estrogen levels and breast cancer risk are more limited, in large part because of the complexities related to sampling during the menstrual cycle. Eight prospective studies have been published to date, although 6 of the 8 had fewer than 100 cases (range 14–98 cases) and, not surprisingly, no significant associations with plasma estrogens were observed in the 6 small studies (150–155). Two much larger studies have recently been published. In the first, conducted in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort, with 285 breast cancer cases and 555 controls, one blood sample was collected per woman, and the day in the menstrual cycle was recorded (156). Controls were matched to cases on age and phase of the menstrual cycle at blood collection (defined in 5 categories). Comparisons between case and control hormone levels were based on residuals from spline regression models; the residuals indicated how much an individual's hormone level deviated from the predicted hormone levels on that day. Overall, no association was observed for either estradiol or estrone (e.g., top to bottom quartile comparison [RR = 1.0; 95% CI, 0.7–1.5] for estradiol). In the second large prospective study, conducted within the NHSII, both early follicular and mid-luteal samples were collected from each woman (157). The analysis included 197 cases with 394 controls also matched on age and luteal day. Follicular, but not luteal, total and free estradiol were significantly associated with breast cancer risk (top to bottom quartile comparison [RR = 2.1; 95% CI, 1.1–4.1] for follicular total estradiol). No association was observed with either estrone or estrone sulfate (in either phase of the cycle). Clearly, additional data, with careful matching of cases and controls and detailed evaluation by timing in the menstrual cycle, are needed.

To date, only one study has examined the role of circulating estrogen levels during pregnancy and subsequent breast cancer risk (158). Among 536 cases and 1,049 controls, higher levels of serum estradiol and estrone in the first trimester of first pregnancies were not associated with higher breast cancer risks overall, but were associated with higher risk of breast cancers diagnosed before age 40 (top vs. bottom quartile RR (95% CI) estradiol = 1.81) (1.08–3.06), *p*-trend = 0.03; estrone = 1.63 (1.01–2.60), *p*-trend = 0.04).

Estrogen Metabolites

A woman's pattern of estrogen metabolism also has been hypothesized to influence her breast cancer risk. Estradiol and estrone can be metabolized through several pathways, including the 2-, 4-, and 16-hydroxylation pathways (159). Products of these pathways have markedly different biologic properties, and opposing hypotheses have been proposed concerning their influence on risk (159). Several epidemiologic studies have examined estrogen metabolites and breast cancer risk, but many have assessed only 2-hydroxyestrone, 16α-hydroxyestrone, and the 2:16α-hydroxyestrone ratio. In three prospective assessments among premenopausal women, nonsignificant inverse associations with the 2-:16α-hydroxyestrone ratio were observed in each (160–162). Six prospective studies of either urinary (161–163) or circulating (164,165) metabolite levels among postmenopausal women who were not using postmenopausal hormones also observed no significant associations for 2-hydroxyestrone, 16α-hydroxyestrone or their ratio and breast cancer risk. While these data do not support an important relationship with these metabolites and risk, these studies do not include other biologically active metabolites.

Two recent studies have measured estrogen metabolites in urine (166) or serum (167), using a high performance liquid chromatography/tandem mass spectrometry (LC/MS-MS) assay that measures 15 estrogens and metabolites simultaneously, including parent estrogens and metabolites in the 2-, 4-, and 16-hydroxylation pathways (168). In premenopausal women, urinary levels of estrogen metabolites, measured in the mid-luteal phase of the menstrual cycle, were assessed among 247 cases and 485 controls (166). Higher levels of one metabolite in the 16-hydroxylation pathway, 17-epiestriol, were associated with higher breast cancer risk (top vs. bottom quartile RR = 1.74; 95% CI, 1.08–2.81, *p*-trend = 0.01). However, higher levels of the parent estrogens, estradiol and estrone, were associated with lower risks of breast cancer (top vs. bottom quartile RR for estradiol=0.51; 95% CI, 0.30–0.86); RR for estrone 0.52; 95% CI, 0.30–0.88). Generally, although not significantly, inverse associations were observed with metabolites in the 2- and 4-hydroxylation pathways. Associations were unchanged with adjustment for plasma estrogens, suggesting women with increased urinary excretion of estrogens are at reduced risk. In postmenopausal women, serum levels of 15 estrogen metabolites were investigated in 277 cases and 423 controls (167). Although several metabolites were individually positively associated with breast cancer risk, none of the associations remained after adjustment for unconjugated estradiol, which was associated with a two-fold increased risk, consistent with other studies. The ratios of 2-hydroxylation pathway:parent estrogens and 4-hydroxy catechols:methylated catechols remained significantly associated with risk after adjustment for unconjugated estradiol: interdecile comparison RR (95% CI) 0.72 (0.52–1.00) and 1.31 (1.03–1.61), respectively.

Androgens and Breast Cancer Risk

Androgens have been hypothesized to increase breast cancer risk either directly, by increasing the growth and proliferation of breast cancer cells, or indirectly, by their conversion to estrogen (60). In animal and *in vitro* experiments, androgens either increase or decrease cell proliferation, depending upon the model system (169). Dehydroepiandrosterone (DHEA) administered to rodents can decrease tumor formation. In humans, DHEA may act like an antiestrogen premenopausally but an estrogen postmenopausally in stimulating cell growth (170); in part because of the estrogenic effect of its metabolite, 5-androstene-3b,17b-diol also can bind to the estrogen receptor (171).

In postmenopausal women, the best summary of evidence on circulating androgens and breast cancer risk is from the pooled analysis of nine prospective studies described

above (135) along with the recently published report from the EPIC study (136). In the pooled analysis, testosterone was positively associated with breast cancer risk: The relative risks (95% CI) for increasing quintile category (all relative to the lowest quintile of levels) were 1.3 (1.0–1.9), 1.6 (1.2–2.2), 1.6 (1.1–2.2) and 2.2 (1.6–3.1). Findings were generally similar for several other androgens measured. In EPIC, similar positive associations were observed for each of the androgens assessed. In each of these analyses, when estradiol was added to the statistical models, relative risks for the androgens were only modestly attenuated, suggesting some independent effect of circulating androgens on breast cancer risk. As with estradiol, associations with androgens and breast cancer have tended to be stronger for ER+ tumors than for ER- tumors (141–143). Whether this differential is because androgens are serving as a source of estrogens at the breast, or because ER+ tumors are more likely to also be AR+ is unclear. Interpretation of these data is complicated because of possible differences between estradiol and the androgens in terms of assay precision, hormone stability within woman over time, and intracellular conversion of androgens to estrogens that cannot be accounted for in epidemiologic analyses.

The association of plasma testosterone levels and subsequent breast cancer risk also was positive and of the same general magnitude in women using postmenopausal hormones (148). In the two studies previously described, the association between circulating testosterone and breast cancer across categories of predicted breast cancer risk has been addressed. No association was observed between testosterone levels and breast cancer risk in the P-1 trial with 89 cases and 141 non-cases (RR for top versus bottom quartile = 0.5; 95% CI, 0.2–1.1) (145), although the association was noted to be quite robust in the larger NHS cohort (147).

Among premenopausal women, although data are much more limited, prospective nested case-control studies are quite consistent in showing a positive association of similar magnitude to that reported among postmenopausal women between circulating androgen levels and risk of breast cancer (153,155–157,172,173).

Progesterone

Progesterone exerts powerful influences on breast physiology and can influence tumor development in rodents (174). Based largely on indirect evidence, progesterone has been hypothesized both to decrease breast cancer risk by opposing estrogenic stimulation of the breast (174) and to increase risk because breast mitotic rates are highest in the luteal (high progesterone) phase of the menstrual cycle (60). In three large prospective studies, results have not been consistent with inverse (156,172) and no association (157) reported. However, progesterone levels vary substantially throughout the menstrual cycle and are difficult to measure in the context of large epidemiologic studies, hence further assessments with better measures are warranted. In postmenopausal women, only a single prospective study has been conducted and no association found (138).

Prolactin

Prolactin receptors have been found on more than 50% of breast tumors (175), and prolactin can increase the growth of both normal and malignant breast cells in vitro (176). Cumulatively, substantial laboratory evidence suggests that prolactin could play a role in mammary carcinogenesis (177) by promoting cell proliferation and survival (178–181), increasing cell motility (182), and supporting tumor vascularization (177,183). Because prolactin is influenced by both physical and emotional stress (184,185), levels in women with breast cancer may not reflect their predisease levels. Thus, evaluation of this association in prospective studies is particularly important.

Prolactin levels and risk of breast cancer have been evaluated in several studies to date (137,150,151,186–190). Most, though not all (137), studies have observed a significant positive association, with case numbers ranging from 26 (151) to 1,539 (188). In by far the largest study to date, an updated analysis within the NHS and NHSII cohorts with 1,539 cases (premenopausal and postmenopausal women combined), a modest but significant association was observed across quartiles of prolactin level, with a top (versus bottom) quartile RR = 1.4; 95% CI, 1.0–1.9, p-trend = 0.05 (188). In this analysis, the association of prolactin with breast cancer did not differ by menopausal status (p = 0.95). The association was stronger for invasive cases (top vs. bottom quartile RR = 1.4; 95% CI, 1.1–1.7, p-trend = 0.001) than in situ cases (comparable RR = 1.2; 95% CI, 0.8–1.6, p-trend = 0.43). In addition, the association was significantly different by ER/PR status of the tumor (p-heterogeneity=0.03) with RRs for top versus bottom quartiles of 1.6; 95% CI, 1.3–2.0, p-trend <0.001 for ER+/PR+, RR = 1.7; 95% CI, 1.0–2.7, p-trend = 0.06 for ER+/PR-, and RR = 0.9; 95% CI, 0.6–1.3, p-trend = 0.70 for ER-/PR-. Cumulatively, epidemiologic data support a role for prolactin in the etiology of breast cancer.

Insulin-like Growth Factor

Insulin-like growth factor I (IGF-I) is a protein hormone with structural homology to insulin. The growth hormone–IGF-I axis can stimulate proliferation of both breast cancer and normal breast epithelial cells (191). Rhesus monkeys treated with growth hormone or IGF-I show histologic evidence of mammary gland hyperplasia. In addition, positive associations have been observed between breast cancer and birth weight as well as height, which are both positively correlated with IGF-I levels (192). These associations were carefully evaluated in a large pooled analysis, combining data from 17 prospective studies and including 4,790 cases and 9,428 controls (193). Overall, a modest but statistically significant positive association was observed (top vs. bottom 20% of IGF levels RR = 1.28; 95% CI, 1.14–1.44) that did not vary by menopausal status at blood collection. Associations were apparent among ER+ tumors (comparable RR = 1.38; 95% CI, 1.14–1.68) but not ER- tumors (comparable, RR = 0.80; 95% CI, 0.57–1.13; p for heterogeneity = 0·007). The primary IGF binding protein IGFBP-3 was not independently associated with breast cancer risk, and the IGF-I association did not vary by level of IGFBP-3. In addition, the association between IGF-I levels during pregnancy and the mother's subsequent risk of breast cancer has been assessed. Of two large prospective studies, a positive association was observed in one (194), while no association was seen in the second (195). Reasons for these differences are not clear. Cumulatively, data point to a modest positive association between circulating IGF-I levels and breast cancer risk.

Insulin

Insulin is a known mitogen and circulating levels have been evaluated in relation to subsequent breast cancer risk. Some studies evaluated insulin levels in fasting or nonfasting subjects; others assessed c-peptide levels, which is a marker of insulin secretion. Among premenopausal women, overall no consistent associations have been observed (132,196–198). Similarly, in postmenopausal women, where at least 10 studies with over 2,500 postmenopausal cases have been published, no consistent associations have been reported (132,197–205).

Melatonin

Laboratory evidence in conjunction with recent epidemiologic data suggests a possible relation between melatonin and breast cancer risk. In vitro studies, although not entirely consistent (206), find that both pharmacological and physiologic doses of melatonin reduce the growth of malignant cells of the breast (207–211). In rodent models pinealectomy boosts tumor growth (212), whereas exogenous melatonin administration exerts anti-initiating (213) and oncostatic activity (214–217) in various chemically induced cancers. The hormone could influence risk through antimitotic or antioxidant activity (218), by modulating cell-cycle length through control of the p53-p21 pathway (211) or by reducing estrogen levels (219,220).

To date, five prospective studies have assessed the association between urinary 6-sulfatoxymelatonin levels (a metabolite of melatonin) and breast cancer risk. In the first, where a 24-hour urine sample was collected, no association between levels and breast cancer were observed (221). In three subsequent analyses conducted in the Nurses' Health Studies and the ORDET cohort and utilizing either a first morning urine or a 12-hour overnight urine, consistent inverse associations were observed, with 30–40% lower breast cancer risk seen among women with the highest (versus lowest) melatonin levels (222–224). In the most recent prospective analysis (225), no significant association was observed overall. However, in this study, a significant positive association was observed in the first two years of follow-up, and a significant inverse association was seen with longer follow-up, suggesting that time from urine collection to diagnosis may be important. Additional studies are clearly needed. There is relatively consistent indirect evidence from observational studies for an association between night work and breast cancer risk (226). Night work is associated with substantially reduced melatonin levels (227,228). Two retrospective studies of flight attendants with occupational exposure to light at night linked employment time to an increased breast cancer risk (229,230). Two nationwide record linkage studies (231,232) and a retrospective case-control study (219) associated night work with an approximately 50% higher breast cancer risk. In the only two prospective studies, working 20 to 30 or more years of rotating night work as a nurse was associated with an increased risk of breast cancer (233,234).

Other Hormones and Hormone Scores

In one prospective study, the influence of multiple hormones, considered simultaneously, on postmenopausal breast cancer risk was evaluated (235). Postmenopausal levels of estrone, estradiol, estrone sulfate, testosterone, androstenedione, dehydroepiandrosterone (DHEA), DHEA sulfate, and prolactin and, secondarily, IGF-I and c-peptide, were evaluated among 265 cases and 541 controls. Several hormone scores were evaluated, including ranking women by the number of hormones above the age- and batch-adjusted geometric mean. Having seven or eight compared to zero hormones above the geometric mean level was associated with total (RR = 2.7; 95% CI, 1.3–5.7, p trend <0.001) and ER+ (RR = 3.4; 95% CI, 1.3–9.4, p trend <0.001) breast cancer risk. Overall, these results suggest that multiple hormones with high circulating levels substantially increase the risk of breast cancer, particularly ER+ disease.

Anti-Müllerian hormone (AMH; also called Müllerian inhibiting substance [MIS]) is produced in ovarian granulosa cells and plays a key role in regulating folliculogenesis (236). Circulating levels vary over a woman's life, being low or undetectable before puberty, peaking from puberty through the premenopausal years, and becoming undetectable after menopause. Although limited laboratory data suggest a protective role of AMH in breast carcinogenesis, the one prospective study to date observed a significant positive association between circulating AMH and breast cancer risk (237). With 105 cases and 204 matched controls, RR (95% CI) with increasing quartile categories were 1.0, 2.8, 5.9, 9.8 (3.3–28.9). Associations appeared somewhat stronger among women ≥55 versus <55 years of age at diagnosis (top vs. bottom quartile RR [95% CI]: <55 years = 3.9 [0.9–16.3]; ≥55 years = 9.6 [2.8–33.3]). This strong association deserves further study, because AMH has not been assessed in any other prospective studies to date.

ORAL CONTRACEPTIVES

Since oral contraceptives were first introduced in the 1960s, they have been used by millions of women (238). Most combined oral contraceptives contain ethinyl estradiol (or mestranol, which is metabolized to ethinyl estradiol) and a progestin. The estrogen dose in oral contraceptives has ranged from at least 100 mg in 1960 to 20–30 mg, the doses most commonly used today; during this same time period, at least nine different progestins have been used (239,240). Patterns of use also have changed considerably over time, with both increasing durations of use and a trend toward earlier age at first use. Over 70 epidemiologic studies have evaluated the relationship between oral contraceptive use and breast cancer risk.

Any Use and Total Duration of Use

Most studies have observed no significant increase in breast cancer risk even with long durations of use. Individual data from 54 epidemiologic studies were collected and analyzed centrally (86). In this large pooled analysis, in which data from 53,297 women with and 100,239 women without breast cancer were evaluated, no overall relationship was observed between duration of use and risk of breast cancer. Similar findings were generally observed when long-term use was evaluated among either postmenopausal women or women over the age of 45 years.

Recency of Use

In the pooled analysis (86), current and recent users of oral contraceptives had an increased risk of breast cancer (for current vs. never-users, RR = 1.24). This increased risk disappeared within 10 years of stopping oral contraceptive use (relative risk by years since stopping use vs. never use: 1–4 years, 1.16; 5–9 years, 1.07; 10–14 years, 0.98; more than 15 years, 1.03) (Fig. 18-8). When the investigators evaluated both time since last use and duration of use, they observed a modestly increased risk only among current and recent users, and no independent effect of long duration of use on the risk of breast cancer even among very young women. In more recent studies, past use of oral contraceptives (generally use in the more distant past) also has not been associated with breast cancer mortality (241–243). Thus, the increased risk of breast cancer observed among young, long-term users of oral contraceptives in past individual studies (and meta-analyses) appears due primarily to recency of use rather than to duration. These data suggest that oral contraceptives may act as late-stage promoters. Importantly, current and recent users, the women who appear to have a modest increase in risk, are generally young (under 45 years of age) and thus have a low absolute risk of breast cancer. Hence, a modest increase in their risk will result in few additional cases of breast cancer. Nevertheless, this apparently

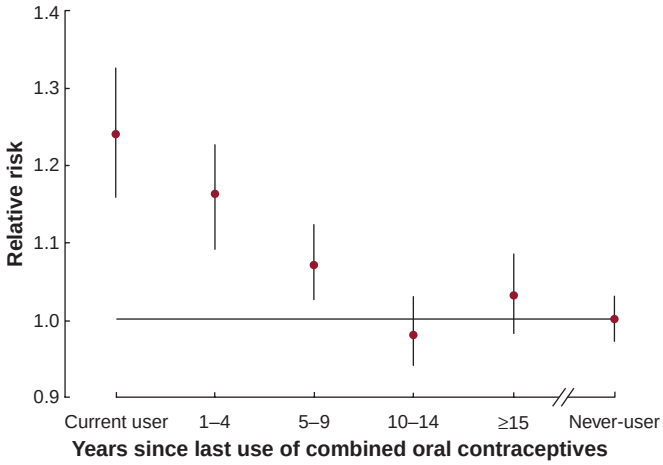


FIGURE 18-8 Relative risk of breast cancer by time since last use of combined oral contraceptives. (Reproduced from Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of individual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996;347:1713–1727, with permission.)

increased risk among current and recent users should be considered in deciding whether to use oral contraceptives. On the basis of these data in conjunction with supporting laboratory evidence, the International Agency for Research on Cancer (IARC) classified oral contraceptives as carcinogenic to humans (i.e., group 1 carcinogens) in 2005 (244).

Use before a First Pregnancy

Because any influence of oral contraceptives on the breast has been hypothesized to be greatest prior to the cellular differentiation that occurs with a full-term pregnancy (245), a number of investigators have evaluated the effect of oral contraceptive use prior to a first full-term pregnancy. In two meta-analyses, the summary relative risk indicated a modest increase in risk with long-term use (246,247). In the pooled analysis (86), a significant trend of increasing risk with first use before age 20 years was observed. Among women ages 30–34 years, the relative risk associated with recent oral contraceptive use was 1.54 if use began before age 20 years and 1.13 if use began at age 20 years or older. Overall, there was no consistent evidence of a differential effect according to type or dose of either estrogen or progestin, but few studies had examined this issue (60).

Risk according to Breast Cancer Risk Factor Profile

Possible interactions with other breast cancer risk factors were evaluated in detail for the first time in the collaborative pooling project (86). In this study, the investigators defined oral contraceptive use in terms of recency and age at first use, rather than "ever use," as done in most previous individual studies. Overall, the relationship between oral contraceptive use and breast cancer did not vary appreciably by family history of breast cancer, weight, alcohol intake, or other breast cancer risk factors. In a recent meta-analysis among women with BRCA1 and BRCA2 mutations (248), neither ever use nor duration of use was associated with breast cancer risk. However, use of oral contraceptives prior to 1975 was associated with a modest increased risk while use after 1975 was not associated with risk, suggesting possible differences by formulation.

Receptor Status and Histologic Subtypes of Breast Cancer

Few studies have addressed possible differences in these associations by estrogen receptor status or by intrinsic molecular subtype (e.g., luminal A, luminal B subtypes). Ever use of oral contraceptives was assessed by hormone receptor status in eight case-control studies (249). Results were inconsistent, and only one study reported a significantly stronger association for ER- than for ER+ breast cancer. Only three of these studies evaluated time since last use, and again results were mixed. Recently, in the Black Women's Health Study, ever use of oral contraceptives was significantly stronger for ER-/PR- breast cancers (ever versus never use RR = 1.7; 95% CI, 1.2–2.3) than for ER+/PR+ breast cancers (comparable RR = 1.1; 95% CI, 0.9–1.4) (250). In the Women's Health Initiative, no association was observed between total duration of use and triple negative breast cancer; recent or current use could not be examined in this older population. In case-case analyses, compared to luminal A breast cancers, luminal B cases were less likely to ever use oral contraceptives in one study (251) but not in a second study (252); no differences were observed with triple negative, basal-like or HER-2 breast cancers, although case numbers were small. More data are needed to determine if oral contraceptives differentially influence breast cancer subtypes.

Newer Oral Contraceptive Formulations and Specific Formulations

Until the time of the large pooled analysis published in 1996, limited data existed regarding the influence of the newer oral contraceptive formulations on breast cancer risk (86) and data on specific formulations was particularly sparse. In a study that assessed risk by hormonal dose/potency, the relative risks associated with recent use of lower dose formulations were generally lower than relative risks associated with higher dose formulations (253). Further, associations appeared to vary by type of progestin used (with borderline significant positive associations observed for levonorgestrel, ethynodiol diacetate, and norethindrone acetate) although these differences were based on small numbers. In the population based Women's CARE case-control study (254), overall no increased risk of breast cancer among current users or former users was observed regardless of estrogen or progestin dose. Among specific formulations, an increased risk was observed for current use of ethynodiol diacetate, and no association was seen with levonorgestrel formulations. In the Nurses' Health Study II, the only prospective cohort to examine newer generation oral contraceptives as well as specific formulations, current use of any oral contraceptives was associated with a modest increase in risk (RR = 1.33; 95% CI, 1.03–1.73) (255). However, this association was largely accounted for by use of a single type of preparation, triphasic contraceptives with levonorgestrel (comparable RR = 3.05; 95% CI, 2.00–4.66). Although no firm conclusions can yet be drawn, accruing data suggest that specific oral contraceptive formulations indeed may have a differential impact on breast cancer risk.

Progestin-only Contraceptives

Progestin-only contraceptives include progestin-only pills ("mini-pill"), depot-medroxyprogesterone (DMPA, an injectable contraceptive), and implantable levonorgestrel

(Norplant); very few epidemiologic studies have evaluated their association with breast cancer risk. Longer-term users of the progestin-only pill have been observed to have either a similar or lower risk of breast cancer than never-users (256). Four of five case-control studies reported relative risks of 1.5–2.2 associated with recent use of DMPA versus non-use (257–259), while a fifth study found no association regardless of recency or duration (260). As with other contraceptives, the risk appears to subside several years after stopping use. In the only study to have assessed these associations, the relative risks didn't vary by tumor hormone receptor subtype or histologic subtype. Norplant, a long-acting contraceptive that is implanted subdermally, was introduced in the United States only in 1990. In the CARE study, no association was observed for ever Norplant use, although only 12 women were exposed (260). Further epidemiologic research is needed for each of these drugs.

POSTMENOPAUSAL HORMONE USE

Postmenopausal estrogens have been used for more than half a century. By the mid-1970s, almost 30 million prescriptions were being filled annually in the United States (261). A challenge in studying the relationship between postmenopausal hormones and breast cancer is the substantial variation in formulations and patterns of use that has occurred over time. By the time sufficient use of one type of hormone has occurred to allow a detailed epidemiologic evaluation, new formulations are already being introduced.

The possible relation between postmenopausal estrogen use and risk of breast cancer has been investigated in more than 50 epidemiologic studies over the past 40 years. Most of these studies focused on unopposed estrogen and have been summarized in meta-analyses (262–267) and a large pooled analysis (268). More recently, data from randomized controlled trials have confirmed the epidemiologic relations of combination estrogen plus progestin hormone therapy to increased risk of breast cancer, and IARC has now classified estrogen plus progestin therapy as a human carcinogen (269). On the other hand, the Women's Health Initiative randomized trial did not observe an increase in risk with short term use (median 5.9 years) of unopposed estrogen (270), although the duration of use was shorter than in the epidemiologic studies that continue to show increased risk with longer durations of unopposed estrogen therapy (15 plus years of current use) (271). A summary of these findings, plus a more detailed discussion of several of the most important and most recent studies, is provided below. Particular attention is focused on use of estrogen alone versus estrogen plus progestin therapy.

Any Use

All meta-analyses have concluded that overall, ever users of postmenopausal estrogens have little or no increase in risk of breast cancer compared with women who have never used this therapy. Depending on the inclusion criteria for the meta-analyses, the RR estimates across studies range from 1.01 to 1.07. The RR observed in the pooled individual patient data analysis was 1.14 (268). However, as for oral contraceptives, ever use is a poor measure of exposure because it fails to distinguish between short and long duration and recent and past users, nor does it distinguish type of hormone therapy used.

Duration of Use

In the meta-analyses, significant increases in risk of approximately 30% to 45% with more than 5 years of use have been observed. In updated results from the Nurses' Health Study (272), with 1,935 breast cancer cases, an excess risk of breast cancer was limited to women with current or very recent use of postmenopausal hormones. Within this group, the risk increased with longer duration of use and was statistically significant among current users who have used for 5 or more years (e.g., compared to never users of postmenopausal hormones, RR for ≥10 years of use =1.47; 95% CI, 1.22–1.76) (272). While the WHI with median duration of use of unopposed estrogen (5.9 years) shows no excess risk of breast cancer (270), longer durations in epidemiologic studies show significant increase in risk (273). With over 5,600 invasive breast cancer cases in the Nurses' Health Study, Chen et al. show that risk is significantly increased beyond 10 years of current use and continues to increase with longer durations (274).

Risk is greater for users of estrogen plus progestin compared to users of estrogen alone (275–277). These epidemiologic results were corroborated by the Women's Health Initiative, a randomized controlled trial of estrogen plus progestin use that showed a significant increase in risk of breast cancer with duration of use of this hormone combination (40). Given the high dropout and noncompliance with therapy during the trial (approximately 40% stopped taking drug or placebo in each arm), analysis of compilers showed a substantially greater increase in risk with duration of therapy (278), closer to that observed in epidemiologic studies that by their nature evaluate risk among compliers or users of hormone therapy.

Recency of Use

Data on recency of use have been sparse because many studies do not distinguish current from past users. One meta-analysis calculated an RR for current use of 1.63 for women with natural menopause and 1.48 for women with surgical menopause. In a second, the summary RR was 1.40 (95% CI, 1.20–1.63) comparing current to never users. In the report from the Nurses' Health Study cohort (272), an excess risk of breast cancer was limited to women with current or very recent use of postmenopausal hormones. In the Breast Cancer Detection Demonstration Project (BCDDP) cohort, a positive association with invasive breast cancer was noted among current users with ≥5 to 15 years of use (279). In the U.K. Million Women Study, risk was likewise substantially larger among current users than past users, and returned to the risk of never users within 4 years of stopping use (280).

These relationships were evaluated in considerable detail in the pooled analysis that combined results of 51 epidemiologic studies (268). Importantly, in these analyses, women with an uncertain age at menopause were excluded (e.g., women with simple hysterectomies) because inadequate accounting for age at menopause in the analysis can lead to substantial attenuation of the observed relationships between postmenopausal hormone use and breast cancer risk (281). The median year of case diagnosis was before 1990 in the majority of studies and accordingly few recorded type of hormone used. The vast majority of use across these 51 studies was unopposed estrogen, but type of hormone therapy was not addressed in the overall assessment of these data. The investigators observed a statistically significant association between current or recent use of postmenopausal hormones and risk of breast cancer; the positive association was strongest among those with the longest duration of use (Fig. 18-9). For example, among women who used postmenopausal hormones within the previous 5 years (compared to never users of postmenopausal hormones), the RRs for duration of use were 1.08 for 1 to 4 years

Duration of use and time since last use	Cases/controls	RR (FSE)
Never used	12,467/23,568	1.00 (0.021)
Last use <5 years before diagnosis		
Duration <1year	368/860	0.99 (0.085)
Duration 1–4 years	891/2,037	1.08 (0.060)
Duration 5–9 years	588/1,279	1.31 (0.079)
Duration 10–14 years	304/633	1.24 (0.108)
Duration ≥15 years	294/514	1.56 (0.128)
Last use ≥5 years before diagnosis		
Duration <1 year	437/890	1.12 (0.079)
Duration 1–4 years	566/1256	1.12 (0.068)
Duration 5–9 years	151/374	0.90 (0.115)
Duration ≥10 years	93/233	0.95 (0.145)

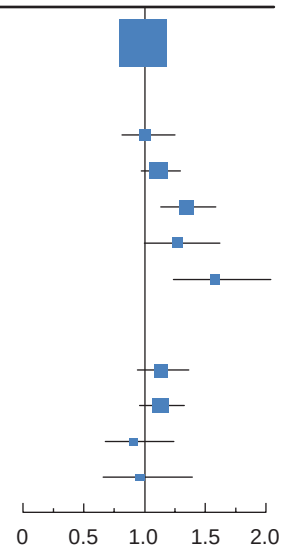


FIGURE 18-9 Relative risk (RR) of breast cancer for different durations of use of hormone replacement therapy. Relative risk is shown in comparison with that of those who never used hormone replacement therapy, stratified by study, age at diagnosis, time since menopause, body mass index, parity, and the age of the woman at the time her first child was born. "Last use ≥5 years before diagnosis" includes current users. Floated standard error (FSE) and floated CI (FCI) were calculated from floated variation for each exposure category. Any comparison between groups must take variation into account. Each analysis is based on aggregate data from all studies. Black squares indicate relative risk, area of which is proportional to amount of information contributed (i.e., to inverse of variance of logarithm of relative risk). Lines indicate 99% FCI (lines are white when 99% FCIs are so narrow as to be entirely within width of square). (Reproduced from Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiologic studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet* 1997;350:1047–1059, with permission.)

of use, 1.31 for 5 to 9 years, 1.24 for 10 to 14 years, and 1.56 for 15 years or more of use. No significant increase in breast cancer risk was noted for women who had quit using postmenopausal hormones 5 or more years in the past, regardless of their duration of use. Whether this holds true for all types and durations of use of hormone therapy remains to be evaluated more precisely.

Type, Dose, and Mode of Delivery of Estrogen

Limited data are available regarding the effects of dose or type of estrogen on breast cancer risk. Again, the best data come from the pooled analysis (268). No significant differences in the RRs were observed according to either the type of estrogen used (conjugated estrogen vs. other) or the estrogen dose (<0.625 versus ≥1.25 mg), although some modest differences in estimates suggested that further evaluation is warranted.

Although the effect of estrogen use on breast cancer risk could be reasonably hypothesized to vary by mode of estrogen delivery (e.g., patch estrogen, by avoiding the first pass effect in the liver, does not increase SHBG to the extent that oral preparations do), no important differences are observed in the largest study to date; the Million Women Study included over 40,000 users of transdermal estrogen and observed no significant difference in relative risk of breast cancer (1.24) compared to that among the 60,000 users of oral therapy (1.32) (277).

Time since Menopause, Initiating Use of Hormone Therapy, and Risk

Considerable evidence has recently accumulated addressing timing of use of hormones and the magnitude of the adverse effect on breast cancer risk (282). A rigorous analysis of the U.K. Million Women Study shows risk is substantially greater among women who start hormone therapy before or less than 5 years after menopause. This effect is observed for estrogen alone and for combination estrogen plus progestin (280). The U.K. Million Women Study contrasts with the WHI where 90% of women in the estrogen-only arm of the trial were more than 5 years beyond menopause at randomization.

Risk according to Breast Cancer Risk Factor Profile

The risk associated with postmenopausal hormone use was assessed in a number of specific subgroups in the pooled analysis (268). Risk did not appear to vary according to reproductive history, alcohol intake, smoking history, or family history of breast cancer. However, the RRs associated with 5 or more years of postmenopausal hormone use were highest among the leanest women (*p* for

heterogeneity = 0.001); this interaction has been consistently observed (271,277,283). Risk for unopposed estrogen therapy is also more clearly observed to increase with duration of use among women with bilateral oophorectomy than those without (271), again consistent with precise statistical control for underlying risk of breast cancer because age at menopause is more accurately assessed in women undergoing bilateral oophorectomy than in those who have hysterectomy without oophorectomy (284). This consistent finding that risk of unopposed estrogen is attenuated among overweight and obese women may account for the apparent lower risk of breast cancer among women in the WHI trial of unopposed estrogen, given the overweight and obese population included in the trial (285).

Use of Estrogen Plus Progestin (E & P)

The addition of a progestin to estrogen regimens became increasingly common through the 1990s because it minimizes or eliminates the increased risk of endometrial hyperplasia and cancer associated with using unopposed estrogens. In the United States, by the mid-1980s, almost 30% of postmenopausal hormone prescriptions included a prescription for progestin (286). The impact of an added progestin to the risk of breast cancer has been evaluated only in the last 25 years.

Two of the first studies to assess this relationship suggested that the addition of a progestin could decrease breast cancer risk (287,288). However, these studies were small and potentially important confounders (e.g., age and parity) were not accounted for in the analyses. Since this time, several additional studies have assessed this relationship and together indicate that a protective effect of typical doses used in postmenopausal hormone therapy can be ruled out (268). Prospective studies reporting on this relationship had similar findings. Bergkvist et al. (289) observed an RR of 4.4 (95% CI, 0.9–22.4) among women who used estrogen plus progestin for 6 or more years compared to never users. Women using hormones for a shorter duration did not appear to be at increased risk, but CIs again were wide and did not exclude either a modest increase or a decrease in risk. In findings from the Nurses' Health Study (272), in which among women using progestins, about two-thirds used 10 mg of medroxyprogesterone for 14 or fewer days per month, the RR associated with current estrogen plus progestin use versus never use was 1.4 (95% CI, 1.2–1.7). The BCDDP found that the risk of breast cancer went up by about 1% for every year that women took estrogen alone and about 8% for every year that they took estrogen plus progestin (290). Although these yearly increases in risk seem minimal, their accumulation over time is of concern. For example, if women take estrogen with progestin for 10 years, their risk of breast cancer will be 80% higher than if they had never used hormones (291). For both types of therapy, however, this increase in risk begins to drop after hormone use stops (268). In the pooled analysis (268), data on the postmenopausal hormone formulation were available from only 39% of women, and only 12% of these reported using estrogen plus a progestin. The RR associated with 5 or more years of recent use, relative to never use, was 1.53. More recent case-control studies also support this increase in risk with combination estrogen plus progestin (292,293). The Women's Health Initiative randomized controlled trial of estrogen plus progestin versus placebo among 16,608 postmenopausal women with an intact uterus, ages 50 to 79, stopped early at the recommendation of the data safety monitoring board (DSMB) in part due to the prespecified harm boundary for breast cancer (40). At an average of 5.2 years of follow-up, women randomized to estrogen plus progestin had a significantly elevated risk of breast cancer, RR compared to placebo 1.26 (95% CI, 1.00–1.59), and analysis accounting for adherence showed an RR of 1.49 for estrogen plus progestin. Importantly, the trend for increasing risk with increasing duration of use of estrogen plus progestin was also significant. These results among women adherent to use of estrogen plus progestin at an average of 5 years of use are consistent with the epidemiologic data, which also shows the trend in risk with duration of use continuing to increase beyond 5 years and no evidence of a plateau (274).

In addition to their effect on breast cancer, postmenopausal hormones also have a major impact on other aspects of women's health. Results from the Women's Health Initiative (a large randomized clinical trial) definitively show that after 5 years of use, estrogen plus progestin does more overall harm to women than good (40), although the Women's Health Initiative studied only one type and dose of estrogen plus progestin (Prempro); because widespread use of estrogen plus progestin is relatively recent, few data are available to evaluate the effect of different formulations, doses, or schedules of use of progestin on risk of breast cancer (294,295). The British Million Women Study with over 9,000 cases of breast cancer during follow-up again confirmed the excess risk of breast cancer among women currently using combination estrogen plus progestin and noted this is significantly greater relative risk than among women using estrogen alone. Risk increased with duration of use but did not vary significantly according to the progestagen content or whether use was sequential or continuous (277). The possibility remains that dose of progestagen is important, including total monthly exposure, but variation in studies to date has not allowed rigorous and valid comparisons. Despite issues such as dose of progestagen that remain open research questions, additional follow-up of the WHI trial participants shows excess breast cancer mortality among the women receiving estrogen plus progestin compared to placebo with almost double the risk of death from breast cancer through 11 years of follow-up (296).

Receptor Status and Histologic Subtypes of Breast Cancer

Consistent evidence from larger epidemiologic studies shows combination estrogen plus progestin and unopposed estrogen therapy are associated with increased risk of ER+ breast cancer (297). While the WHI did not observe any significant difference in the distribution of invasive cancer by receptor status, the trial had limited power to detect an association with fewer than 500 cases of breast cancer. Some have suggested that risk is limited to lobular subtypes of breast cancer (298), but the majority of evidence does not support this claim. Also, given the higher proportion of receptor positive tumors in lobular rather than ductal cancers, a stronger relative risk observed for lobular cancer (297) would be expected for this subset of breast cancers. This is confirmed in the Million Women Study with over 8,000 cases of invasive ductal and over 1,500 invasive lobular cancers, where significant increases in risk of ductal carcinoma are observed for estrogen alone and for combination therapy (273).

Decline in Breast Cancer Incidence

Numerous studies in the United States and internationally have reported on the decline in breast cancer incidence after 2002. Based on data from the San Francisco mammography registry, prescribing of E&P peaked in 1999. Before publication of the Heart and Estrogen/progestin Replacement Study (HERS) the use of hormone therapy was increasing at 1% per quarter, but declined by 1% per

quarter after the publication (299). This decline in prescribing continued until the publication of the WHI in 2002, at which point a more substantial decline of 18% per quarter was observed. The peak and decline through 1999 to 2002 is concordant with the HERS report (300) in 1998 showing a significant increase in coronary heart disease (CHD) in the first year of therapy among women with prevalent coronary disease, and in addition, no long-term benefit in reducing CHD (301). The growing epidemiologic evidence published since 2000 on the adverse effects of combination therapy on breast cancer added further evidence against the use of this therapy. Based on a prevalence of use of E&P in California, Clarke et al. estimated a population attributable risk (PAR or the proportion of cases caused by E&P) of up to 11% based on a prevalence of use of 30% and a relative risk of 1.4 (302). Given that substantially higher relative risks of 2 or more have been reported (277), this estimate of the PAR is conservative. Assuming a prevalence of use of 17.5%, the average reported for California in 2001 (302), a relative risk of 1.49 gives a PAR of 7.9% and a relative risk of 2.0 gives a PAR of 14.9%.

Evidence for breast cancer incidence rates now clearly shows a parallel drop in breast cancer consistent with the pattern of decreased prescribing. The rigorous, state-of-the-art analysis by Jemal et al. (303) using joint point analysis and drawing on SEER incidence data from 1975 through 2003 shows that there is a significant decrease in incidence of invasive breast cancer from 1999 to 2003 in all 5-year age groups from 45 years and above, and a sharp decrease largely limited to ER positive tumors in age groups 50 to 69 between 2002 and 2003. Furthermore, while others have suggested that a 1% to 3% drop in screening mammography may account for this drop in incidence, Jemal et al. show strong evidence against this. If screening was to account for a drop in incidence, rates of *in situ* disease would also need to drop because they are almost only detected by mammography. Prior to screening becoming widespread, Jemal et al. show *in situ* rates were low and rose with the uptake of screening to plateau from 1999 through 2003. The lack of a drop in *in situ* cancer offers compelling evidence that a reduction in screening does not account for the drop in incidence of invasive breast cancer.

Others have analyzed SEER data over a shorter period (30) or draw on the unique resources of the California tumor registry and the health maintenance organization (HMO) data sets (304) to show similar relations between change in hormone therapy and a decrease in breast cancer incidence. Robbins and Clarke (305) have also evaluated the change in prescribing as estimated from the California Health Interview Survey (CHIS) for almost 3 million non-Hispanic white women aged 45 to 74 against the change in breast cancer incidence across 58 counties in California. This thoughtful analysis shows that from 2001 to 2004, incidence declined by 8.8% in the counties with the smallest E&P reductions, by 13.9% in those with intermediate reductions, and by 22.6% in counties with the largest reductions in combination postmenopausal hormone therapy (305). Between 2001 and 2003, CHIS data did not show any significant change in the proportion of women who reported having a mammogram in the previous two years adding further evidence against this as a plausible major explanatory factor in the observed declines in incidence. Analysis of women undergoing routine mammography in San Francisco rules out a drop in screening as a cause of the decrease in incidence and confirms other reports of the changes in incidence of invasive breast cancer (306). Even more evidence in support of this relation between decrease in E&P and breast cancer comes from declines in incidence that parallel those in the United States as reported in New Zealand (307), Australia (308), and Germany (309). Based on these data and the IARC classification of estrogen plus progestin as a carcinogen, we can conclude that removal of estrogen plus progestin acting as a promoter accounts for this rapid drop in incidence (310).

Summary of Postmenopausal Hormone Use and Breast Cancer Risk

Although some aspects of the relationship between postmenopausal hormones and breast cancer risk remain unresolved, several areas of clear agreement have emerged. The finding of no increase in risk comparing ever users to never users is consistent and reassuring. However, much of that observation reflects the experience among short-term users and hormone use in the past, predominantly unopposed estrogen.

Overall, the findings also indicate an increased risk in two important subgroups of users: users of long duration and current users. These increases are particularly marked among women beginning use within 5 years of menopause. In general, users of long duration are more likely to be current users, so in many studies these two groups overlap substantially. From a biological perspective, these are the groups one would most expect to demonstrate a relation with breast cancer risk, because exogenous estrogens appear to act as a promoter at a late stage.

The increase in breast cancer risk associated with estrogen plus progestin use appears considerably greater than that for use of estrogen alone. Combination estrogen plus progestin therapy increases mortality from breast cancer, not just incidence of disease. The impact on risk of differing progestins and patterns of use of progestins remains to be resolved.

GENETIC SUSCEPTIBILITY TO BREAST CANCER

Hereditary Syndromes

Family history of breast cancer is an accepted risk factor for breast cancer; however, the proportion of breast cancer estimated to be due to rare highly penetrant genes such as *BRCA1* and *BRCA2* is less than 10% (311), perhaps as low as 3% (312). A few highly penetrant genes and hereditary syndromes for breast cancer are described below; however, a more extensive discussion of this topic is covered in Chapter 17, Inherited Genetic Factors and Breast Cancer. Among 2,389 incident cases of breast cancer occurring in the Nurses' Health Study between 1976 and 1988, the age-adjusted RR associated with having a maternal history of breast cancer was 1.8 (95% CI, 1.5–2.0) (313). This risk rose to 2.1 if the mother's breast cancer was diagnosed before age 40. Having a sister with breast cancer was associated with a RR of 2.3, and this rose to 2.5 for having both and mother and a sister with breast cancer. Risk of developing breast cancer by age 70 for a 30-year-old woman with both a mother and sister history of breast cancer was estimated to be 17.5%. Segregation analyses of breast-cancer-prone families showed that inheritance in these families is consistent with an autosomal dominant mode of inheritance (314). These families represent a heterogeneous group of syndromes such as the Li-Fraumeni syndrome (a disorder that includes predisposition to sarcomas, lung cancer, brain cancer, leukemia, lymphoma, and adrenal-cortical carcinoma), Cowden disease (a syndrome involving mucocutaneous and gastrointestinal lesions and breast cancer), and a syndrome called by some "early onset breast cancer" (314) in which

breast cancer often occurs in the 20s and 30s. The molecular basis for certain of these syndromes is associated with high penetrance mutations. The Li-Fraumeni syndrome is due to germline mutations in the *p53* gene (315). Cowden syndrome is due to germline mutations of the *PTEN* gene (316). The breast cancer susceptibility gene on chromosome 17q was called *BRCA1* and was cloned in 1994 (317). A second breast cancer susceptibility locus, *BRCA2*, was localized on chromosome 13q and cloned in 1995 (318). Estimates of the cumulative lifetime risk of breast cancer in *BRCA1* and *BRCA2* carriers range from about 85% (estimated from the families selected for linkage analysis) to 50% or even less (estimated from population-based studies) (311). The higher estimates from the linkage analysis studies could be due to higher penetrance mutations in these families or to ascertainment bias resulting in failure to select families in which *BRCA1* and *BRCA2* mutations are present but do not give rise to a sufficiently striking breast cancer predisposition to qualify for enrollment into the linkage studies. In case series from "high-risk" clinics to which women with a notable family history of breast cancer are referred, *BRCA1* mutations may be responsible for 20% to 30% of early-onset breast cancer (319). However, estimates in unselected breast cancer cases are much lower, in the range of 2% to 3% (319,320). Estimates for *BRCA2* tend to be lower (319). In unpublished data from the Nurses' Health study, only 2 of 192 consecutive cases had truncation mutations in *BRCA1*, and 1 of 192 had a truncation mutation in *BRCA2*. Genetic testing and management of patients with highly penetrant mutations is discussed in Chapter 19. Moderate penetrance genes with minor allele frequencies (MAFs) ranging from .0005–.01 such as *CHEK2* (rare deletion mutation) and *PALB2* also increases breast cancer risk (321).

"Sporadic" and Later-onset Breast Cancers

As the high-penetrance genes responsible for single gene disorders have been found, the field of genetic epidemiology has seen a shift to studies using unrelated controls, often described as "association studies." This has been largely motivated by the lack of power in family-based studies if allele penetrance is low, as few members of even large families will be affected. There are additional parameters that can be calculated in association studies; for instance, to assess the population attributable risk for alleles associated with familial risk or specific allelic variants, it is necessary to screen population-based case series.

Low-penetrance Alleles and Breast Cancer Risk

Until recently, the main method used in the search for these low-penetrance alleles has been the "candidate gene" approach in which polymorphic variants in genes that plausibly influence breast cancer risk are assessed in conventional epidemiologic studies (i.e., case-control or cohort studies). The principal candidates studied have been genes involved in steroid hormone metabolism, carcinogen metabolism genes, and genes that may influence cell proliferation. Despite a large number of positive reports of association in a single study, few of these reports have been replicated (322). The failure to replicate initially positive findings has been ascribed to a variety of factors including publication bias, the "winner's curse" phenomenon (the first report of an association is often more positive than subsequent studies), underpowered studies, multiple comparisons, and genetic heterogeneity (322). The major problem with candidate gene studies may be the low prior probability associated with any specific candidate gene chosen from among the approximately 24,000 human genes. Despite this, when all published studies are combined, approximately 20% to 30% of association studies yield statistically significant pooled estimates, usually of modest effects (322,323). Until recently, none of these replicated positives have applied to breast cancer. Recent results from the Breast Cancer Association Consortium suggest that a nonsynonymous polymorphism in a coding variant (D302H) in Caspase 8 (*Casp8*) is associated with lower risk of breast cancer (324).

Genome-wide Scans and Cancer Susceptibility

Advances in genotyping technology coupled with decreases in genotyping cost have enabled genome-wide association studies (GWAS) in large-scale study populations. In contrast to the candidate gene approach, GWAS offer the potential to conduct a comprehensive and unbiased search for modest associations (325). The generation of a draft sequence of the human genome led to subsequent efforts to define the spectrum of variability in the sequence. These efforts include the International HapMap and 1000 Genomes Project.

The International HapMap provides a database of common SNPs (single nucleotide polymorphisms; defined as SNPs with minor allele frequency, MAF, >5%) at an average spacing of every 1,250 bases across the 3 billion base pairs of genomic sequence (326). Analysis of this dataset indicates that over 90% of the nearly 10 million common SNPs estimated to exist are highly correlated with at least one other SNP (a phenomenon known as linkage disequilibrium). This observation suggests that much of the information on genetic variation can be extracted with the genotyping of a carefully chosen subset of SNPs called tagSNPs, which can serve as surrogates for untested SNPs. The informativeness of a set of tagSNPs can be increased by selecting SNPs that maximize the r^2 to untyped SNPs in a region, and further increased by ranking SNPs according to the number of proxies they have (327). The extent of diversity in population genetics history is evident in the substantial differences in patterns of linkage disequilibrium between the multiple continental populations studied in HapMap 1 included European, East Asian, and West African populations. Draft 1 of the HapMap 3 data release includes 1,301 samples from 11 populations.

The 1000 Genomes Project provides an extensive catalog of SNPs, structural variants and their haplotype context. Using the next generation sequencing technologies, this international collaboration will sequence genomes from approximately 2,500 individuals from about 25 populations around the world. The Phase I data, an integrated release of genetic variation from 1,092 human genomes is currently available.

Replication in Whole Genome SNP Studies

However, testing 500,000 or more independent SNPs at conventional levels of statistical significance will generate a very large number of "statistically significant" results. Consideration of other factors, such as whether an SNP is in a known candidate gene pathway or network or a candidate genomic region (identified for instance, by previous linkage analyses or cytogenetic abnormalities in tumors) might be useful in advancing SNPs of interest, but since so little is known about the majority of the genes in the genome, this exercise will only apply to a small portion of genic regions. Thus, while there is considerable novelty for the first whole genome scan conducted for a specific disease, the reality is that it does not do much more than identify a list of SNPs for further testing in follow-up replication studies.

Fortunately, simulations have shown that carefully designed multistage studies in large consortia in which the best candidate SNPs identified in the first stage are advanced in subsequent studies of comparable cases and controls maintain high statistical power and enable a substantial decrease in genotyping cost (328,329).

Results from Genome-wide Scans of Breast Cancer

Results from 12 GWAS for sporadic breast cancer were published from 2007-2012 (330-337). The studies identified 25 loci as strongly associated with overall breast cancer risk, eight of which contained genes (*FGFR2, TOX3, MAP3K1, LSP1, ESR1, RAD51L1, TERT* and *PTHLH*) plausibly related to breast cancer. The *ESR1* variant is located upstream of the exon 1 transcription start site. *ESR1* encodes the ER-alpha gene involved in regulation of estrogen signaling pathways. However, several loci are located in non-genic regions such as 8q24. Variants in *FGFR2, MAP3K1,* 8q24, and 5p are associated with ER+ breast cancer. Studies on ER- breast cancer have identified three loci (TERT, Chr 19, MERIT40*)* (336,337). Additional studies by breast cancer molecular subtype are ongoing. Collectively, the 25 variants explain approximately 9% of the heritability of breast cancer. A meta-analysis of nine GWAS that includes over 10,000 breast cancer cases and over 12,000 controls of European ancestry have been conducted to identify new variants. Replication of the new variants is ongoing. The variants identified to date have modest effect sizes (RR = 1.05–1.6 per allele), emphasizing the need for large-scale replication. Studies have also been mainly conducted in postmenopausal breast cancer cases. In the CGEMS-NHS (331), the RRs for SNPs in 10q26 of intron 2 of *FGFR2* for premenopausal women in the Nurses' Health Study II were similar to those in postmenopausal and older-onset breast cancer case series, demonstrating the generalizability of the findings for this gene to premenopausal cases.

These findings, and additional loci that will almost certainly be discovered in further follow-up of these and further GWAS, have established new loci that collectively are likely to robustly identify a much larger fraction of women at modest genetic risk of breast cancer than the very small fraction at very high risk identifiable through analysis of the high penetrance genes such as *BRCA1* and *BRCA2.* Deriving the appropriate risk prediction models, integrating SNPs with molecular phenotypes, and then understanding how they can be applied clinically will be a substantial challenge over the next several years.

Since many of the GWAS SNPs identified to date are located in non-coding regions of the genome, future collaborative investigations will require functional follow-up to uncover the mechanistic association with breast cancer (338). A recent study shows that GWAS SNPs associated with breast cancer risk are located in enhancer regions and alter binding affinity for the pioneer factor FOXA1 (339). Efforts to link the risk alleles in non-coding regions to genes using expression quantitative trait analyses and to identify the causal alleles using next-generation sequencing are in progress.

DIETARY FACTORS

Nutritional factors have been prominent among the hypothesized environmental determinants of breast cancer that account for the large variation in breast cancer incidence around the world and the large increases in rates among the offspring of migrants from countries with low incidence to countries with high incidence. The dominant hypothesis has been that high fat intake increases risk. In this section, evidence for this relationship is reviewed and alternative hypotheses are suggested.

Dietary Fat and Breast Cancer

Animal Studies

High-fat diets have long been known to increase the occurrence of mammary tumors in rodents. However, the interpretation of these and other animal data is controversial. Fat is the most energy-dense macronutrient (9 kcal/g compared with 4 kcal/g for protein and carbohydrate); thus, high-fat diets tend to be higher in energy intake unless care is taken to keep energy intake constant. Many animal experiments have not done this, resulting in confounding of fat consumption by energy intake. In a meta-analysis of diet and mammary cancer experiments in mice, Albanes (340) observed a weak inverse association with fat composition (adjusted for energy), whereas total energy intake was positively associated with mammary tumor incidence. Freedman, Clifford, and Messina (341) conducted a similar meta-analysis of experiments in both rats and mice and reported that both higher fat intake and higher caloric intake independently increase mammary tumor incidence. In studies specifically designed to determine the independent effects of fat and energy intake, the effect of fat was either weak in relation to that of energy intake (342) or nonexistent (343). Furthermore, the relevance to human experience of rodent models in which animals are given high doses of specific carcinogens, to which humans are rarely exposed, is questionable. Notably, in a very large study of rats and mice fed substantially different amounts of corn oil without administration of a carcinogen, no effect of fat intake was found on spontaneous mammary cancer incidence (344). In a case-control study in dogs, fat intake, which ranged from 10% to 70% of energy, was not associated with risk of breast cancer (345). The clearest message from the animal data is the importance of total energy intake and the need to consider energy balance in epidemiologic studies.

International Correlation (Ecologic) Studies

The dietary fat hypothesis is largely based on the observation that national per capita fat consumption is highly correlated with breast cancer mortality rates (346). A serious problem with ecologic comparisons of diet and breast cancer is the potential for confounding by known and unknown breast cancer risk factors. National fat consumption per capita is highly correlated with level of economic development; thus, any factor that characterizes affluent Western countries would also be correlated with national rates of breast cancer. Prentice et al. (347) found that the ecologic relation between fat consumption and breast cancer incidence rates was still statistically significant after adjustment for Gross National Product (GNP) per capita and average age at menarche. However, other breast cancer risk factors such as low parity, late age at first birth, greater body fat, and lower levels of physical activity are more prevalent in Western countries and would be expected to confound the association with dietary fat. Thus, there is good reason to question whether the international correlation between fat intake and breast cancer represents a causal relationship.

Secular Trends

Estimates of per capita fat consumption based on "food disappearance" data (the food available rather than the amount actually eaten), and breast cancer incidence rates have both increased substantially in the United States during the twentieth century. However, surveys based on measures of actual individual intake, rather than food disappearance, indicate

that consumption of fat as a percentage of energy has declined in the last several decades, a time during which breast cancer incidence has increased. Higher dietary fat consumption has been implicated in the increase in breast cancer incidence in Japan since 1950. However, this increase could also be due to the increasing prevalence of reproductive and other lifestyle risk factors that characterize Western populations.

The famine that occurred in Norway during World War II provided a natural experiment on the effects of nutritional deprivation on breast cancer risk (348). Women who were adolescents during the famine have subsequently experienced a reduction in breast cancer risk (about 13% lower) at all ages. These data on time trends indicate the sensitivity of breast cancer rates to nutritional and lifestyle factors but do not specifically support a role of dietary fat.

Data from special populations with distinct dietary patterns are valuable, because adherence to a particular diet over many years may represent a more stable long-term exposure than that applicable to most free-living adults whose diet may change substantially over time. Because these populations often have unusual distributions of potential nondietary risk factors such as alcohol consumption, smoking, and reproductive behavior, care must be taken in attributing differences in cancer rates to diet alone. Seventh-Day Adventists, who consume relatively small amounts of meat and other animal products, have substantially lower rates of colon cancer, but only slightly lower breast cancer rates than other U.S. white women of similar socioeconomic status (349). Breast cancer rates among British nuns who ate no meat, or very little meat, were similar to rates among single women from the general population (350), also suggesting there is no substantial association between animal fat and risk of breast cancer.

Case-control Studies

In a typical case-control study of diet and breast cancer, the diet before diagnosis reported by women with breast cancer (cases) is compared with the diet reported by women who have not been diagnosed with breast cancer. An early large study was that of Graham et al. (351), who used a food frequency questionnaire to compare the fat intake of 2,024 women with breast cancer to that reported by 1,463 female controls seen at the hospital with benign conditions. Animal fat and total fat intake were almost identical in the two groups. In a meta-analysis, Howe et al. (352) summarized the results from 12 smaller case–control studies including 4,312 cases and 5,978 controls. The overall pooled RR for a 100-g increase in daily total fat intake (an unrealistic change) was 1.35; the risk was somewhat stronger for postmenopausal women (RR= 1.48). The main concern with this finding is that associations in case-control studies of diet may easily be due to selection bias (the controls are drawn from a population with a different distribution of fat intake than the distribution in the population that gave rise to the cases) or recall bias (the cases, knowing their diagnosis, differentially misreport their prediagnosis diet) (353). We now have many examples in which findings from case-control studies of diet and cancer have not been confirmed in prospective studies (354).

Cohort Studies

In a cohort (prospective) study, the diets of a large group of women are measured, and the subsequent rates of breast cancer among those with different levels of dietary factors are compared. Selection bias should not be a problem because the population that gave rise to the cases is known (the starting members of the cohort), and recall bias should not occur because dietary information is collected before knowledge of disease. The results for postmenopausal breast cancer (for which fat intake has been hypothesized to be strongest because the international differences are largest for this group) from prospective studies with at least 200 incident cases of breast cancer are shown in Table 18-1 (355–366). The number of breast cancer cases in some of

TABLE 18-1

Results from Large Prospective Studies of Total and Saturated Fat Intake and Risk of Breast Cancer

Study (Reference No.)	*Total Women in Cohort*	*Years of Follow-Up*	*No. of Cases*	*Relative Risk (95% CI) (High vs. Low Category)*	
				Total Fat	*Saturated Fat*
Nurses' Health Study (365)	89,494	8	1,439	0.86 (0.67–1.08)	0.86 (0.73–1.02)
Nurses' Health Study (356)	88,795	14	2,956	0.97 (0.94–1.00)[a]	0.94 (0.88–1.01)[a]
Canadian study (358)	56,837	5	519	1.30 (0.90–1.88)	1.08 (0.73–1.59)
New York State cohort (355)	17,401	7	344	1.00 (0.59–1.70)	1.12 (0.78–1.61)[b]
Iowa women's study (359)	32,080	4	408	1.13 (0.84–1.51)	1.10 (0.83–1.46)
Netherlands cohort study (363)	62,573	3	471	1.08 (0.73–1.59)	1.39 (0.94–2.06)
Adventists health study (361)	20,341	6	193		1.21 (0.81–1.81)
Swedish mammography screening cohort (366)	61,471	6	674	1.00 (0.76–1.32)	1.09 (0.83–1.42)
Breast Cancer Detection Demo Project (364)	40,022	5	996	1.07 (0.86–1.32)	1.12 (0.87–1.45)
California teachers study (357)	115,526	2	711	0.8 (0.6–1.2)	0.8 (0.6–1.2)
NIH—AARP study (362)	188,736	4	3,501	1.11 (1.0-1.24)	1.18 (1.06-1.31)
Malmö Diet Cohort (360)	11,726	10	342	1.36 (0.96-1.94)	—
EPIC (768)	319,826	9	7119	1.04 (0.96-1.13)	1.10 (1.01-1.19)
Swedish Women's Cohort (769)	49,261	13	974	1.02 (0.72-1.45)	1.12 (0.69-1.81)

[a]Animal fat.
[b]Continuous.

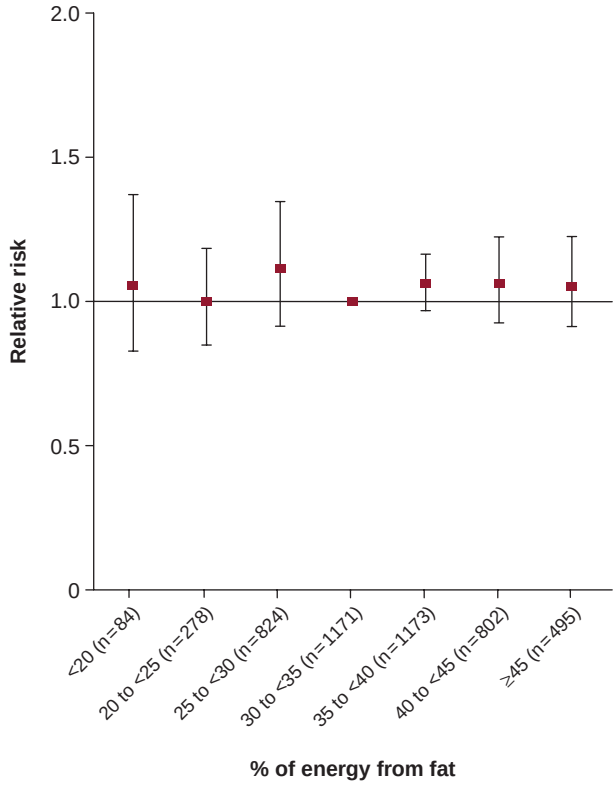


FIGURE 18-10 Pooled relative breast cancer risk and 95% CIs associated with percentage of energy derived from fat intake. (Reproduced from Hunter DJ, Spiegelman D, Adami HO, et al. Cohort studies of fat intake and the risk of breast cancer: a pooled analysis. *N Engl J Med* 1996;334:356–361, with permission.)

these studies far exceeds the number in the pooled analysis of case-control studies referred to earlier, and the size of the comparison series (i.e., noncases) is much larger. Only in the AARP study was a weak positive association between fat intake and risk of breast cancer observed (comparing highest with lowest category of intake, RR = 1.11 (95% CI, 1.00–1.24) (362). In all other studies no significant association was seen. A collaborative pooled analysis has been conducted that included most of the prospective studies shown in Table 18-1 that included 4,980 cases of breast cancer among 337,819 women (367). In addition to providing great statistical precision, the pooled analysis allowed standard analytic approaches to be applied to all studies, an examination of a wider range of fat intake, and a detailed evaluation of interactions with other breast cancer risk factors. Overall, no association was observed between intake of total, saturated, monounsaturated, or polyunsaturated fat and risk of breast cancer. As noted in Figure 18-10, no reduction in risk was seen even for fat intakes as low as 20% of energy. When the relatively few women with fat intake lower than 15% of energy were examined, their risk of breast cancer was actually increased twofold; this could not be accounted for by other dietary or nondietary factors.

Substudies were available for each cohort in the pooled analysis in which the measurement errors of the dietary questionnaires were quantified and these were used to adjust the overall RRs and CIs to take into account errors in measuring diet. Without correction, the RR for a 25-g/day increment in fat intake was 1.02 (95% CI, 0.94–1.11). After accounting for measurement error, the RR was 1.07 (95% CI, 0.86–1.34). The upper bound of the adjusted 95% CI excludes the RR of 1.4 to 1.5 predicted by the international correlations. In calculations based on a series of theoretical assumptions, Prentice has claimed that the pooled analysis of breast cancer failed to find a positive association because the measurement error correction did not account for underreporting of fat by more obese women. However, actual studies do not support this assumption, and the other predictions based on this theoretical model are also not supported by the data (368). In analyses with extended follow-up of these cohorts (7,329 cases of breast cancer), the lack of association with total fat intake was confirmed (RR for an increment of 5% of energy from fat per day = 1.00 (95% CI, 0.98–1.03) (369). Based on a small cohort (168 cases) in which a positive association with fat intake was reported when assessed with a 1-week dietary record but not when assessed with a food frequency questionnaire, Bingham et al. suggested that the lack of association seen in the large cohort studies was due to the use of the latter method (370). However, in a recent analysis that combined four cohorts that used both methods, including extended follow-up of Bingham's cohort, the two methods yielded almost identical weak inverse associations between fat intake and incidence of breast cancer (371). In the Nurses' Health Study, additional analyses have been conducted with 20 years of follow-up (3,537 postmenopausal cases) (372); up to six assessments of fat intake were available, which substantially improves the measurement of long-term dietary intake. The RR for a 5% increase in percentage of energy from total fat was 0.98 (95% CI, 0.95–1.00), and no suggestion of any reduction in risk was seen for fat intakes even lower than 20% of energy (356). Thus, the prospective studies provide strong evidence that no major relation exists between total dietary fat intake over a wide range during midlife and breast cancer incidence. It remains possible that total fat intake during childhood and/or early adult life may affect breast cancer risk decades later. Notably, in the Nurses' Health Study II, which was established to evaluate the influence of dietary and other potential risk factors earlier in life, intake of animal fat (but not vegetable fat) before menopause was positively associated with risk of breast cancer (373). This finding, which needs to be replicated, was mainly due to consumption of red meat and high-fat dairy products. In this same cohort, a large subset of women also completed a detailed questionnaire about their diet during high school. A marginally significant association was seen between total fat intake and risk of premenopausal breast cancer (RR = 1.35; 95% CI, 1.00–1.81) (374), but this could not be clearly distinguished from intake of red meat, which was also associated with increased risk (375).

Intervention Studies

Some have suggested that the relation between dietary fat and breast cancer can be established only by randomized trials of fat reduction. In the Women's Health Initiative, 48,835 women were randomly assigned either to reduce their total fat intake to 20% of calories from fat or to their regular diet (376). After 8 years of follow-up, the relative risk for the low fat compared to the control group was 0.91 (95% CI, 0.83–1.0, p = .09), indicating no significant benefit of the intervention. However, as has been the experience in other large dietary intervention trials (377), maintaining compliance with a diet very different from prevailing food consumption habits proved to be difficult, and the reported difference in fat intake between groups was only 8% of energy at year 6 rather than the 14% of energy anticipated. Moreover, self-reported compliance in dietary intervention studies tends to be overreported, and no differences were seen between groups in blood levels of HDL cholesterol or triglycerides (378). Because reduction in dietary

fat would be expected to reduce HDL cholesterol and increase triglycerides (379), this lack of effect on blood lipids suggests that the WHI did not really address the dietary fat and breast cancer hypothesis, despite being the most expensive study ever conducted (380). Prentice et al. suggested that, even though not significant, the slightly lower (9%) risk of breast cancer in the low fat group may represent a real effect of fat reduction that may become significant with longer follow-up. However, even if a significant effect were to be seen, it would not be possible to conclude that this was due to reduction in dietary fat because there was an approximately 1.5-kg weight loss in the low fat group, which is typically seen with intensive dietary interventions independent of percentage of energy from dietary fat (381). This degree of weight loss, although modest, could account for most of a 9% difference in breast cancer risk (382). Furthermore, as pointed out by the Women's Health Initiative investigators, women in the dietary intervention group were counseled to adopt a dietary pattern that is high in fruits, vegetables, and grain products and low in total fat and saturated fat (383). Thus, the trial is unable to distinguish between a decrease in risk due to increased intake of fruits, vegetables, and grains or a decrease due to lower fat intake. Also, this trial could not address whether dietary fat reduction at an earlier age may reduce breast cancer risk. The lack of association with fat intake in the 20-year follow-up of the Nurses' Health Study (372) suggests that insufficient follow-up time is not a likely explanation for the nonsignificant results of the WHI trial. A second trial of dietary fat reduction was conducted in Canada among women with elevated risk of breast cancer (384,385); after an average of 10 years of follow-up, there was a nonsignificant 19% increase in risk of breast cancer among those on a low-fat diet. In contrast to the WHI trial, women assigned to the low-fat diet experienced the expected changes in blood lipid levels. Although this trial was consistent with findings from prospective cohort studies, it could not exclude an effect of diet earlier in life.

Type of Fat

In addition to overall fat intake, specific types of fat could differentially affect risk of breast cancer. In most animal studies, diets high in polyunsaturated fat (linoleic acid), but typically at levels beyond human exposure, have increased the occurrence of mammary tumors. As noted earlier, however, a positive association has not been found in prospective epidemiologic studies (369).

Some animal studies have suggested that monounsaturated fat, in the form of olive oil, may be protective relative to other sources of energy (386); the abundant antioxidants in this oil could contribute to this effect. In a Spanish study specifically undertaken because of the high consumption of olive oil and low breast cancer rates in this population, no association was observed with total fat intake (387). However, higher intake of olive oil was associated with reduced risk of breast cancer. Similar inverse associations with olive oil or monounsaturated fat were seen in case-control studies in Greece, Italy, and Spain (388). In the pooled analysis of cohort studies (369), saturated fat (compared to carbohydrate) was weakly associated with higher risk of breast cancer (RR for 5% of energy=1.09; 95% CI, 1.00–1.19), and compared to monounsaturated fat, the RR was 1.18 (95% CI, 0.99–1.42).

High intake of N3-fatty acids from marine oils has inhibited the occurrence of mammary tumors in animals. However, case-control and cohort studies have in general not found intake of N3-fatty acids or fish (the major source of long-chain N3-fatty acids) to be associated with lower risk of breast cancer (356,388).

Height, Weight, and the Risk of Breast Cancer

As noted earlier, energy restriction powerfully reduces mammary tumor incidence in rodents (340,341). This relationship is difficult to evaluate directly in humans because estimates by adults of their energy intake, especially during childhood, are unlikely to be sufficiently precise and any analysis would need to also account for physical activity with high accuracy. However, because children who experience energy deprivation during growth do not attain their full potential height, attained height may be used as a proxy for childhood energy intake, although this is not a specific indicator as protein restriction and genetic factors also affect stature. In Japan, for instance, a substantial increase in average height has occurred during the twentieth century, presumably because of improved nutrition. Among countries, height is positively correlated with breast cancer rates (389), supporting the hypothesis that childhood and adolescent energy intake may influence breast cancer rates decades later.

Most of the case-control and cohort studies of attained height and risk of breast cancer suggest a modest positive association (390). In a follow-up of the National Health and Nutrition Examination Survey-I (NHANES-I) population in which women at risk for malnutrition had been oversampled, a nearly twofold increase in risk was observed across the range of height (391). In a pooled analysis of large cohort studies (4,385 cases among 337,819 women), the RRs for an increment of 5 cm of height were 1.02 (95% CI, 0.96–1.10) for premenopausal women and 1.07 (95% CI, 1.03–1.12) for postmenopausal women (392) (Fig. 18-11) and in a meta-analysis of 15 published cohort studies, the relative risk for a 5 cm

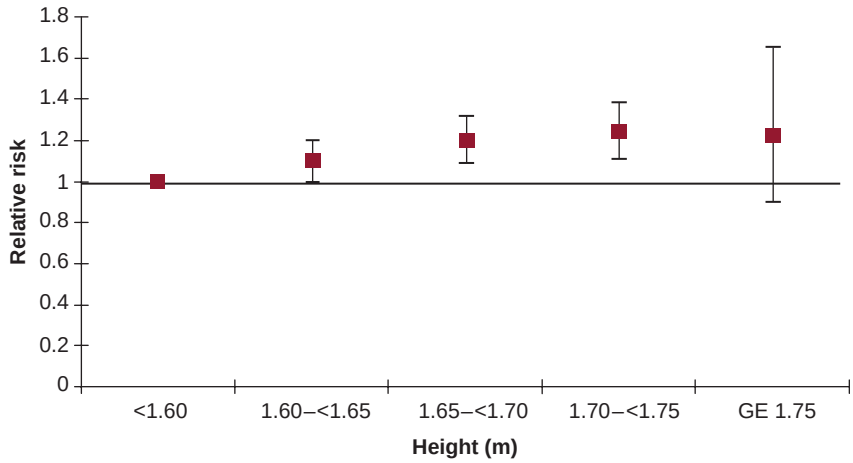


FIGURE 18-11 Results of prospective studies of the association between height and breast cancer. (Adapted from van den Brandt PA, Spiegelman D, Yaun SS, et al. Pooled analysis of prospective cohort studies on height, weight, and breast cancer risk. *Am J Epidemiol* 2000;152:514–527.)

increment was 1.11 (95% CI, 1.09–1.13) among postmenopausal women and 1.09 (95% CI, 1.05–1.14) among premenopausal women (393). In the studies of Vatten and Kvinnsland (394,395), the positive trend between height and risk of breast cancer was most nearly linear in the birth cohort of women who lived through their peripubertal period during World War II (1929–1932), a time in which food was scarce and average attained greater height reduced. Collectively, these data provide convincing evidence that attained greater height is associated with a modest increased risk of breast cancer.

Age at menarche, an established risk factor for breast cancer, provides a second indirect indicator of energy balance during childhood. Nutritional factors, in particular energy balance, appear to be the major determinants of age at menarche. In prospective studies among young girls, the major predictors of age at menarche were weight, height, and body fatness (396–399). A marginally significant inverse association between dietary fat and age at menarche was seen in one study (398), but no relation was observed in others. The potential for energy balance to influence breast cancer risk through age at menarche is greater than might be appreciated by examining the distribution of this variable in modern Western countries. Although the average age at menarche in these countries is now 12 to 13 years, in rural China the typical age has been approximately 17 to 18 years (400), similar to that of Western countries 200 years ago. An effect of growth rate on breast cancer risk may begin even before birth, because an inverse relation between birth weight and breast cancer risk has been observed mainly in premenopausal women (401,402).

The relation between preadolescent body fatness and risk of breast cancer appears to be complex; even though greater adiposity reduces the age at menarche, adiposity at this age has been associated with lower rather than greater risk of breast cancer (401,403). Notably, in the Nurses' Health Study II cohort, women who were the most overweight at ages 5 and 10 had only half the risk of breast cancer before menopause compared to those who were the leanest at these ages (403), and adjustment for age at menarche had little effect on this association. This finding has been hypothesized to be due to earlier differentiation of breast tissue and reduced susceptibility to carcinogens (401), but further examination of these relationships is needed.

The mechanisms by which age at menarche and attained height are related to risk of breast cancer are probably multiple. Early onset of menstrual cycles exposes the breast to ovarian hormones at a younger age and for a longer duration over a lifetime. Also, in several studies, an early age at menarche has been associated with higher estrogen levels at later ages (404). Height has been suggested to be a surrogate for mammary gland mass (405), which may be related to higher risk, or it may be a surrogate for exposure to high levels of IGF-I or other anabolic hormones during childhood. IGF-I is directly involved in regulation of growth during childhood and is hypothesized to increase risk of breast cancer, although the relation of blood levels during adulthood to cancer risk is complex and remains unsettled (406). IGF-I levels are in part determined by genetic factors, but energy restriction reduces IGF-I levels, and infusion of IGF-I appears to negate the effects of energy restriction tumorigenesis in animals (407). Also, high consumption of dairy products increases blood levels of IGF-I (408–414), and in addition it appears to accelerate growth in height (413,415,416). However, data on milk consumption during childhood and risk of breast cancer are limited.

Weight and Weight Change during Adulthood

Attained weight and weight change in adults provide sensitive measures of the balance between long-term energy intake and expenditure. Although the relation between these variables and breast cancer risk has been complex and confusing, recent findings provide a coherent picture and indicate a major contribution of weight gain during adulthood clearly contributes importantly to risk of postmenopausal breast cancer risk. Two reproducible findings have been particularly enigmatic: (a) In affluent Western populations with high rates of breast cancer, measures of body fatness have been *inversely* related to risk of premenopausal breast cancer; and (b) body fatness after menopause has been only weakly related to postmenopausal breast cancer risk despite strong associations between body fat and endogenous estrogen levels.

The inverse relation between body weight (typically used as body mass index [BMI], calculated as weight in kilograms divided by height in meters squared, to account for variation in height) and incidence of premenopausal breast cancer has been consistently seen in recent prospective studies (283,392,393). In the most recent meta-analysis the relative risk for a 2-unit increment in BMI was 0.94 (95% CI, 0.92–0.95) (393). Little relation of BMI to breast cancer mortality has been observed in premenopausal women, probably because delayed detection and diagnosis in heavier women counterbalances the lower incidence among heavier women. Heavier premenopausal women, even at the upper limits of what are considered to be healthy weights, have more irregular menstrual cycles and increased rates of anovulatory infertility (417), suggesting that their lower risk may be due to fewer ovulatory cycles and less exposure to ovarian hormones. Increased rates of menstrual irregularity and anovulatory infertility are also seen among very lean women, but such women are uncommon in Western populations. Although irregular menstrual cycles have been associated with reduced risk of breast cancer (61), adjustment for details of menstrual characteristics accounted for little of the inverse relation between BMI and risk of premenopausal breast cancer (418). This suggests that other factors, yet to be determined, account for most of the lower risk of breast cancer among overweight premenopausal women.

In both case-control and prospective studies conducted in affluent Western countries, the association between BMI and risk of breast cancer among postmenopausal women has often been only weakly positive or nonexistent (352,390,392). The lack of a stronger association has been surprising because obese postmenopausal women have plasma levels of endogenous estrogens nearly twice as high as those of lean women, because of conversion of androstenedione to estrogens in adipose tissue, and levels of SHBG are lower (419). The lack of a stronger positive association appears to be due to two factors. First, like the protective effect of early pregnancy, the reduction in breast cancer risk associated with being overweight in early adult life appears to persist through later life (283,420). Thus, an elevated BMI in a postmenopausal woman represents two opposing risks: a protective effect due to the correlation between early weight and postmenopausal weight and an adverse effect due to elevated estrogens after menopause. For this reason, weight *gain* from early adult life to after menopause should be more strongly related to postmenopausal breast cancer risk than would attained weight. Indeed, the relation between weight gain and risk of postmenopausal breast cancer has been consistently supported by both case-control (421–423) and prospective studies (283,393,420,424,425). A second reason for failing to appreciate a greater adverse effect of excessive weight or weight gain on risk of postmenopausal breast cancer is that the use of postmenopausal hormones obscures the variation in endogenous estrogens due to

adiposity and elevates breast cancer risk regardless of body weight (283,425). To appreciate fully the impact of weight or weight gain, an analysis should be limited to women who never used postmenopausal hormones. Thus, among women who never used postmenopausal hormones in the Nurses' Health Study, those who gained 25 kg or more after age 18 years had double the risk of breast cancer compared with women who maintained their weight within 2 kg (283) (Fig. 18-12). In this population, the combination of either using postmenopausal hormones or gaining weight after age 18 years accounted for one-third of postmenopausal breast cancer cases. Greater BMI has generally been more strongly associated with breast cancer mortality than with incidence (283,426). This may relate to greater difficulty in detecting small tumors in fatter breasts, which could influence prognosis, as well as the greater endogenous estrogen levels.

The relation between body weight and breast cancer risk among lower risk mainly non-Western countries is somewhat different in higher risk countries (427). In general, the inverse relation between weight and premenopausal breast cancer risk has not been observed, and the association between weight and postmenopausal risk has been stronger. This difference is likely to be due to the lower prevalence of overweight among premenopausal women in these low-risk countries; few women are likely to be sufficiently overweight to cause anovulation and a reduction in premenopausal breast cancer risk. As a result, BMI after menopause would only reflect the adverse effects of high endogenous estrogens, unopposed by a residual protective effect due to correlation with overweight in early adult life.

In summary, as in animal studies, energy balance appears to play an important but complex role in the causation of human breast cancer. During childhood, rapid growth rates accelerate the occurrence of menarche, an established risk factor, and result in greater attained stature, which has been consistently associated with increased risk. During early adult life, overweight is associated with a lower incidence of breast cancer before menopause, but no reduction in breast cancer mortality. However, weight gain after age 18 years is associated with a graded and substantial increase in postmenopausal breast cancer that is seen most clearly in the absence of hormone replacement therapy.

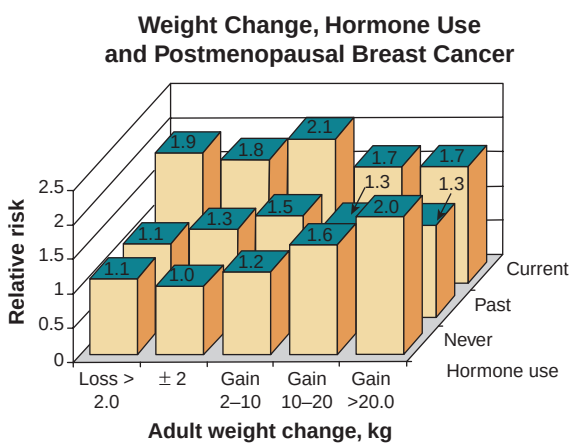


FIGURE 18-12 Relative risk (RR) of breast cancer by adult weight change and hormone use among postmenopausal women. (Reproduced from Huang Z, Hankinson SE, Colditz GA, et al. Dual effects of weight and height gain on breast cancer risk. *JAMA* 1997;278:1407–1411, with permission.)

Carbohydrates, Glycemic Index, and Glycemic Load

Higher intakes of carbohydrates increase blood insulin levels, which have been hypothesized to promote tumor growth. Glycemic index (GI) is a measure of carbohydrate quality, referring to the incremental elevation in blood glucose levels after a standard amount of carbohydrate, and glycemic load (GL) combines the amount of carbohydrate in a food or diet and its glycemic index (428). The adverse metabolic response to glycemic load is augmented by underlying insulin resistance in epidemiologic studies often represented by BMI (429). Among premenopausal women, carbohydrate intake and glycemic load tended to be inversely related to risk of breast cancer among lean women, but positively associated with risk among postmenopausal women (430). In a recent meta-analysis of prospective studies, greater glycemic index, but not glycemic load or carbohydrate intake, was associated with a small increase in risk of breast cancer (429,431). In the large EPIC study, GI, GL, and carbohydrate intake were not related to overall risk of breast cancer. However, among postmenopausal women, GL and carbohydrate intake were significantly associated with an increased risk of estrogen receptor-negative tumors (comparing highest vs. lowest quintiles for glycemic load RR = 1.36; 95% CI, 1.02–1.82; p-trend = 0.01), and for carbohydrate intake the relative risk was 1.41 (95% CI, 1.05–1.89; p-trend = 0.009) (432). Because these are potentially important findings, further examination of these relationships by hormone receptor status is needed.

Dietary Fiber

Diets high in fiber have been hypothesized to protect against breast cancer, perhaps due to inhibition of the intestinal reabsorption of estrogens excreted via the biliary system. A high-fiber diet was associated with reduced incidence of mammary cancer in animals (386). Dietary fiber includes crude fiber that is excreted unchanged, and various soluble fiber fractions that may have different biologic effects. In a meta-analysis of 10 case-control studies with estimates of dietary fiber intake, a statistically significant RR of 0.85 for a 20-g/day increase in dietary fiber was observed (352). In a recent meta-analysis of 16 cohort studies, a significantly lower risk of breast cancer among women with the highest compared to lowest intakes was seen in only one study (433). However, a weak, statistically significant inverse association was seen in the combined analysis; the RR for highest versus lowest intake of total dietary fiber was 0.93 (95% CI, 0.89–0.98). When examined separately, no significant association was seen for intakes of fiber from fruits, vegetables, or cereals.

Micronutrients

Vitamin A

Vitamin A consists of preformed vitamin A (retinol, retinyl esters, and related compounds) from animal sources and certain carotenoids found primarily in fruits and vegetables that are partially converted to retinol in the intestinal epithelium (carotenoid vitamin A). Many carotenoids are potent antioxidants and thus may provide a cellular defense against reactive oxygen species, which damage DNA. Vitamin A is also a regulator of cell differentiation and may prevent the emergence of cells with a malignant phenotype. Retinol inhibits the growth of human breast carcinoma cells *in vitro* (434), and retinyl acetate reduces breast cancer incidence in some rodent models (435).

In the earliest large case-control study of total vitamin A intake (retinol plus carotenoids vitamin A) (351), a significant

inverse trend was seen (RR of 0.8 for highest vs. lowest quartile of vitamin A intake). In a meta-analysis of nine other case-control studies with data on vitamin A intake (352), a significant inverse association between total vitamin A and breast cancer was reported. However, when preformed vitamin A and carotenoids were examined separately, the data from these case-control studies are more strongly supportive of a protective association for carotenoid vitamin A than for preformed vitamin A. In more recent case-control studies, inverse associations were observed between dietary intakes of β-carotene and lutein/zeaxanthin and risk of breast cancer in premenopausal women (436).

Prospective data have supported a modest inverse relation between carotenoids and breast cancer. In a cohort of Canadian women (519 cases) (437), a marginally significant protective association between total vitamin A intake and breast cancer was seen, with both preformed vitamin A and β-carotene contributing to the inverse association. With 14 years of follow-up in the Nurses' Health Study (2,697 cases), an inverse association with total vitamin A was seen only among premenopausal women (438). This inverse association was primarily accounted for by carotenoid sources of vitamin A; when specific carotenoids were examined, intakes of β-carotene and lutein/zeaxanthin were associated with reduced risk, but intake of lycopene was not. In a recent pooled analysis including 18 cohort studies and over 33,000 incident cases of breast cancer, higher intakes of β-carotene, α-carotene, and lutein/zeaxanthin were inversely associated with risk of estrogen receptor-negative breast cancer (439). For the highest versus lowest quintile of β-carotene, the relative risk was 0.84 (95% CI, 0.77–0.93). No association was seen for estrogen receptor-positive tumors.

An alternative to the dietary assessment of vitamin A intake and carotenoids is the measurement of vitamin A-related compounds in blood. Studies of blood retinol are minimally informative about vitamin A intake in well-nourished populations because the liver maintains relatively constant blood retinol concentrations. However, blood levels of β-carotene do reflect β-carotene intake. In a meta-analysis, blood levels of β-carotene were more strongly and consistently associated with lower risk of breast cancer than was dietary intake of β-carotene (440). In a recent pooled analysis of primary data from prospective cohort studies, including 3,055 cases of breast cancer, inverse associations were seen with blood levels of α-carotene, β-carotene, lutein/zeaxanthin, and total carotenoids (441). The association with β-carotene was stronger for estrogen-receptor-negative tumors (for highest vs. lowest quintile, RR = 0.52; 95% CI, 0.36–0.77) than for estrogen receptor positive tumors (RR = 0.83; 95% CI, 0.66–1.04; test for heterogeneity by receptor status = 0.01). Recent progress in genomics has identified variants in the β-carotene monooxygenase genes, which convert β-carotene to two molecules of retinol, and thus influences plasma β-carotene intake independent of dietary intakes. Following the concept of "Mendelian randomization," evidence that these genetic variants are related to risk of breast cancer would provide strong support for the role of β-carotene (or its precursors). In an analysis examining these genetic variants in relation to risk of breast cancer, no association was seen (442). However, the confidence intervals were too wide to exclude the effect predicted by published associations between blood carotenoids and incidence of breast cancer; very large sample sizes are needed for such analyses.

Thus, available data are suggestive of a modest protective effect of vitamin A intake on breast cancer, although the evidence is stronger for benefits of carotenoid sources of vitamin A. Also, evidence of benefit for β-carotene is stronger for ER- tumors. However, it is possible that other anticarcinogens in vegetables and fruits, including carotenoids such as lutein, are responsible for the apparent benefits. Ideally, the effect of vitamin A supplements, in the form of either preformed vitamin A or carotenoids, should be evaluated in randomized trials. In a randomized trial of fenretinide, a powerful synthetic retinoid, in the prevention of contralateral breast cancer among women already diagnosed with a first breast cancer, no overall effort was seen (443), although a significant benefit was seen in premenopausal women. The Women's Health Study of 40,000 female health professionals was a randomized trial designed to test whether β-carotene or vitamin E supplements reduce breast cancer risk. However, the β-carotene arm was terminated in 1996 after reports from trials in Finland and the United States that β-carotene supplements appeared to increase risk of lung cancer among smoking men. Thus, data from randomized trials on specific carotenoids and breast cancer risk, particularly among premenopausal women, may never be available.

Vitamin E

Vitamin E is also an antioxidant and has inhibited mammary tumors in rodents in some, but not all, experiments (444). Although relatively few studies have assessed the association between dietary vitamin E (α-tocopherol) intake and breast cancer, evidence of benefit has not been seen in prospective studies (437,438,445,446), including with high doses of supplement use for long durations. In a 10-year randomized trial using 600 IU of vitamin E on alternate days, there was no effect on breast cancer incidence (447).

Vitamin C

Vitamin C (ascorbic acid) is also an antioxidant that can block the formation of carcinogenic nitrosamines. Few animal studies have assessed the effect of vitamin C on mammary cancer; in a study in rats, there was no effect of ascorbic acid on the growth of either transplanted or dimethyl benzanthracene–induced mammary tumors (448).

In a meta-analysis of nine case-control studies with data on vitamin C (352), a significant inverse association (RR = 0.7 for each 300-mg/day increase in vitamin C) was observed. However, in prospective studies, intake of vitamin C has not been associated with risk of breast cancer (437,438,445,446,449,450). In the 14-year follow-up of the Nurses' Health Study, no evidence of any reduction in risk was seen with long-term use of vitamin C supplements (438). Thus, the available prospective data do not support benefits of high vitamin C intake for reducing breast cancer risk.

Vitamin D

Vitamin D and its metabolites can reduce cell proliferation, enhance apoptosis, and inhibit tumor progression in animal models (451). Epidemiologic studies provide some support for reduced risk of breast cancer with higher intake, particularly in premenopausal women (452–454). However, vitamin D is unique among nutrients in that the dominant source is obtained by the action of sunlight on a precursor molecule in the skin, rather than by diet. Plasma levels of 25-OH vitamin D (25(OH)D) provide an integrated biomarker of vitamin D from all sources that can be used in epidemiologic studies. Although many studies have shown an inverse relation between plasma 25-OH vitamin D levels and risk of colon cancer (455), the epidemiologic evidence is less clear for breast cancer (456). Eleven nested case-control and retrospective studies have been conducted, and in only two was a significant inverse association observed (457). In

a meta-analysis of these 11 studies, a modest and marginally significant inverse relation was seen (summary relative risk comparing the highest with the lowest category = 0.86 (95% CI, 0.75–1.00) (457). A second meta-analysis restricted to nine prospective studies found a nonlinear inverse association among postmenopausal women, whereby between the range of 27-<35 ng/mL, a 5 ng/mL increase in 25(OH)D was associated with a 12% lower risk of breast cancer (RR = 0.88 per 5 ng/mL; 95% CI, 0.79–0.97) (458). In contrast, no association was found among premenopausal women. In addition to possibly reducing incidence of breast cancer, higher intakes or blood levels after diagnosis could potentially improve prognosis. However, in several studies utilizing blood samples collected after diagnosis, no relation with recurrence was seen (456). Because 25-OH vitamin D levels can be readily increased by supplements, resolution of the relationship between vitamin D and risk of breast cancer should be a high priority.

Selenium

Selenium, an important component of the antioxidant enzyme glutathione peroxidase, inhibits cell proliferation and in animal studies protects against a variety of cancers, although usually at high levels of intake (459). Ecologic studies have shown strong inverse associations between county-specific (in the United States) and national measures of selenium exposure and breast cancer rates (460). Selenium intake cannot be measured accurately by means of dietary assessment in geographically dispersed populations because of the high variability in the selenium content of individual foods, depending on the geographic area in which the foods were grown. However, selenium levels in tissues such as blood and toenails do reflect selenium intake (461) and thus provide an informative measure of diet.

Several studies using these biomarkers of selenium intake have been performed. In most prospective studies (462–464), no association between toenail selenium and risk of breast cancer has been observed. Of the prospective studies, only that of Knekt et al. (465) from Finland showed any evidence of an increased risk among women in the lowest category of selenium. Because Finland at that time had extremely low selenium intakes, this observation is consistent with the possibility that a threshold exists below which low selenium intake does increase breast cancer risk. In a small randomized trial, breast cancer was the only malignancy that occurred more often among those receiving selenium supplements (466). Taken together, these data suggest that increases in selenium intake are unlikely to reduce risk of breast cancer in countries with existing moderate or high levels of selenium intake.

Other Dietary Constituents

Alcohol

Substantial evidence now supports the existence of a positive association between alcohol consumption and breast cancer risk (393). In a pooled analysis of the six largest cohort studies with data on alcohol and dietary factors (467), the risk of breast cancer increased monotonically with increasing intake of alcohol (Fig. 18-13) with no statistical evidence of heterogeneity among studies. For a 10-g/day increase in alcohol, breast cancer risk increased by 9% (95% CI, 4–13%, and in the Million Women's Study a small but statistically significant excess was seen beginning at one drink per day (468). In an update of the Nurses' Health Study with 28 years of follow-up and repeated measures of alcohol consumption, a 15% increase in risk was seen even with 2 to 6 drinks per week (469). Alcohol consumption both before and after age 40 independently contributed to risk. In these analyses, adjustment for known breast cancer risk factors and dietary variables hypothesized to be related to breast cancer had little impact on the association with alcohol. In the collective literature, beer, wine, and liquor all contribute to the positive association (393,467,469-471), strongly suggesting that alcohol *per se* is responsible for the increased risk.

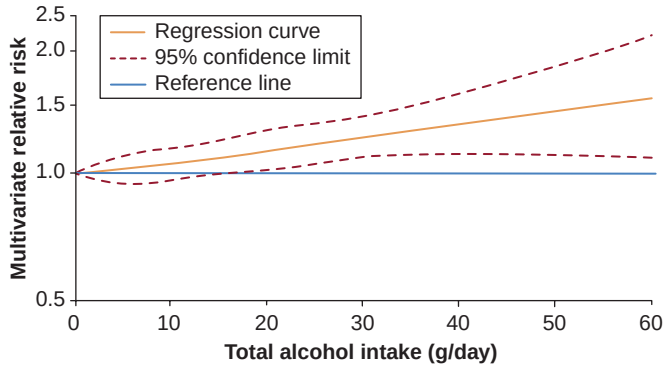


FIGURE 18-13 Nonparametric regression for the relationship between total alcohol intake and breast cancer. One drink of beer, wine, or liquor equals 10 to 15 g of alcohol. (From Smith-Warner SA, Spiegelman D, Yaun S-S, et al. Alcohol and breast cancer in women: a pooled analysis of cohort studies. *JAMA* 1998;279:535–540, with permission.)

Whether reducing alcohol consumption in middle life will decrease risk of breast cancer is an important practical issue. In one early report (472), women who drank before age 30 years and later stopped experienced a similar elevation in risk compared to those who continued to drink. However, in a large study designed to address this issue (473), recent consumption of three or more drinks per day was associated with an RR of 2.2, whereas the RR was 0.9 for consumption of three or more drinks per day from aged 16 to 29 years. This suggests that recent adult drinking may be more important than drinking patterns earlier in life and that reductions in consumption in midlife should reduce risks of breast cancer.

In short-term intervention studies, consumption of approximately two alcoholic drinks per day increased total and bioavailable estrogen levels in premenopausal women (474), and single doses of alcohol acutely increased plasma estradiol levels in postmenopausal women (475), suggesting a mechanism by which alcohol may increase breast cancer risk. In a cross-sectional study, alcohol intake was associated with elevated plasma levels of estrone sulfate, a long-term indicator of estrogen status (419), which in turn has been associated with future risk of breast cancer (124). In several large prospective studies, high intake of folic acid appeared to mitigate the excess risk of breast cancer due to alcohol, although the findings have not been consistent (470,476–479). This relationship was confirmed using plasma folic acid levels (480). Because alcohol inactivates folic acid metabolites and low folate levels are associated with increased misincorporation of uracil into DNA, this finding suggests another possible mechanism for the adverse effects of alcohol.

Of all the associations between dietary factors and breast cancer risk, the relation with alcohol is by far the most consistent. This association has been observed in many diverse

populations, and rigorous attempts to account for this relation by other variables have been unsuccessful. Moreover, the effect of alcohol on endogenous estrogen levels provides a plausible mechanism. Together, this body of data provides strong evidence for a causal relationship between alcohol consumption and breast cancer risk. However, the public health implications of this knowledge are complicated by the fact that consumption of one to two alcoholic beverages per day is almost certainly protective against cardiovascular disease. Because cardiovascular disease is the leading cause of death among women, moderate drinking is associated overall with a modest reduction in total mortality among groups with appreciable risk of coronary heart disease (481). This would not apply to young adults or those with very low levels of risk factors. Although still complex, reduction of daily alcohol consumption appears to be one of relatively few methods for actively reducing breast cancer risk, whereas many methods exist to reduce risk of cardiovascular disease. For women choosing to consume alcohol regularly, use of a multivitamin to assure adequate folic acid intake appears prudent.

Coffee and Tea

Considerable speculation that caffeine may be a risk factor for breast cancer followed a report that women with benign breast disease experienced relief from symptoms after eliminating caffeine from their diet. In prospective studies, no increase in breast cancer risk has been seen with intakes of caffeine or its main sources, coffee or tea (449,482–484), and in one (485) a weak, but significant, inverse association between coffee and caffeine consumption and breast cancer risk was observed. Similarly, no evidence for an association between tea consumption and risk of breast cancer has been seen in epidemiologic studies (486). Thus, the epidemiologic evidence is not compatible with any substantial increase in breast cancer risk associated with drinking coffee or tea.

Phytoestrogens

Phytoestrogens in soy products have attracted scientific and popular attention, in part because they are highly consumed in Asian countries, such as Japan and China, which have low rates of cancer (487). These compounds, which include daidzen and genistein, can bind ERs but are much less potent than estradiol. Thus, these substances may act like tamoxifen by blocking the action of endogenous estrogens to reduce breast cancer risk. Dietary supplementation with a large amount of soy protein slightly lengthened menstrual cycle (488), which would be predicted to decrease breast cancer risk only minimally. Also, soy protein consumption is not the primary explanation for low rates breast cancer in Japan and China because rates are similarly low in other parts of China, elsewhere in Asia, and in many developing countries where soy and related foods are not regularly used. In case-control studies in Singapore (489) and China (490), and in Asian Americans (491), intake of soy products, particularly during adolescence, was associated with lower risk of breast cancer. However, in two other case-control studies in China (492,493) and in a prospective study from Japan (494), little relation was seen. However, in the large prospective Shanghai Women's Study (495), women who consumed a higher amount of soy during adolescence or early adulthood had a lower risk of premenopausal, but not postmenopausal, breast cancer. Thus, the overall evidence suggests that high consumption of soy products during adolescence or young adulthood, when endogenous estrogens are high, may reduce risk of breast cancer, but intakes later in life have little or no effect (495–497).

Another group of compounds formed from glucosinolates found in cruciferous vegetables (such as broccoli, cauliflower, and cabbage) are hypothesized to alter the balance of estrogen metabolism toward less potent forms, but data on humans have not been supportive (498). The possibility that phytochemicals that block the estrogen function or modulate estrogen metabolism may provide a nontoxic means of altering breast cancer risk has obtained some support from studies of soy consumption in Asia. Further data on the effect of amounts and ages when a benefit is possible would be valuable.

Specific Foods

Foods contain an extremely complex mix of essential nutrients and other compounds that could individually or collectively influence breast cancer risk in ways that may not be detected by the study of individual nutrients. Thus, an examination of foods and food groups in relation to risk of breast cancer could be informative. However, because the foods examined in most studies are too numerous to be reported individually, published results are likely to reflect a bias toward reporting findings that are statistically significant or that fit preexisting hypotheses.

Inverse associations between intakes of fruits and vegetables and breast cancer risk have been reported in a many case-control studies (471). These associations have been more consistent for vegetables than for fruits and for green vegetables in particular. However, in the pooled analysis of eight large prospective studies (7,377 cases among 351,825 women), only weak and nonsignificant associations were seen with increasing consumption of fruit and vegetables (498). Comparing highest to lowest quartiles, RRs were 0.93 (95% CI, 0.86–1.00) for total fruits, 0.96 (95% CI, 0.89–1.04) for total vegetables, and 0.93 (95% CI, 0.86–1.00) for total fruits plus vegetables. A thorough search among specific fruits and vegetables and botanical groups did not reveal any significant associations. A similar lack of association was seen in a large multicentered cohort study in Europe (499). In a meta-analysis of prospective studies that included over 16,000 cases of breast cancer, similar weak inverse associations to the earlier pooled analysis were seen, but the associations for total fruits and vegetables were statistically significant (500). For a 200-gram per day increment (about 2 servings per day), the RRs were 0.96 (95 % CI, 0.93–1.00) for total fruits and vegetables and 0.94 (95 % CI, 0.89–1.00) for fruits. Recent findings suggest that a reduction in risk of breast cancer with higher intakes of fruits and vegetables may be specific for estrogen receptor negative tumors (501); the relative risk comparing highest with lowest quintiles of vegetables intake was 0.68 (95% CI, 0.51–0.91) for ER- cancers but no association was seen with ER+ cancers. This specificity has been confirmed in the Black Women's Health Study (502) and the EPIC Study (503), and it is also consistent with the findings noted above for intake and blood levels of carotenoids.

Associations between red meat consumption and risk of breast cancer have been reported sporadically (504). However, in the pooled analysis of large cohort studies (7,379 cases) (505), no association was seen with consumption of red meat, white meat, or dairy products. In an analysis that retrospectively assessed degree of cooking (506), consumption of well-done red meat was associated with breast cancer incidence. This will require evaluation in prospective analyses. In a prospective study among premenopausal women, intake of red meat was associated with a two-fold increase in risk of breast cancers that were positive for estrogen and progesterone receptors (373). Fat *per se* was not associated with breast cancer risk, suggesting that

other constituents of red meat consumed early in adult life may increase breast cancer risk. Approximately half of this cohort also completed a detailed questionnaire about their diet during high school; consumption of red meat during this period was also associated with risk of premenopausal breast cancer (375). This finding is consistent with a greater susceptibility of breast tissue to carcinogens during this period of life but needs replication; unfortunately, few such studies exist.

Although a protective effect of fish consumption has been suggested in a few studies, the overall evidence from case-control and cohort studies suggests little relationship (505). Intake of nuts and legumes has received limited attention in reports on diet and breast cancer, but in general, no relation has been seen (471,486).

Dietary Patterns

Overall dietary patterns have been examined in relation to breast cancer incidence. In the Nurses' Health Study, the Alternative Healthy Eating Index and a Mediterranean dietary pattern were associated with a lower risk of ER- but not ER+ breast cancer (501); this association was mainly due to higher intake of fruits and vegetables. Notably, the Healthy Eating Index, reflecting the 2000 U.S. dietary guidelines, was not associated with risk of either lower risk of either ER+ or ER- breast cancer. Similar findings for a Mediterranean dietary score were seen in the EPIC study (for high compared to low score, the relative risk of ER+/PR- tumors was HR 0.80; 95% CI, 0.65-0.99, p for trend = 0.04) (503).

Diet and Breast Cancer Survival

Regardless of whether diet is related to the occurrence of breast cancer, if postdiagnosis diet were related to risk of recurrence or survival, then dietary modifications might assist in breast cancer treatment. In one study of diet after diagnosis (albeit in the 1 to 5 months immediately after the diagnosis), no association was seen between dietary fat intake and survival (507). Among premenopausal women, higher consumption of butter, margarine, and lard after diagnosis was associated with greater likelihood of reoccurrence (508). In a larger study, diet was assessed before and after breast cancer diagnosis (509). Greater fat intake after diagnosis was associated with a nonsignificantly worse survival outcome. However, higher protein consumption, mainly from poultry, fish, and dairy sources, was related to a better prognosis, even after controlling for protein consumption prior to diagnosis. Although overall dietary patterns after diagnosis were not associated with breast cancer mortality in this cohort, a prudent dietary pattern was associated with lower mortality, and Western pattern with higher mortality, from causes other than breast cancer (510). Similarly, higher intake of trans fat and saturated fat after diagnosis of breast cancer was associated with higher overall mortality, although not breast-cancer-specific mortality (511). This is important because with early diagnosis and good treatment, the large majority of women will survive their breast cancer, but they remain at risk for diseases of women in general.

In a recent pooled analysis, alcohol consumption after diagnosis of breast cancer has overall not been associated with survival (512), although a marginally significant increase in recurrence was seen in postmenopausal women. Also in a pooled analysis, higher soy consumption after diagnosis was associated with a nonsignificantly lower risk of breast-cancer-specific mortality, and a significantly lower risk of breast cancer recurrence (513). Also, regular use of supplements of vitamin E and vitamin C was associated with lower risk of breast cancer recurrence (514).

Several randomized trials have been conducted among women with early-stage breast cancer to determine the effects of dietary change on recurrence or mortality. In one trial, 2,437 women with breast cancer were randomized to a low fat diet or their usual diet and followed for an average of 5 years (515). Dietary fat intake was reduced to 33 grams per day in the intervention group compared to 51 grams per day in the control group, and weight was also six pounds lower in the intervention group. In a preliminary report, 9.8% of women in the intervention group experienced a relapse compared to 12.4% of women in the control group (RR = 0.76; 95% CI, 0.60–0.98, p = .077 for stratified log rank test and p = .034 for adjusted Cox model analysis). These results were suggestive of a possible benefit of the intervention, but not conclusive, and it is not possible to know whether any benefit is due to reduction of fat intake or lower weight gain (potentially due to the intense intervention because the overall evidence does not support a specific benefit of fat reduction on body weight).

In another trial among 3,088 women, one group was assigned to a diet high in fruits, vegetables, and fiber and low in fat (516). During an average of 7.3 years of follow-up, 256 women in the intervention group (16.7%) versus 262 in the comparison group (16.9%) developed an invasive breast cancer event (RR = 0.96; 95% CI, 0.80–1.14; p = .63), and 155 intervention women in the intervention group (10.1%) versus 160 women in the control group (10.3%) died (RR = 0.91; 95% CI, 0.72–1.15; p = .43). The increase in fruit and vegetable consumption was large, and documented by a 50% increase in blood carotenoid level, but the reported difference in fat intake was small (-15%), so this study primarily tested the benefit of increasing fruit and vegetable intake.

Summary of Diet and Breast Cancer

The role of specific dietary factors in breast cancer causation is not completely resolved. Enthusiasm for the hypothesis that dietary fat intake was responsible for the high rates of breast cancer rates in Western countries was based largely on the weakest form of epidemiologic evidence—ecologic correlation studies. Results from prospective studies and randomized trials do not support the concept that fat intake in middle or later life has a major relation to breast cancer risk. Excess energy intake in relation to physical activity during adulthood, which accelerates growth and the onset of menstruation during childhood, leads to weight gain in middle life and thus can contribute substantially to breast cancer risk. These effects of energy balance clearly account for an important part of international differences in breast cancer rates. Some evidence suggests that carotenoids or other compounds in carotenoid-rich foods may reduce breast cancer risk modestly, but these findings are not conclusive and deserve further consideration. Alcohol intake, even at very low levels, is a well-established risk factor for breast cancer, and studies demonstrating that even moderate alcohol intake increases endogenous estrogen levels provide a potential mechanism, thus supporting a causal interpretation. Diet during childhood has been relatively unstudied, but recent evidence suggests that higher intake of soy products and lower intake of red meat during this period may reduce risk of breast cancer. Other recent findings suggest that characterization of breast cancers by hormone receptor status, and potentially other features, may be important in studies of diet. A Mediterranean dietary pattern, higher intakes of vegetables and fruits, and lower intake of carbohydrates and glycemic load appear to be related specifically

to risk of ER- breast cancer. Because of the importance of ER- breast cancer and limited progress in the identification of preventive strategies, these findings are promising and need to be pursued further.

Although our understanding of diet and breast cancer is incomplete, evidence can be considered conclusive that breast cancer risk can be reduced by avoiding weight gain during adult years and by limiting alcohol consumption. Although less conclusive, some evidence suggests that breast cancer risk can be modestly reduced by limiting intake of red meat during early adult life, by replacing saturated fat with monounsaturated fat, and by consuming more fruits, vegetables, and whole grains (which characterizes the Mediterranean dietary pattern). Even with some uncertainty regarding their relationships with breast cancer, these dietary behaviors can be strongly recommended because they will substantially reduce risks of coronary heart disease (354) and diabetes (517).

PHYSICAL ACTIVITY

Regular physical activity has been hypothesized to prevent breast cancer and in 2002 the International Agency on Cancer Research concluded that there was "convincing" evidence that physical activity reduces the risk of breast cancer (518). A number of potential mechanisms have been proposed including changes in menstrual cycle characteristics, lowering sex hormones and insulin-like growth factors, and/or improving immune function (519,520). A recent review of potential mechanisms concluded that BMI and estrogens were the most likely links between physical activity and breast cancer risk (521). The mechanisms by which physical activity reduces exposure to hormones vary by period of life. Young girls participating in strenuous athletic training such as running and ballet dancing have delayed menarche (522–524), which is known to reduce risk of breast cancer, and even moderate-intensity physical activity may delay menstruation (398). This effect of activity at young ages may be reflected in lower body weight and body fat, both of which are determinants of delayed menstruation (399,522). A later menarche is associated with a later onset of regular ovulatory cycles and lower serum estrogen concentrations during adolescence (525). Once menstruation has been established, anovulatory and irregular menstrual cycles may be more common among moderately and strenuously active women than among inactive women (396,524,526), although there is disagreement regarding the degree to which the intensity of physical activity influences menstrual abnormalities (527). Further, a substantial degree of ovarian dysfunction may occur even among physically active women who appear to have normal menstrual cycles (528). Among older women, levels of past and current physical activity influence fat stores (522,523,528–531), which after the menopause are primary sites of conversion of androstenedione to estrogen (532,533).

A number of epidemiologic studies have reported an inverse association between physical activity and postmenopausal breast cancer, although the evidence is less consistent for premenopausal breast cancer (519,520,534–537). However, there are a number of aspects regarding this association that remain unclear. Methodologic differences in physical activity assessment are likely to have contributed to inconsistencies in study results. Studies have differed in the ages at which physical activity was assessed, methods for measuring intensity, frequency, and duration of physical activity, definition and categorization of physical activity levels (including consideration of only recreational, or recreational and occupational, activity), and age at breast cancer diagnosis. However, results have varied even among studies that have tried to assess physical activity at similar times in life using similar tools.

One of the strongest reductions in breast cancer risk associated with increased physical activity was reported in a population-based case-control study of women younger than 40 years (538). The RR was 0.42 (95% CI, 0.27–0.64) comparing women with a lifetime average of 3.8 hours or more of physical activity per week to those with an average of 0 hours per week. This was the first study explicitly devoted to the relationship between physical activity and breast cancer, and it was also the first to use a detailed physical activity assessment instrument to quantify the average number of hours per week of recreational physical activity over the reproductive life span, beginning at menarche. Activities such as housework, gardening, and easy walking not for the explicit purpose of physical exercise were not counted in the measure of physical activity. These researchers concluded from their various analyses that lifelong physical activity is the critical exposure of interest with regard to breast cancer risk.

Since publication of this study, many other studies (537,539–554) have assessed the relationship between lifetime physical activity and breast cancer risk. In one of these studies (547), results support those reported above, with reduced risk of breast cancer in premenopausal women with higher lifetime physical activity. The RR for average lifetime total activity was 0.77 (95% CI, 0.64–0.93) comparing the equivalent of 3.25 hours or more of running/jogging per week to those with less activity. In contrast, another study found no association between activity in earlier periods of life and postmenopausal breast cancer (548).

Types of activity are widely varied across individuals, as well as across studies. Broad categories of recreational, household, and/or occupational activity have been assessed in many studies. In one study among postmenopausal women, recreational physical activity was not associated with breast cancer risk, whereas household and occupational physical activity was inversely associated with risk (odds ratio [OR] = 0.57, 95% CI, 0.41–0.79; and OR = 0.59, 95% CI, 0.44–0.81), comparing highest to lowest quartiles of household and occupational activity, respectively. The findings of inverse associations with household and occupational physical activity, but not with recreational activity, suggest that residual confounding by sociodemographic and reproductive factors are at least partly responsible for the observed inverse relationships. Among types of recreational activities, some studies have observed stronger associations for more moderate or vigorous activities, compared with less intense activities (555). However, even brisk walking appears to be beneficial, as was reported in one study (556).

A case-control study conducted among premenopausal and postmenopausal women in urban Shanghai (544) found significant inverse dose–response relationships between years of (recreational) exercise participation and breast cancer risk, as well as between lifetime occupational activity and breast cancer risk. In contrast, a case-control study nested within the Women's Health Study (543), which also assessed lifetime physical activity (recreational only), found no association between physical activity (lifetime or at any specific time in life) and breast cancer risk.

It has been hypothesized that high levels of physical activity during adolescence are particularly important with respect to influencing breast cancer risk. A retrospective cohort study of college alumnae (557) found that women who had been former college athletes had a 40% lower risk

of breast cancer later in life than their nonathletic peers (OR = 0.61, 95% CI, 0.44–0.84). However, other studies that have examined the association between physical activity during adolescence and breast cancer risk have found little evidence for a protective effect. Indeed, some studies have observed stronger associations with more recent, or later in life, physical activity.

In contrast to the detailed measurement of lifetime physical activity employed by some of the studies mentioned earlier, a relatively simple measure of physical activity was used in a prospective cohort study of Norwegian women aged 20 to 54 years at baseline (558). Over a period of 3 to 5 years, women were administered two surveys about their current patterns of physical activity during leisure hours; they were asked to rank themselves on a four-point scale with respect to activity level. The RR was 0.63 (95% CI, 0.42–0.95) for consistently active women compared to consistently sedentary women, which is one of the strongest RRs reported in the literature.

Several recent studies have examined physical activity by tumor type and survival. The association with invasive breast cancer appears consistent across several studies, while an association with in situ disease has been observed in some studies but not others (559,560). Although a few studies have observed differences in the association by hormone receptor status, the differences are not consistent, with some studies finding stronger associations with ER+ disease and others finding stronger associations with ER- disease (550,559,561). However, there are several studies that have investigated ER and/or ER/PR status and have found the reduced risk with physical activity to be apparent with both hormone receptor positive and negative tumors (547,548,556,562,563). A large pooled analysis of physical activity after breast cancer diagnosis reported reduced breast cancer mortality with at least 2.5 hours of moderate intensity physical activity per week, compared to those with lower activity (RR = 0.75; 95% CI, 0.65–0.85) (564). Risk of recurrence, however, was not reduced among those more physically active.

There would be obvious public health significance to an association between a modifiable lifestyle risk factor such as physical activity and breast cancer. There are already more than 70 observational epidemiologic studies of this issue, a number of them published in the last five years (547–550,552,556,559–561,563,565–573). Despite the wealth of data on the subject, it is difficult to come to a clear conclusion on the topic given numerous methodologic issues. These issues include the resolution of whether a critical lifetime period exists during which increased physical activity exerts its strongest effect on breast cancer risk, or whether lifetime physical activity is the critical exposure of interest for most women. It is also unclear if the effects of physical activity on breast cancer differ in particular subgroups of women. For example, studies have suggested the association is modified by family history of breast cancer (539,540,545,561), menopausal status (535,570), menopausal hormone therapy (561), or BMI (545,561,570,574). A second important issue relates to the quantification of physical activity and how information on frequency, intensity, duration, and time span of activity can and should be combined into a single measure or a small number of measures that can be readily modeled. A third issue pertains to the validity of women's reports of past physical activity. In case-control studies, random error in recall of past activity levels that is not dependent on disease status would be expected, on average, to dilute any inverse association that might truly exist. If errors are differential by disease status, however, findings may be biased in either direction away from their true point estimates. A fourth issue concerns the need to consider recreational, occupational, and household physical activity together. In studies of physical activity, the potential exists for confounding by reproductive characteristics for several reasons. Women in physically active jobs are more likely to be of lower socioeconomic status and thus may be more likely to have a lower risk reproductive profile. Women with higher levels of household activity may be more likely to be homemakers with children, and thus, again, to have a lower risk reproductive profile. Women with higher levels of recreational physical activity may be more likely to have lower levels of occupational and household activity; they may be more likely to be of higher socioeconomic status than women with lower levels of recreational activity and thus to have a higher risk reproductive profile. It is difficult in observational studies to control thoroughly for such potential confounding. Finally, although a hormonal mechanism linking physical activity and breast cancer risk has been postulated, there are few data relating physical activity over sustained periods to lower endogenous ovarian hormone levels. Available studies have been very short term, based on small numbers of women, and often limited to comparisons between young women who engage in high levels of activity and inactive young women.

Although numerous studies have examined the association between physical activity and risk of breast cancer, a number of issues remain unsettled. While the association appears somewhat weaker in cohort compared with case-control studies, taken together, the weight of the evidence suggests that regular physical activity modestly protects against breast cancer (518), and this is most evident for postmenopausal breast cancer. Evidence relating higher physical activity to risk of postmenopausal breast cancer is strong because of the important role of activity in controlling weight gain, an important cause of postmenopausal breast cancer. This, in addition to many other benefits of staying lean and fit, provides sufficient justification for including regular physical activity in daily life.

IONIZING RADIATION

More is probably known about radiation-induced breast cancer than about any other radiation-induced malignancy, with the possible exception of radiation-induced leukemia. The knowledge that ionizing radiation to the chest in cumulative moderate to high doses (e.g., 1 to 3 Gy) at young ages substantially increases breast cancer risk comes from several lines of evidence, including atomic bomb survivor studies, studies of diagnostic/therapeutic uses of radiation, and occupational studies.

Among survivors of the atomic bombing of Hiroshima and Nagasaki (575), breast cancer risk was strongly associated with estimated breast tissue dose of radiation. Further, the RR of breast cancer associated with each radiation dose depended heavily on the age at the time of the bombing, being highest for women exposed before age 10 years. For women exposed after age 40 years, there was no significant elevation in subsequent breast cancer risk.

Studies of diagnostic radiation have revealed a similar pattern of excess risk of breast cancer associated both with higher doses and with younger ages at exposure. In a study of women who received substantial radiation to the chest as a result of repeated fluoroscopic examinations for tuberculosis (576), the maximum excess risk was among women with first exposure between the ages of 10 and 14 years, whereas women first exposed at age 35 years or later had virtually no excess risk. Girls examined frequently for scoliosis with full

spinal x-rays also faced an increased risk of breast cancer later in life (577).

Studies of therapeutic radiation for nonmalignant and malignant disease have revealed the same pattern. In a study of women exposed to radiation therapy to the chest as treatment for Hodgkin's disease (578), the excess risk of breast cancer again was dependent on dose and age at irradiation. In a study of radiation treatment of breast cancer and development of second breast cancers (579), risk of second cases was significantly elevated (above its already high level) among women who underwent radiation at younger than 45 years. Women who are heterozygous for the ATM gene are hypothesized to be at increased risk of breast cancer and at increased risk of radiation-induced breast cancer (580). One report (581), however, found no ATM mutations in women with contralateral breast cancer and failed to support the hypothesis that ATM carriers account for a significant fraction of breast cancer cases that arose in women after radiation therapy. Studies of women who have developed subsequent breast cancer after radiation therapy for Hodgkin's disease also reported no association with ATM heterozygosity (582).

Studies of radionuclide therapy have shown that women treated with such regimens have an increased risk of breast cancer later in life. A German study of young persons injected with radium-224 for bone diseases in 1945 to 1955 showed subsequent high rates of bone cancer, and there was an increased risk of breast cancer observed in both women and men in the cohort (583).

Occupational studies provide a final set of evidence about radiation-induced breast cancer. Increased breast cancer incidence was observed among some groups of women who in the early part of the twentieth century painted watch dials and gauges with radium-226 (584); such increased risk has also been observed among women in China who pioneered in the fields of radiology and medical x-ray work (585). Some of this excess may have been due to higher breast cancer risk profiles of the women in such occupations, that is, a higher proportion of them tended to be nulliparous in comparison to the general population of women. The slightly increased risk of breast cancer observed among women who worked during World War II as x-ray technologists might have been due to nulliparity; there were a disproportionate number of Catholic nuns in these cohorts (586). Studies of women employed in subsequent times as x-ray technologists have not found this increased risk of breast cancer (587,588).

The risk associated with infrequent low-dose radiation exposure to the chest has been difficult to quantify, because the expected excess of breast cancers is small relative to the background risk (576). Thus, the risk of breast cancer associated with low-dose radiation, such as mammography, has been estimated by extrapolating the dose–response relationship from studies of women exposed to higher doses of radiation (589). In this way, <1% of all cases of breast cancer have been estimated to result from diagnostic radiography (589).

Genetic variation in DNA repair genes may modify the risk of breast cancer associated with low to moderate exposures of ionizing radiation (590). Initial studies among women with *BRCA1* and *BRCA2* mutations genes involved in the repair of double-strand breaks have reported inconsistent finding on the effect of exposure to mammography and chest x-rays on breast cancer risk among mutation carriers (591–593).

Additional studies of genetic variation and low-dose exposure to radiation may yield useful information about which women face an identifiably higher risk of radiation-induced breast cancer from mammographic surveillance.

ENVIRONMENTAL POLLUTION

Evidence of geographic variation in incidence and mortality rates of breast cancer within the United States, the steady increase in incidence over time, and the identification of suspected breast cancer clusters have stimulated interest in the possibility that industrial chemicals or electromagnetic fields may be environmental risk factors for breast cancer. The experimental and epidemiologic evidence for associations of certain specific synthetic chemicals with breast cancer are considered in the following sections and have been comprehensively reviewed with detailed citations elsewhere (594–597).

Organochlorines

Epidemiologic studies of breast cancer and environmental exposures to synthetic chemicals have concentrated on biologically persistent organochlorines. This class of compounds includes pesticides, such as 2,2-bis(*p*-chlorophenyl)-1,1,1-trichloromethane (DDT), chlordane, hexachlorocyclohexane (HCH, lindane), hexachlorobenzene (HCB), kepone, and mirex; industrial chemicals, such as polychlorinated biphenyls (PCBs) and polybrominated biphenyls (PBBs); and dioxins (polychlorinated dibenzofurans [PCDFs] and polychlorinated dibenzodioxin [PCDDs]), produced as combustion byproducts of PCBs or contaminants of pesticides. Many of these chemicals are weak estrogens and are, therefore, hypothesized to increase breast cancer risk by mimicking endogenous estradiol. Furthermore, they are excreted in breast milk, suggesting that ductal and other cells in the breast are directly exposed. Other compounds, specifically the dioxins and some PCB congeners, exhibit antiestrogenic activity; therefore, despite the established carcinogenicity of dioxin at other anatomic sites in animal tests, they might be protective against breast cancer.

The organochlorines are highly lipophilic and resistant to metabolism. Thus, many of these compounds bioaccumulate in the food chain and persist in the body. These chemicals can be measured in breast milk, adipose tissue, and blood. Most of the epidemiologic literature on organochlorines focuses on DDT, DDE (1,1-dichloro-2,2,-bis (*p*-dichlorophenyl)ethylene, the main metabolite of DDT), and PCBs because they are among the most persistent in humans. The general population was thought to be exposed to these compounds predominantly through ingestion of fish, dairy products, and meat. Almost everyone in the United States has had some measurable exposure; however, the average body burden of some of these chemicals (e.g., DDT) has been decreasing with time since the cessation of their production in this country (1972 for DDT and 1977 for PCBs).

In a study of PCB-contaminated fatty fish from the Baltic Sea, breast cancer rates among fishermen's wives from the contaminated east coast were higher than rates among fishermen's wives from the noncontaminated west coast (RR = 1.35; 95% CI, 0.98–1.86) (598). However, there was no control for other known breast cancer risk factors. In a study of consumption of sports fish in the U.S. Great Lakes region (sports fish in this region have been shown to be a source of exposure to PCBs and organochorine residues), no association was observed across all women studied (n = 1,481 cases), however, a positive association was observed among premenopausal women (n = 386, RR = 1.70; 95% CI, 1.16–2.50) (599). An accidental explosion in 1976 in a chemical plant near Seveso, Italy, provided the opportunity to evaluate exposure to high levels of dioxin. Breast cancer incidence during the decade after the accident in the areas closest to the accident was slightly but not significantly lower than expected (600).

The results of small case-control studies of organochlorine levels and breast cancer risk have been inconsistent. In a large European case-control study (265 cases), a significantly inverse trend between levels of adipose DDE and risk of breast cancer was observed after controlling for known breast cancer risk factors; the authors did not evaluate PCBs (601). In a case-control study in Buffalo, New York, lipid-adjusted serum levels of DDE, HCB, mirex, and total PCBs were evaluated among 154 incident breast cancer cases and 192 community controls. There was no evidence of a positive association between any of these compounds and breast cancer risk with the possible exception of less chlorinated PCBs (602). Lopez-Carrillo et al. (603) analyzed serum DDE levels in a case-control study in Mexico, where the pesticide is still in use. Serum DDE levels were not associated with risk of breast cancer. However, in one small study, contrary to expectation, the levels of octachlorinated dibenzo-*p*-dioxin (OCDD) were slightly elevated in the cases (604), although no differences were observed for six other polychlorinated dibenzo-*p*-dioxin isomers. In a large case-control study conducted on Long Island, New York, no association with breast cancer risk was seen for blood levels of DDE, chlordane, dieldrin, or common PCB congeners (605). African American women have been shown in some studies to have higher levels of exposure to these chemicals; however, in a case-control study of 355 breast cancer cases, no elevation in risk was seen for those with the highest serum levels of a PCBs or organochlorine pesticide residues (606).

Several prospective studies have used stored blood samples collected prior to diagnosis to evaluate the relationship between DDE and total PCBs with breast cancer (607–609). In a cohort in New York City of 14,290 women, a strong association between serum DDE levels and risk of breast cancer was initially reported (609), but no relation was seen with longer follow-up (610). No association with PCB levels was observed in this cohort. In a prospective study of 57,040 San Francisco Bay area women who had provided blood in the late 1960s, when DDT and PCBs were still in production (608), 50 white, 50 African American, and 50 Asian breast cancer cases occurring after blood draw and prior to 1991 were selected and compared with 150 age- and ethnicity-matched control women. Risk of breast cancer was not associated with either DDE or PCB level when all ethnic groups were combined, although nonsignificant elevated risks were observed for DDE for African Americans and whites. Among 236 breast cancer cases and their matched controls in the Nurses' Health Study, there was no evidence of a positive association of breast cancer with either DDE or PCBs (607). The multivariate RRs for women in the highest quintile compared to women in the lowest were 0.72 (95% CI, 0.4–1.4) for DDE and 0.66 (95% CI, 0.32–1.37) for PCBs. For women in the highest quintiles of both DDE and PCBs, the RR was 0.43 (95% CI, 0.13–1.44) for joint exposure. In further follow-up in this cohort, adding an additional 143 postmenopausal cases, results were similar (611). A pooled study reanalyzing data from the five large studies in the Northeast has also found no association between PCBs and DDE levels and breast cancer risk when comparing the highest and lowest quintiles (595). In a large nested case-control study from Denmark, concentrations of 14 pesticides and 18 PCBs measured in adipose tissue samples collected at baseline, no association was seen for any of these chemicals with breast cancer risk among 409 postmenopausal cases; a lower risk of estrogen-receptor negative cancer was seen in the highest category of exposure for several of the PCBs and organochlorines (612). However, in a recent nested case-control study of 129 cases who were diagnosed an average of 17 years after they had blood drawn shortly after childbirth at an average age of 26 years, a positive association was observed for serum DDT levels and early life breast cancer risk (613).

In summary, recent large studies have not found evidence of increased breast cancer risk among postmenopausal women associated with blood levels of DDE or total PCBs; however, a small effect will always be difficult to exclude, as will hypotheses relating to specific subgroups such as premenopausal women. All available studies address exposure to organochlorines in the decade or two prior to enrollment; it will be very difficult to obtain data to address the hypothesis that childhood or even *in utero* exposure is associated with breast cancer risk 50 or more years afterward. Nonetheless, organochlorines appear unlikely to be an important breast cancer risk factors or an explanation for secular changes in breast cancer rates.

Electromagnetic Fields

Electromagnetic fields (EMFs) have been proposed to alter breast cancer risk, perhaps by altering melatonin secretion by the pineal gland. Although animal evidence is suggestive, few data address the relation of melatonin levels to human breast cancer risk. Exposure to light at night suppresses melatonin secretion, and in some studies, breast cancer risk has been lower among blind women (614,615). Gathering high-quality epidemiologic data on EMF and nocturnal light exposure is challenging, and these hypotheses are unlikely to be resolved definitively anytime soon. Evidence of an elevated risk of male breast cancer associated with presumed occupational EMF exposure based on job title has been observed in some studies, but these results are based on small numbers of cases. No evidence of an increased risk of breast cancer was observed in the studies that also included female employees. In case-control studies designed specifically to study occupational exposure to EMF and breast cancer in women, small increases in risk have been inconsistently observed. However, in those studies misclassification of exposure is a major concern. Because classifications are based on subjects' "usual" occupation, often obtained from death certificates, duration of exposure and personal work tasks could not be accounted for in most of the studies and adjustment for known breast cancer risk factors was limited or entirely absent.

The general population is exposed to EMF primarily from power lines, transformer substations, and electrical appliance use. In an initial 1987 study of mortality from all cancer subtypes and residential wiring configurations, a statistically significant elevation in female breast cancer incidence was associated with magnitude of exposure at the current residence (616). However, other studies in Britain, the Netherlands, and Taiwan did not observe an association between female breast cancer deaths and residence in the vicinity of electricity transmission facilities. Again, these studies are limited by the indirect methods used to assess EMF exposure.

Use of electric blankets (produced before 1990) throughout the night approximately doubles an individual's average exposure to EMFs, because the blanket is placed close to the body. In one case–control study, the use of electric blankets continuously throughout the night was associated with marginally significant increases for postmenopausal breast cancer (OR = 1.46; 95% CI, 0.96–2.20) (617) and for premenopausal breast cancer (OR = 1.43; 95% CI, 0.94–2.17) (618). However, in a recent large case-control study of breast cancer in women younger than 55 years, no association was seen (619), and no association was seen in retrospective or prospective analyses within the large Nurses' Health Study cohort (620), or in the large Long Island case-control study based on 1,354 cases (621).

In 2001, IARC conducted a formal review of the available evidence and concluded that the evidence at that time was inadequate to assess the effects of magnetic fields and breast cancer. Since that report, five additional studies of occupational exposure and four of residential exposure have been conducted (622). At present the biological plausibility and most recent epidemiologic studies do not support an important relation between EMF exposure and breast cancer risk (622).

Active and Passive Smoking

The relation between active cigarette smoking and risk of breast cancer has been extensively evaluated in both case-control and cohort studies; collectively, the data provide strong evidence against any major overall relationship. It has been hypothesized that initiation of smoking early in adolescence, when breast tissue may be maximally sensitive to carcinogenic influences, may increase risk of breast cancer, although study results have been inconsistent (596,623,624). Among large, prospective cohort studies, there is suggestive evidence of a positive association with long-term smoking prior to the first birth (625–629). In the Norwegian-Swedish Women's Lifestyle and Health Cohort Study of over 100,000 participants, women who initiated smoking during their teenage years and continued to smoke for 20+ years were at an increased risk of breast cancer (comparing women who initiated smoking before age 15 to never smokers RR = 1.48; 95% CI, 1.03–2.13) (626). This increased risk of breast cancer was not observed among women who smoked for 20+ years, but started smoking after their first birth. These results are consistent with the hypothesis that breast tissue is particularly susceptible to carcinogens between early puberty and the first full-term pregnancy (66).

Passive smoking has been suggested to be an important risk for breast cancer in part because sidestream smoke contains more carcinogenic activity per milligram than mainstream smoke. In several case-control studies, increases in risk of breast cancer have been seen, but usually without evidence of a dose response. Despite these positive associations, it is difficult to reconcile the absence of an effect of heavy smoking for decades with an effect of exposure to much lower amounts of environmental smoke. A likely explanation for the positive association seen in case-control studies is methodologic bias related to the selection of controls or the retrospective recall of exposure to passive smoke. In the Nurses' Health Study, passive smoking in childhood or adulthood was not associated with breast cancer risk (628). In general, results from the Women's Health Initiative Observational Study are consistent with no association with passive smoking, although they did report that women that were exposed to extensive long-term exposure to passive smoking (e.g., ≥10 years during childhood and ≥20 years adult at home and ≥10 years adult at work) were the only group at an increased risk (629).

Silicone Breast Implants

Most studies examining the relation of silicone breast implants with breast cancer risk have actually reported lower rates of breast cancer among women with implants (630–635); thus, a direct association between silicone breast implants and the occurrence of breast cancer is unlikely.

Early anecdotal reports (636–639) of breast cancer among women whose breasts had been augmented with silicone raised concerns about a causal link with the disease. Since then, a number of observational studies, both case control and cohort, have been conducted. Most of these studies have found *reduced* breast cancer risk among women with implants compared to either the general population or women without implants. Reported reductions in risk in some of these studies have been large (on the order of 50% or 60%). A large retrospective cohort study (640) 10,778 women who had breast implants before 1989 and 3,214 comparison women who had had plastic surgery not involving silicone during the same time responded to a medical questionnaire. In analyses based on external and internal comparisons, the women who had had breast implants were not at elevated risk of breast cancer. The overall SIR comparing breast cancer incidence among the breast implant cohort to the Atlanta SEER incidence rates was 0.89 (95% CI, 0.8–1.1). The RR of breast cancer comparing the implant cohort to the comparison group of other patients who had undergone plastic surgery was 0.79 (95% CI, 0.6–1.1). There was no statistically significant heterogeneity in risk according to age or calendar year in which implants were received (in part, this calendar-year variable was a surrogate for the type of implant), and there was no variation in risk of breast cancer by preimplantation chest or cup size. There was indication of a slight decrease in risk of breast cancer in both the external and the internal comparisons during the initial 10-year period following breast implantation. This likely reflects a preimplantation screening/selection bias. The authors note that characteristics of patients who had breast implants could predispose to the discovery of a lower risk of breast cancer among such women; these characteristics include small breasts and thinness. In a follow-up of 2,763 women who underwent cosmetic breast implant surgery in Denmark on average about 15 years previously, breast cancer incidence was nonsignificantly reduced compared to a series of 1,736 who had other forms of plastic surgery (635). In a large series of 24,588 women who underwent bilateral augmentation mammoplasty in Quebec or Ontario, breast cancer rates were actually significantly lower after a median of about 15 years, than among women who had other forms of plastic surgery (632). In both these studies, results were similar when restricted to women who received silicone implants.

In summary, there is strong epidemiologic evidence that breast implants do not lead to increased risk of breast cancer (641). Further, findings of significantly decreased risks in some studies probably reflect a combination of short duration of follow-up after implantation (i.e., bias due to preimplantation screening and selection for women who do not have breast abnormalities) and favorable breast cancer risk profiles of women who tend to seek breast augmentation.

Summary of Evidence on Environmental Pollution and Breast Cancer Risk

In general, current evidence does not support any substantial relationship between exposure to human made chemicals or electrical fields in the environment and breast cancer risk. The best recent evidence in prospective analyses does not support an association between exposure to organochlorines and breast cancer risk. Although occupational studies of EMF exposure have been inconclusive, residential studies imply that there is no risk associated with overhead power lines. Overall increases in breast cancer incidence due to active or passive smoking are not supported by prospective data, but modest increases due to smoking at early ages cannot be excluded.

Although other environmental exposures that have not been identified may warrant evaluation, with the exception of ionizing radiation, no environmental exposure can be confidently labeled as a cause of breast cancer based on current evidence.

OCCUPATION

A review of 115 studies published between 1971 and 1994 (642) found little support for an association between specific occupations and breast cancer risk. Limited evidence suggested that cosmetologists, beauticians, and pharmaceutical manufacturing workers had a modestly elevated risk of breast cancer, but conclusions were not possible because of lack of adequate exposure data. Although ionizing radiation is a recognized risk factor for breast cancer and studies conducted in the early part of the century confirmed this, none of the more recent studies of radiation workers, including x-ray technicians, workers at uranium fuel plants, and atomic energy plants found an elevation of breast cancer risk among women in these occupations. The few studies carried out on specific occupational agents have not provided any evidence of association. In particular, although organic solvents may increase risk of various cancers in animals, women who worked in dry cleaning, shoe manufacturing, or who were exposed to trichloroethylene did not have an elevated risk of breast cancer (642).

Despite the large literature on occupation as a risk factor, most studies have simply examined associations between occupational title and breast cancer risk; specific information on exposure to potential carcinogens was collected in only a few studies. Although some studies collected detailed information on lifetime occupational history, often broad occupational groupings representing only the most recent occupation were used in analyses. Further, most studies have not controlled adequately for known breast cancer risk factors, in particular, reproductive factors, that are likely confounders of any observed association with occupation (643). Employment outside the home, and in a specific occupation, is likely to be highly correlated with educational attainment and socioeconomic status, and thus with reproductive characteristics. In the few studies that have controlled for sociodemographic and reproductive risk, breast cancer risk did not vary across occupational groups. In contrast, a consistent finding across studies that were unable to control for important confounders has been an increased breast cancer risk among more highly educated women, rather than a consistently observed association for any specific occupation. Thus, further analyses of occupational titles without consideration of known breast cancer risk factors or actual workplace exposures are unlikely to be informative.

PERSONAL FACTORS AND MEDICAL CONDITIONS

Mammographic density and benign breast diseases are two factors that have been studied as intermediate markers of breast cancer risk. In general, they are believed to be generalized markers of increased risk of breast cancer. In addition, a variety of diseases and medications are known or suspected to cause or to be associated with modifications of hormones and/or growth factors and thus may influence breast cancer risk (644).

Mammographic Density

Percent mammographic density (PMD) is one of the strongest risk factors for breast cancer and is predictive of breast cancer risk for at least 10 years in the future. Women with the highest mammographic density are at a four- to six-fold greater risk of breast cancer than women with the lowest density (645–647). Because of this strong association, mammographic density has been suggested as a surrogate marker of breast cancer risk (648) that may be used as an endpoint in intervention trials (648–652). The radiographic appearance of the breast on a mammogram varies depending on the composition of the breast. Fat is radiolucent and appears dark. In contrast, epithelial cells and connective tissue are radiodense; they appear light on a mammogram and are considered to be "mammographically dense." Thus, both epithelial and stromal cells are responsible for the appearance of dense tissue on a mammogram (653). The biologic mechanism underlying the strong association with breast cancer risk is unclear; however, it has been hypothesized that it may represent a cumulative exposure to estrogens, mitogens, and/or mutagens (654), or the number of breast cells at risk (655).

The PMD measure used in the clinic today is the breast-imaging reporting and data system (BI-RADS) density measure proposed by the American College of Radiology, which is visually assessed by the radiologist (656). However, the motivation for assessing BI-RADS is to alert radiologists because sensitivity of mammography is lower in women with dense breasts; the intention was not for risk assessment. Extensive data support the association between BI-RADS classifications and Wolfe's parenchymal patterns, another mammographic density measure, and breast cancer risk (645,657–662). The standard measurement of PMD in the research setting is based on an operator-assisted thresholding method that provides a more reliable quantitative assessment of percent mammographic density; these methods have also found a remarkably consistent positive association between PMD and breast cancer risk (645,663). While both qualitative and quantitative assessments of mammographic density predict breast cancer risk, they are subject to reader differences and measurement error, which will bias study results toward the null (664). Future work to develop reliable, automated measures of breast density is needed.

Benign Breast Disease

Benign breast disease (BBD) is a heterogeneous group of component histologic subtypes. Considered as a single entity, benign breast disease has been associated with breast cancer in most (665–668), but not all studies (669,670). As early as 1945, certain lesions have been implicated in conferring a greater increased risk of breast cancer more than others (671). Foote and Stewart (671) reported atypical epithelial hyperplasia and duct papillomatosis of atypical structure to be more common in breasts with cancer than in normal breasts. Subsequent retrospective investigations, with systematic review and reclassification of histopathology slides, have confirmed an association between proliferative lesions, especially those with atypia, and breast cancer (672–679), but not all have supported such a relation (680-682). In prospective studies, where investigators have examined the risk associated with histologic subtypes of benign breast disease, the proliferative—and, in particular, atypical—lesions were associated with the highest risk (683–685).

In a large follow-up study, Page and collaborators systematically reviewed and reclassified 10,366 consecutive breast biopsies from three Nashville hospitals. They reported results of 17 years median follow-up on 3,303 patients from this group in two initial publications (683,686). All proliferative lesions were associated with an increased risk of subsequent breast cancer (RR = 1.9), while those with nonproliferative lesions were not at increased risk (RR = 0.9). In this study, proliferative lesions were found in approximately 27% of biopsies. Page et al. found the proliferative lesions of highest risk to be atypical lobular hyperplasia (RR = 4.5) and atypical ductal hyperplasia (RR = 4.1). They defined these lesions as having some, but not all, features of carcinoma

in situ, which is associated with an 11- to 12-fold increase in invasive breast cancer risk.

Data from the Nurses' Health Study are consistent with study from Dupont and Page; they reported an intermediate risk among women with previous proliferative disease without atypia (RR = 1.5; 95% CI, 1.2–2.0) and the highest risk of breast cancer among women with atypical hyperplasia (RR = 4.1; 95% CI, 2.9–5.8). In this study, proliferative lesions accounted for approximately 57% of all benign breast diseases. However, the magnitude of the breast cancer risk differed according to histologic type of atypical hyperplasia (AH). The OR for the subsequent development of breast cancer was higher among women with atypical lobular hyperplasia (ALH) (OR 5.5, 95% CI, 3.3–9.2) than for those with atypical ductal hyperplasia (ADH) (OR = 3.1; 95% CI, 2.0–4.8). Overall, 58.9% of invasive breast cancers that developed in women with AH were in the ipsilateral breast. While the risk of ipsilateral breast cancer was somewhat higher among women with ALH than those with ADH (61.3% vs. 55.9%), this difference was not statistically significant (p = .66) (687).

The biologic meaning of atypical lobular and atypical ductal lesions is controversial, primarily because their natural history is unclear (688). A central issue is whether these atypical lesions are markers of general breast cancer risk, precursor lesions, or perhaps both. Most studies that have examined the laterality of benign and subsequent malignant lesions have found that only about half of the invasive breast cancers are in the same breast in which the atypical hyperplasia was previously diagnosed, suggesting that these lesions are markers of generalized risk (689). However, data are limited on laterality with regard to the type of atypical lesion. Although data are limited, two independent studies report that atypical lobular and ductal hyperplasias may also be different, in that atypical lobular hyperplasia may in fact increase the risk of breast cancer in the same breast as the benign lesion (687,690).

Diabetes

Type 2 diabetes has been suggested to increase risk of breast cancer. Hyperinsulinemia, as occurs in adult-onset diabetes, may promote breast cancer because insulin may be a growth factor for human breast cancer cells (691). Further, insulin levels are inversely related to levels of SHBG, and thus are positively related to available estrogens and androgens (644). Many studies have lacked information about the type and severity of diabetes, making the interpretation of the various findings difficult (644). A meta-analysis of 39 independent studies reported that women with diabetes had a 27% (95% CI, 1.16–1.39) increased risk of breast cancer that was limited to postmenopausal women (692). When limited to studies that adjusted for BMI, the risk estimate was attenuated (RR = 1.16; 95% CI, 1.08–1.24). Recently, there has been interest in the potential protective effects of metformin, an insulin-lowering agent used to treat diabetes, on cancer risk (693). A meta-analysis of seven studies reported a 17% reduced risk of breast cancer comparing diabetics treated with metformin to women with diabetes treated with other therapies (694). In the Women's Health Initiative, compared to women without diabetes, women with diabetes treated with metformin were at a 25% lower risk of breast cancer (RR = 0.75; 95% CI, 0.57–0.99), while those with diabetes not treated with metformin were at a nonsignificant increased risk of breast cancer (RR = 1.16; 95% CI, 0.93–1.45) (695). The exact mechanism by which metformin may reduce cancer risk is unclear; however, it is hypothesized that it may be through activation of the AMP-activated protein kinase (AMPK) pathway and inhibition of cell growth. A better understanding of the pathway involved and studies that can tease apart the effects of changes in BMI, metabolic profiles, and sex hormones will be necessary for determining if these associations are causally related to metformin. There are also suggestive studies that metformin use may improve breast cancer prognosis, although studies to date have been relatively small.

Thyroid Cancer

There have been reports that women with a diagnosis of thyroid cancer are more likely to develop breast cancer than women without such a diagnosis; this association was first noted in 1966 (696). A study published in 2001 (697) sought to overcome the problem of small sample size that plagued many of the previous studies by using SEER registry data from 1973 to 1994. In this analysis, premenopausal white women who had thyroid carcinoma were more likely to develop breast cancer 5 to 20 years later than women without a diagnosis of thyroid carcinoma (RR = 1.41; 95% CI, 1.18–1.68). There was no evidence of such increased risk among postmenopausal white women. Point estimates of RR were elevated in both premenopausal and postmenopausal black women (RR = 1.54; 95% CI, 0.66–3.03 and RR = 1.29; 95% CI, 0.52–2.67, respectively), but statistical power was poor due to low numbers. There was no increased risk of subsequent thyroid cancer following an initial diagnosis of breast cancer, suggesting that a woman's susceptibility to breast cancer after thyroid cancer may be related to treatment of the thyroid cancer rather than to genetic or environmental susceptibility to these two cancers simultaneously.

Anti-inflammatory Drugs

Strong evidence suggests that nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, inhibit colon carcinogenesis in humans (698,699), thereby providing a rationale to investigate an inhibitory role of NSAIDs in breast carcinogenesis. However, evidence on the association between NSAID use and breast cancer is conflicting. In a large case-control study (700), women who had used an NSAID three or more times per week for at least 1 year were at decreased risk of breast cancer compared to nonusers (OR = 0.66). Similarly, the observational study of the Women's Health Initiative found that regular NSAIDs users (2+ tablets/week) had a 21% decreased risk of breast cancer (RR, 0.79; 95% CI, 0.60–1.04) (701). In contrast, a large prospective study (702), found no relationship with regular or heavy use of aspirin compared to nonusers. The California Teachers Study also observed no overall association between regular NSAID use and incidence of breast cancer (703). The Nurses' Health Study found a nonsignificant 9% (HR = 0.91; 95% CI, 0.81–1.01) reduced risk of breast cancer with regular aspirin use for more than 20 years (704). In addition, this study did not find any differences by hormone receptor status or cyclo-oxygenase (COX2) expression. Unanswered questions remain regarding the effect of regular NSAID use for long durations, the effect of different doses, and the effects of different nonaspirin NSAIDs on breast cancer incidence (705). In contrast, prospective cohort and randomized control data support a protective effect on breast cancer recurrence and survival (706).

Statins

A growing body of literature suggests that statins have antitumor activity by interrupting cell-cycle progression and inducing apoptosis. Statins are a class of lipid-lowering drugs prescribed for the prevention of cardiovascular disease. A meta-analysis of randomized trials (707) and two large prospective studies (708,709) suggest that statins as a group are

not associated with breast cancer incidence. However, one study reported that the lipophilic class of statins (e.g., simvastatin and lovastatin) was associated with an 18% (HR = 0.82; 95% CI, 0.70–0.97) reduction in breast cancer incidence (708). However, this association with lipophilic statins has not been confirmed in other large population-based studies (710–712). Further evaluation of specific classes of statins and long-term use are necessary.

Pregnancy-related Conditions

A history of eclampsia, preeclampsia, or pregnancy-induced hypertension has been associated with a reduced risk of breast cancer in parous women in at least three case–control studies (713–715) and one cohort study (716). Further, women born to mothers who had preeclamptic pregnancies also appear to have reduced risk of breast cancer (717). Explanations for these findings have focused on hormone-related factors: Women who develop preeclampsia have been found to have relatively low estrogen levels during pregnancy, and the lower exposure to estrogens *in utero* may confer a benefit to the female fetus in terms of lifetime breast cancer risk reduction (717). High levels of α-fetoprotein, a glycoprotein with antiestrogenic properties, are associated with preeclampsia and thus may mediate the association between preeclampsia and reduced breast cancer risk in female offspring (717). Nonspecific cellular immune responses may be involved as well (718,719).

Epstein-Barr Virus

Epstein-Barr virus (EBV) is the most ubiquitous viral (herpes) infection among humans, with >90% of the adult population worldwide affected by it. In the vast majority of individuals, the persistent infection remains asymptomatic, but a small minority of individuals develop EBV-associated tumors, including Burkitt's lymphoma and Hodgkin's lymphoma. Based on several lines of evidence, it has been hypothesized (720–722) that breast carcinoma is also an EBV-associated tumor. However, the limited data on the relationship between EBV and breast cancer are conflicting (723–729). For instance, Bonnet et al. (723) detected the EBV genome by polymerase chain reaction (PCR) in 51% of 100 primary invasive breast carcinomas, whereas the virus was detected in only 10% of a sample of healthy tissues adjacent to the tumors. Further, the virus was more frequently associated with the most aggressive tumors. Other studies have found no molecular or immunohistochemical evidence for an association between EBV and the development of breast carcinoma (724,726,727,730,731). Results of at least one study (732) suggest that EBV DNA detected in breast carcinoma tissues is likely related to the presence of EBV-infected lymphocytes in the tumor stroma and does not indicate infection of the tumor cells with the virus; thus, that breast carcinoma is not an EBV-associated tumor.

Selective Serotonin Reuptake Inhibitors (SSRIs)

At least two studies reported that selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants promote mammary tumors in rodents (733,734). Epidemiologic studies in humans have produced inconsistent results. One study conducted before SSRIs were widely available found an increased breast cancer risk among tricyclic antidepressant users (735). A more recent study also found such an increased risk (736). One study found a decreased risk of breast cancer among tricyclic antidepressant users (737), although some studies have found no association (738,739). Research findings are similarly inconsistent for SSRIs. Two studies that employed prescription databases to assess exposure found no association between SSRI use and breast cancer risk (738,740), although a study that relied on self-report of medication usage found an elevated risk of breast cancer among recent SSRI users (739). Future epidemiologic studies of this topic must control adequately for possibly strong confounders such as alcohol use and obesity, which may be associated with use of antidepressants, and should rely on an objective assessment of medication usage, because cancer cases may be more likely to recall medication use than noncases. Further, the indication for antidepressant use may itself be associated with increased cancer risk, and depression may be an early symptom of occult cancer.

Cytotoxic drugs, used in the treatment of cancer, may exert their own carcinogenic effects. One category of cytotoxic drugs, alkylating agents, may lead to an increased risk of solid tumors, including breast cancer, although evidence for this hypothesis is weak (741).

ETIOLOGIC SUMMARY

Much is known about the behavioral factors that influence breast cancer risk, and more recently the links between these factors and the pathophysiology of the disease have become clearer. Known and suspected risk factors are described in Table 18-2, grouped by reproductive, hormonal, nutritional, and other variables. Approximate strengths of association are also given for specific comparisons. These comparisons are somewhat arbitrary because many of these risk factors are continuous variables and the RRs will depend on the levels chosen for comparison. For example, we have compared ages at menarche of 15 years with 11 years, but the RR would be stronger if age 17 years were contrasted with age 11 years. Although most of these risk factors are established with a high degree of certainty, some such as low consumption of monounsaturated fat will require further research for confirmation.

Mechanisms linking known and suspected risk factors to the development of breast cancer are known with varying levels of certainty. Early events involve mutations of breast stem cells. These mutations can be inherited (e.g., mutations in *BRCA1, BRCA2*, or *p53*) or acquired, such as by exposure to ionizing radiation. At present there is little evidence that classic chemical carcinogens play an important role in human breast cancer by causing early mutations; oxidative damage from endogenous metabolism is hypothesized to contribute to DNA damage (742), but the importance of this mechanism is difficult to quantify. To the extent that oxidative damage is important, dietary carotenoids and other antioxidants in fruits and vegetables might reduce risk and higher intake of monounsaturated fat will result in cell structures that are less easily oxidized. Low availability of folic acid, which is exacerbated by high alcohol intake, leads to the incorporation of uracil rather than thymine into DNA and can be a cause of DNA damage. Pregnancy appears to render the breast substantially less susceptible to somatic mutations, although the exact mechanisms are unclear; thus, earlier first pregnancies will minimize the period of susceptibility. Vitamin A also plays a role in maintaining cell differentiation, but it may be that only quite low intakes are related to increased risk.

High endogenous estrogen levels are well established as an important cause of breast cancer, and many known risk factors operate through this pathway. The additional contribution of cyclic estrogen exposure (as opposed to

TABLE 18-2

Risk Factors for Breast Cancer and Approximate Strength of Association

Reproductive Factors	*Hormonal Factors*	*Nutritional/Lifestyle Factors*	*Other Factors*
Early age at first period +	OC use (current vs. none) +	Obesity (>30 BMI vs. <25) Premenopausal – Postmenopausal +	Family history (mother and sister)[a] +++
Age at first birth (>35 vs. <20) ++	Estrogen replacement (10+ yr vs. none) +	Adult weight gain (postmenopausal) ++	Family history (first-degree relative)[b] ++
No. of births (0 vs. 1 child) +	Estrogen plus progesterone replacement (>5 yr vs. none) ++	Alcohol (1 or more drink/day vs. none) +	Jewish heritage (yes vs. no) +
Age at menopause (5-yr increment)	High blood estrogens or androgens (postmenopause) +++	Height (>5 feet 7 inches) +	Ionizing radiation (yes vs. no) +
Breast-feeding (>1 yr vs. none) –	High blood prolactin ++	Physical activity (>3 hr/wk) –	Benign breast diseased (MD diagnosed)[d] ++
		Monounsaturated fat[c] – (vs. saturated fat)	Mammographic density (highest category vs. lowest) +++
		Low intake of fruits and vegetables[c] (specifically for ER- breast cancer) +	

Note: BMI, body mass index; OC, oral contraceptives; +, relative risk (RR) = 1.1–1.4; ++, RR = 1.5–2.9; +++, RR = 3.0–6.9; –, RR = 0.7–0.8.
[a]Two first-degree relatives who have a history of breast cancer before age 65 years versus no relative.
[b]First-degree relative who has a history of breast cancer before age 65 years versus no relative.
[c]Upper quartile (top 25%) versus lower quartile (lowest 25%).
[d]Clinically recognized chronic cystic, fibrocystic, or other benign breast disease versus none.

continuously high levels) is less clear, but much available evidence indicates that progestins add to breast cancer risk. Factors that increase lifetime exposure to estrogens and progestins include early age at menarche, regular ovulation, and late menopause. Lactation and overweight during young adult life result in anovulation and this probably accounts for some of their protective effects. Extreme underweight also causes anovulation and would be expected to reduce risk, but direct evidence is lacking. Alcohol consumption increases endogenous estrogen levels and may, at least in part, account for the observed increase in risk among regular drinkers. The increase in risk of breast cancer among current or recent users of oral contraceptives is also presumably due to their estrogenic (and probable progestational) effects. After menopause, the major determinants of estrogen exposure are the amount of body fat and use of postmenopausal hormones; these are both important risk factors for breast cancer. Increases in physical activity can delay the onset of menarche and can reduce risk of breast cancer by helping to control weight gain and decrease endogenous estrogen exposure.

Estrogens, by their mitotic effect on breast cells, appear to accelerate the development of breast cancer at many points along the progression from early mutation to metastasis and death. By increasing cell multiplication, estrogens may also increase the probability that DNA lesions become mutations. Although earlier exposure to high estrogen levels during adolescence increases risk decades later, reduction in levels late in life abruptly reduces risk, whether this be by castration, cessation of postmenopausal hormones, or the administration of antiestrogens. Other growth factors in addition to estrogens, particularly IGF-I and prolactin, also appear to contribute to risk of breast cancer, but these relationships are less firmly established.

Although this broad outline of breast carcinogenesis is unlikely to change substantially with further research, many details are incomplete and other contributing factors will probably be documented. For example, genetic polymorphisms yet to be identified may contribute to variation in endogenous levels of, or responsiveness to, estrogens, IGF-I, and prolactin. Dietary and other behavioral determinants of these factors are incompletely defined. Also, other molecular mechanisms such as DNA repair and apoptosis are thought to be important in carcinogenesis in general, but the extent to which exogenous factors influence these processes in the context of human breast cancer is not known.

ATTRIBUTABLE RISK: THE QUANTITATIVE CONTRIBUTION OF KNOWN RISK FACTORS

As noted early in this chapter, the search for specific breast cancer risk factors has been stimulated by the large differences in rates of breast cancer among countries and by changes in rates among migrating populations and within countries over time. The extent to which known risk factors account for these differences in rates is, therefore, of considerable interest. An often-quoted estimate is that only 30% of breast cancer cases are explained by known risk factors (743,744). This has been widely used to suggest that other major risk factors remain to be discovered, in part fueling the search for environmental pollutants that may be responsible. However, a study of population attributable risks in a nationwide survey estimated that at least 45% to 55% of breast cancer cases in the United States may be explained by later age at first birth, nulliparity, family

history of breast cancer, higher socioeconomic status, earlier age at menarche, and prior benign breast disease (745). In another analysis, parity and age at menarche, first birth, and menopause appeared to explain more than half of the difference between breast cancer rates in China and in the United States (98). The rapid decline in age at menarche in Korea since World War II (746), a drop in parity to very low levels, and the rise in premenopausal breast cancer incidence to rates comparable to Western countries (747), further attests to the power of these reproductive patterns to account for variation in incidence. Among postmenopausal women, just the combination of weight gain after age 18 years and use of postmenopausal hormones accounted for approximately one-third of breast cancer incidence (283). Among women who do not use postmenopausal hormones, weight gain from age 18 accounts for 24.2% of postmenopausal breast cancer (748). Combined with the reproductive variables, this would clearly account for a large majority of the international differences.

A precise determination of the degree to which changes in the prevalence of known breast cancer risk factors account for the increases in breast cancer rates over time is difficult. Changes in age at first birth do not appear to account for appreciable increases in overall U.S. breast cancer rates through 1990, although more delayed childbearing by women born after 1950 should ultimately contribute to an approximately 9% increase in rates (749). However, since the 1940s, adiposity, use of postmenopausal hormones, and alcohol consumption by women have increased dramatically. Although further work is needed to quantify these contributions to the secular trends, novel risk factors are not required to account for substantial increases in breast cancer rates.

COMMUNICATING RISK TO PATIENTS

Women and their healthcare providers are increasingly exposed to information on epidemiologic risk factors for breast cancer, benefits of prevention strategies, and treatment options. The Gail et al. model of breast cancer risk prediction (750) is increasingly used by clinicians to assess breast cancer risk for women with differing risk factor profiles. This model has been validated but identifies as high risk only a minority of women who will go on to develop breast cancer (751). However, evidence suggests that the understanding of personal risk by women is poor. For example, in a sample of women with a family history of breast cancer, more than two-thirds of women overestimated their lifetime risk of breast cancer, even after participating in a counseling session (752). The overestimation of risk was substantial and perhaps could lead to inappropriate behaviors, such as overscreening, excessive breast self-exam, or inappropriate decisions regarding prophylactic mastectomy or other strategies.

Factors that appear to influence perception of risk include numeracy (753). Women with higher numeracy scores had significantly higher accuracy in gauging the benefits of mammography. Lower education, obesity, having three or more comorbidities, and current cigarette smoking were related to unrealistic pessimism about breast cancer in a nationally representative sample of women (754). Importantly, when discussing risk and risk reduction, research indicates that both absolute risk and RR must be included in the message to maximize the accuracy of risk perception. A presentation must be capable of presenting probabilities about a variety of possible outcomes in a comprehensible manner. It must also attempt to counter "side effect aversion" (755,756). Furthermore, any tool that aids the presentation of risks and benefits must address potential misperceptions about the magnitudes of breast cancer risks, and it must not overwhelm people with the complexity of reducing risk with, for example, a selective estrogen receptor modulator (SERM) (752,757,758). While more effective formats for presentation of risk and benefits are required, the evidence supports discussion of "risk in 1,000 women exactly like you," as well as the magnitude of risk reduction, perhaps as a percentage.

PREVENTION OF BREAST CANCER

Approaches for primary prevention of breast cancer according to period of life are discussed here briefly and are considered in more detail elsewhere (759). Although many reasons for the high rates of breast cancer in affluent Western populations are known, this knowledge does not necessarily translate easily into strategies for breast cancer prevention. Some risk factors (such as age at menarche) are well established but difficult to modify; some (such as postmenopausal hormone use) are well established but carry benefits as well as risks; and others (such as replacing saturated fat with monounsaturated fat) are unproven but have other strong benefits that justify the strategy, with reduction in breast cancer being a possible additional benefit. Also, known risk factors for breast cancer are modest in magnitude; RRs are usually in the range of 1.3 to 1.8 for attainable changes. Although these RRs are far less dramatic than that between smoking and lung cancer, they should still be considered important. To provide perspective, the RR of death from breast cancer for women who do not have mammography compared to those who receive regular mammograms is about 1.3. As we give great importance and resources to the provision of mammography, the avoidance of a risk factor with a similar magnitude of effect should have even higher priority because this prevents both the occurrence and the need for treatment of breast cancer as well as death. When considering primary prevention, it is important to remember that even small changes at the individual level can produce substantial changes in the population rates of disease (760).

Some strategies for prevention can be implemented by individuals themselves, but the health system and governments and society as a whole can take actions that will influence rates of breast cancer importantly. In Table 18-3 possible prevention strategies are listed, along with actions that can be taken at these different levels to reduce rates of breast cancer.

Early onset of menarche in the United States and other affluent countries is largely the result of rapid growth and weight gain of children related to an abundant food supply, excellent sanitation, and low levels of physical activity (including sitting in school). Much of this is desirable for many reasons, and there is no reasonable expectation that we could or would want to increase the average age at menarche to 17 years, as has been typical in rural China. Yet, generally desirable increases in physical activity, such as greater recreational activities, have been associated with modest delays in age at menarche (398,761) and should thus contribute to reductions in breast cancer, and we now have more direct evidence that higher levels of activity during this period of life are associated with lower risk. Society, through the provision of daily physical activity in schools and safe environments for recreational activity, must play a major role in these efforts.

Early age at first birth will substantially reduce breast cancer, but the societal trends are in the opposite direction because of delay of childbirth until after educational

TABLE 18-3

Possible Strategies and Levels of Action for Primary Prevention of Breast Cancer

Strategy	*Individual*	*Health System*	*Society/Government*
Delay menarche	Provide parental support for recreational activity and limit television watching	Encourage regular activity	Provide daily physical activity in schools and safe play environment
Breast-feed	Breast-feed at least 6 mo/ pregnancy	Encourage lactation	Provide infant child care at work and/or long maternal leaves
Limit alcohol	Limit intake to several drinks per week	Provide education	Develop social norms for low alcohol intake by women
Avoid long-term estrogen therapy, especially if combined with progestagens	Limit use to treatment of symptoms	Educate patients on risks and benefits	
Avoid adult weight gain	Engage in regular physical activity, moderately restrain total calorie intake	Counsel patients on the importance of avoiding weight gain	Provide safe environment for pedestrians and bicycle riding; provide work-site and community recreational facilities
Eat five servings of fruit and vegetables per day; limit red meat consumption; and replace saturated fat with olive, canola, and other oils high in monounsaturated fat	Make healthy dietary choices	Encourage healthy diets	Provide healthy choices in work site and schools, and provide best current information on diet and health

programs are completed and careers are established. Further, unplanned early pregnancies and more than an average of two completed pregnancies per woman have undesirable social and ecologic consequences. Nevertheless, a social norm that encouraged carefully planned first pregnancies at the beginning of advanced education and career development would reduce breast cancer rates. This would require major behavioral changes and social supports, such as for childcare, to be practical on a widespread basis. Because of the complex social changes needed for this to be a practical strategy for breast cancer prevention and potential undesirable consequences, we have not included it in Table 18-3.

At least 6 months of breast-feeding is recommended for optimal infant health (762) and evidence suggests this will modestly reduce risk of breast cancer, particularly among premenopausal women. Improved physician counseling (763) can encourage this practice, but changes at workplaces to allow breast-feeding and longer maternity leaves will also be needed for many women to adopt this practice.

Alcohol consumption has a complex mix of desirable and adverse health effects, one being an increase in breast cancer. Among adolescents and young adult women, the increases in breast cancer will not be counterbalanced by a reduction in heart disease, as risk of this is extremely low. Individuals should make decisions considering all the risks and benefits, but for a middle-aged woman who drinks alcohol on a daily basis, reducing intake is one of relatively few behavioral changes that is likely to reduce risk of breast cancer. Taking a multiple vitamin containing folic acid greatly reduces risks of neural tube defects and may prevent coronary heart disease (764) and colon cancer (765), and some evidence suggests this may mitigate the excess risk of breast cancer due to alcohol (480). Thus, taking a multiple vitamin appears sensible for women who do elect to drink regularly.

Postmenopausal hormone use, like alcohol consumption, involves a complex trade-off of benefits and risks. From the standpoint of breast cancer risk, the optimal strategy would be to use estrogens not at all or for less than 10 years to relieve menopausal symptoms. Most importantly, combined use of estrogen plus progestin for more than 1 year should be avoided. The range of options, however, is increasing with the demonstration that tamoxifen and raloxifene, two selective estrogen receptor modulators, can be effective in the primary prevention of breast cancer. Physicians will need to play a key role in advising women in this rapidly evolving field.

Avoiding weight gain during adult life can importantly reduce risk of postmenopausal breast cancer, as well as cardiovascular disease and many other conditions. Individual women can reduce weight gain by exercising regularly and moderately restraining caloric intake, which is facilitated by overall quality of diet (766). Healthcare providers play an important role in counseling patients throughout adult life about the importance of weight control. However, the incorporation of greater physical activity into daily life will be difficult for many persons unless governments provide a safer and more accessible environment for pedestrians and bicycle riders. The provision of work-site and community exercise facilities can also contribute importantly.

Few specific aspects of diet that influence risk of breast cancer are well established, but recent evidence based on multiple prospective studies of dietary intake and measurements of blood carotenoid levels strongly suggest that an abundant consumption of fruits and vegetables will reduce risks of estrogen receptor negative breast cancer. Other

evidence suggests that limiting red meat (particularly in childhood and early adult life) and replacing saturated and trans-fat with monounsaturated fat may also reduce risk. These strategies are consistent with an overall Mediterranean-type dietary pattern, which is reasonable to adopt because this will reduce risk of cardiovascular and other diseases, and modestly lower risk of breast cancer may be an added benefit. Physicians can assess dietary habits and provide guidance, and governmental policies influence diets in many ways. Providing the best current information on diet and health is one such role.

With demonstration that tamoxifen and probably other selective ER modulators can be effective in the primary prevention of breast cancer (117,119), chemoprevention has become an option for women at elevated risk. Many other pharmacologic agents are being evaluated and are likely to increase the alternatives. The availability of effective chemopreventive agents raises many questions about the optimal criteria for use of these drugs. Evaluation of an individual woman's risk of breast cancer has become much more important because this risk can now be modified. Until recently, risk has been primarily based on an evaluation of family and reproductive history and history of benign breast disease. New information on risk based on genotype, detailed histologic characteristics of benign breast disease (767), and serum hormone levels (124) now allows a much more powerful prediction of risk for an individual woman. Screening for elevated estrogen levels in postmenopausal women to help identify those who would most benefit from an estrogen antagonist, as is done for serum cholesterol, may become part of medical practice. Physicians will play a key role in keeping abreast of this rapidly developing area and counseling patients appropriately.

In summary, available evidence provides a basis for strategies that can reduce risk of breast cancer, although some of these represent complex decision making. Attainable objectives can make an important impact on individual risk of breast cancer. However, even the collective implementation of all lifestyle strategies will not reduce population rates of breast cancer to the very low levels of traditional agrarian societies because the magnitude of the necessary changes is unrealistic or undesirable. Thus, a role will exist for hormonal and other chemopreventive interventions that may be appropriate for women at particularly high risk and, potentially, for wide segments of the population because few women can be considered to have very low risk. Together, the modification of nutritional and lifestyle risk factors and the judicious use of chemopreventive agents can have a major impact on incidence of this important disease.

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CHAPTER 19

Management of Other High Risk Patients

Seema A. Khan

CHAPTER CONTENTS

INTRODUCTION

Breast cancer risk can be attributed to three major sources: increasing age, lifetime estrogen exposure (endogenous and exogenous), and genetic susceptibility. These major factors play a critical role in breast epithelial transformation and appear to converge in the phenotypic expression of proliferative precursor lesions of the breast epithelium, as observed in the unaffected breasts of women who are genetically susceptible (e.g., BRCA mutation carriers) as well as women at risk for the so-called "sporadic" breast cancer. This chapter will focus on the identification and management of women at higher than average risk for sporadic breast cancer; management of women who are genetically susceptible and those with lobular carcinoma *in situ* is covered in Chapters 12 and 16. The following discussions of breast cancer "risk" will apply to women who do not carry mutations of known breast cancer susceptibility genes. Additionally, a full discussion of the epidemiology of sporadic breast cancer can be found in Chapter 18, along with pertinent references; these risk factors are reviewed here only from the perspective of identification and management of individuals (rather than populations) at risk for breast cancer.

The management of women at increased risk for breast cancer includes: a) identification of high risk women (or risk estimation); b) recommendations for life-style modifications that may reduce risk; c) a plan for breast surveillance; d) discussion of pharmacologic prevention; and e) discussion of prophylactic mastectomy (if appropriate and sought by the patient).

IDENTIFICATION OF HIGH RISK WOMEN

Age: The relation of age to breast cancer risk is discussed fully in Chapter 18 but it is worthwhile noting here that breast cancer risk estimation for individuals is heavily influenced by age. Incidence rates rise sharply with age, starting in the mid-to-late 30s, and all currently used statistical risk estimation models relate the known relative risk (RR) for a particular risk factor to the age-specific breast cancer frequency in that population. This is important to recognize in terms of breast cancer risk management, as a 5-year risk estimate of 1.7% using the Gail model-2 (National Cancer Institute (NCI) Breast Cancer Risk Assessment Tool) has been widely used as a benchmark measure of breast cancer risk. The 5-year breast cancer Gail model probability for an average 45-year-old woman is 1%, while the similar estimate for an average 65-year-old woman is 2%. Thus a 45-year-old woman who has a 5-year breast cancer probability of 1.7% is at higher lifetime risk than her 65-year-old counterpart. However, as the same 45-year-old woman ages, if she does not acquire any new risk factors and does not develop breast cancer, her estimated risk declines and approaches the average risk for her age group. Thus longer-term risk estimates (e.g., 10-or 20-year estimates) may be a more useful framework for risk counseling, and life-time risk estimates (calculated to age 85 or 90) have become a commonly used benchmark for comparison of risk groups, most useful for younger women.

Risk Factors Related to Reproductive Hormones: A wide array of established risk factors for breast cancer relates to endogenous life-time estrogen exposure. These include young age at menarche, late age at first full-term pregnancy,

no exposure to lactation, and late age at menopause. Among postmenopausal women, higher serum estradiol levels are robustly linked to breast cancer risk, and among premenopausal women there is a suggestion of higher levels of the androgenic estradiol precursors in breast cancer cases but these differences are not sufficient to utilize serum hormone levels for risk estimation in clinical practice. Although the risk associated with reproductive variables has been generally attributed to estrogen exposure, the hormones progesterone and prolactin also deserve consideration. Thus, the number of ovulatory cycles during a woman's reproductive life-span (with their luteal phase progesterone surge) is a stronger determinant of breast cancer risk than the length of time from menarche to menopause, and the short-term increase in breast cancer risk following pregnancy is at least partially attributed to the high progesterone exposure of pregnancy. Furthermore, exogenous progestin exposure in the form of combination postmenopausal hormone therapy (CMHT) carries a larger breast cancer risk than therapy with estrogen alone. In premenopausal women, current oral contraceptive use has long been associated with a modest increase in breast cancer risk, but recent data on the use of depo-medroxyprogesterone acetate (DMPA) shows a twofold increase in breast cancer risk, with a trend toward higher grade and triple negative tumors (1). Prolactin exposure, too, is now clearly implicated in breast cancer causation, and the protective effect of pregnancy is mediated, at least partially, through a long-term lowering of serum prolactin. Epidemiological studies have shown that breast cancer cases demonstrate higher serum prolactin levels than controls, prior to the onset of breast cancer.

Other well-established risk factors also appear to operate through the endocrine axis: postmenopausal obesity is associated with increased aromatization of androgenic precursors in adipose tissue, lower sex hormone-binding globulin, and higher free estradiol. Physical activity in adolescence delays menarche and the onset of ovulatory cycles; later in life, it protects against obesity and may operate through other mechanisms as well. Moderate to heavy alcohol consumption is associated with higher circulating sex steroid levels and may retard the hepatic metabolism of hormones.

In general, the contribution of these individual risk factors to overall risk is modest, and relative risk estimates for each of these factors from most studies are in the range of 1.5–2.0. It is therefore difficult to apply this information to individual risk estimation unless it is incorporated into multifactorial statistical models, the prototype of which is the Gail model (2), validated in the Breast Cancer Prevention Trial (3). More recently developed models (Tyrer-Cusick) do include additional endocrine risk factors (age at menarche, use of postmenopausal hormone therapy, height, weight) and family history (4). Breast cancer risk estimation is discussed more fully below.

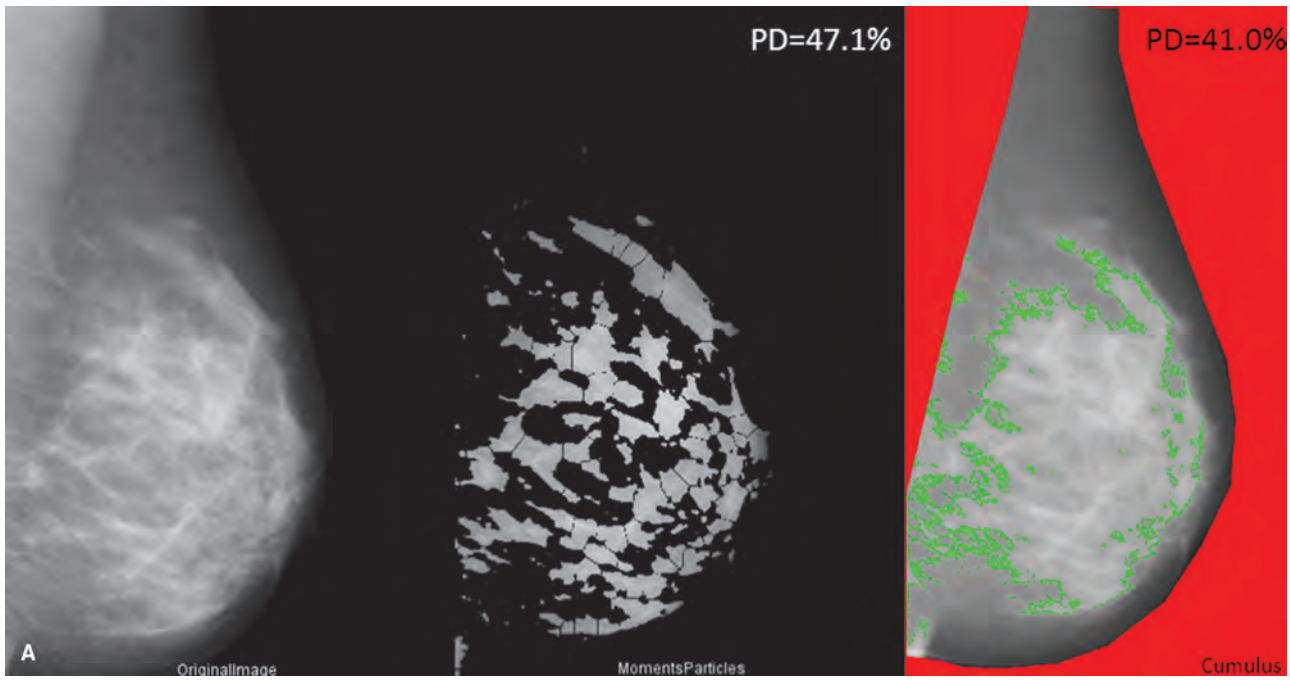
Mammographic Density

The radiographic appearance of the breast varies according to differences in the relative distributions of fat and fibroglandular tissues, where fat appears dark and radiographically dense areas appear light. It is reported on mammography reports using the standard reporting lexicon as BIRADS 1 through 4 (mostly fatty, scattered densities, heterogeneously dense, or very dense). These categories are intended to correspond to the percent dense area (<25%, 25%–50%, 51%–75%, and >75%) measured by application of a computer algorithm to digitized film screen images. Much of the published literature is based on a semiautomated algorithm (the CUMULUS software, developed by Byng et al.) but additional algorithms based on publically available software are being developed as shown in Figure 19-1. Volumetric, three-dimensional measurements are also being tested and may be more closely related to breast cancer risk. Mammographic density is at least partially genetically determined and a recent genome-wide association study has shown that polymorphisms associated with mammographic density are also associated with breast cancer risk (5).

There is now a substantial body of evidence showing that extensive mammographic density is strongly associated with an increased risk of breast cancer. The relative risk for the highest category of breast density (>75% of breast area is dense) has been reproducible across several large studies, and, on meta-analysis of these, the RR for the highest density category ranges from 3.25 to 6.49 (6). Additionally, a combined analysis of three nested case-control studies which included 1,112 participants of breast cancer screening programs (7) showed that women with mammographic density of more than 75% had a breast cancer RR of 4.7 (95% CI 3.0,7.4) compared to women with mammographic density less than 10%. In particular, women with the highest density category had a very high risk of being diagnosed with breast cancer within 12 months of the screening mammogram (RR = 17), suggesting that high mammographic density might mask the cancer. Among postmenopausal women, the association of percent dense area with breast cancer risk is stronger for those using hormone therapy; other data suggest an interaction between alcohol use of more than 1 drink daily and mammographic density. Based on these results, it is important to identify women with high percent density to counsel them about modifiable risk factors. Research on alternative imaging techniques for earlier detection is also needed.

The importance of mammographic density as a strong and independent risk factor for breast cancer is amplified by its high prevalence, with about one-third of the general population of women displaying dense areas of 50% or greater on mammography. Because of this prevalence, the fraction of breast cancer cases attributable to high mammographic density is in the range of 16% to 32% and higher in premenopausal women (7). Thus, the impact of breast density on cancer risk is far stronger than any of the known endocrine-related risk factors and in the same range as the risk associated with atypical proliferative lesions of the breast.

Studies examining the correlation between serum sex-steroid levels and mammographic density have not shown any consistent associations, with one large study by Verheus et al. in 2007 showing no relationship between circulating sex steroid levels and mammographic density but a more recent examination of hormonal variation in premenopausal women showing a positive association with mean estrogen level through the menstrual cycle. It would be of interest to determine if local breast estradiol levels (e.g., those in nipple aspiration fluid) are related more closely to breast density than circulating levels; these studies are ongoing. On the other hand, mammographic density and serum sex steroids (estradiol and testosterone) may have independent and additive effects on breast cancer risk as suggested by a recently reported case-control study nested within the Harvard Nurses' Health Study. Other hints that mammographic density is modulated by the endocrine environment come from the significant correlation between mammographic density and serum insulin-like growth factor-1 (IGF-1) that has been observed in premenopausal women (8). Prolactin is a potentially important hormone in breast carcinogenesis—higher levels in the serum are associated with increased breast cancer risk in both pre- and postmenopausal women—and several studies now suggest an association between serum prolactin levels and mammographic density.



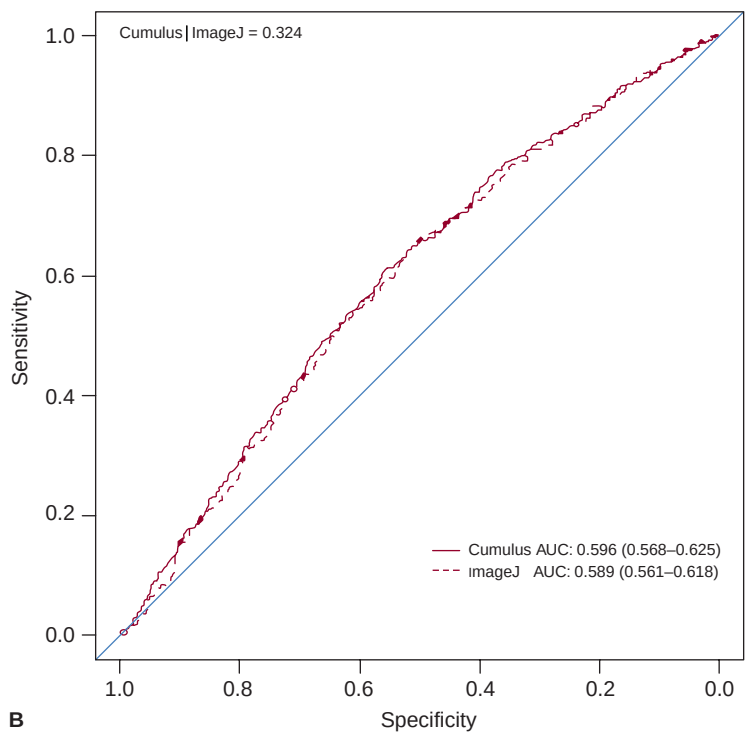


FIGURE 19-1 Mammographic density measurement. Examples of processed images. **(A)** An example of a digitized mammogram before and after thresholding and application of the watershed algorithm (one image, one particular thresholding algorithm, Moments), and the same image thresholded by using Cumulus **(B).** Discriminatory powers of Cumulus and ImageJ for predicting breast cancer risk, as measured by area under curve (AUC). Legend on the top-left corner summarizes *P* values for the Delong test between two receiver operating characteristic (ROC) curves. Legend on the bottom-right corner summarizes the AUC for each model with corresponding 95% confidence intervals. There were 3,593 participants with eligible film mammograms (1,784 cases and 1,809 controls). (From Li et al. High-throughput mammographic-density measurement: a tool for risk prediction of breast cancer. *Breast Cancer Res* 2012;14(4):R114.)

Studies relating breast density to histological findings have shown that high mammographic density is associated with an increased risk for atypical hyperplasia. However, in breast epithelial samples obtained from high risk women using random fine needle aspiration, no correlation was seen between cytologic atypia or cell proliferation (measured by Ki-67 labeling) and mammographic density. Quantitative microscopy of the autopsied breast shows relationships between mammographic density and total nuclear area, epithelial and nonepithelial nuclear area, glandular structures, and amount of collagen. Similarly, in reduction mammoplasty samples, the epithelial cell volume was concentrated in areas of high density connective tissue, and was significantly related to the mammographic density. This increased epithelial and stromal area in dense tissue does not translate into increased cell proliferation or steroid receptor expression in epithelial cells. Thus, there is no clear biological explanation for the association of breast density with cancer risk, and much remains to be done in order to incorporate the measurement and modulation of mammographic density into algorithms for breast cancer risk assessment.

An important, and potentially the most useful, aspect of breast density is the possibility that it is modifiable. This is most evident by the fact that the use of combination

postmenopausal hormone therapy (PMHT) increases percent breast density whereas tamoxifen therapy not only reduces it, but a decrease in mammographic density appears to predict preventive benefit. In a post-hoc sub-study of the International Breast Cancer Intervention Study (IBIS) trial, women who demonstrated a 10% or greater reduction in density following 12 months of tamoxifen use demonstrated a two-thirds reduction in breast cancer risk, whereas no significant risk reduction was seen in women whose mammographic density did not change (9). Small studies of ovarian suppression with a gonadotrophin-releasing hormone agonist in premenopausal women, and in BRCA1 mutation carriers, suggest another avenue of breast density reduction. Other data are more mixed; a meta-analysis of physical activity and mammographic density showed no significant effect, and vitamin D supplementation in the Women's Health Initiative similarly had a null effect. Aspirin use, which appears to reduce breast cancer risk, shows no relationship to breast density. Therefore, although modification of breast density is possible, not all pathways of breast cancer risk reduction are reflected as reductions in breast density.

Breast Epithelial Hyperplasia and Involution

The present paradigm for the development of breast cancer suggests that in the breast, as in other epithelial organs, the etiologic pathways of malignancy converge in the occurrence of breast epithelial hyperplasia or intraepithelial neoplasia (IEN). This concept is supported by data going back several decades, relating benign breast disease (specifically epithelial proliferation) to an increased risk of subsequent breast cancer; several studies have shown that the breast cancer risk of women with hyperplasia without atypia is roughly twofold greater than women without; and the risk associated with atypical hyperplasia is increased approximately fourfold (10,11). The specific lesions included in the category of hyperplasia without atypia consist of moderate or florid duct hyperplasia, intraductal papilloma, sclerosing adenosis, and radial scar. The lesions usually included in the category of atypical proliferation include atypical duct hyperplasia (ADH), atypical lobular hyperplasia (ALH), atypical papilloma, and flat epithelial atypia (see Chapter 9 for more detail). Although data from the large retrospective cohort from Nashville, TN, showed a strong interaction between atypical hyperplasia and a positive family history for breast cancer (the risk associated with a history of first degree relative with breast cancer and atypical hyperplasia was increased almost 10-fold), two recent studies do not substantiate these findings and show no added increase in risk for women with atypical hyperplasia and a positive family history (11,12). Although there was a suggestion of a more marked risk increase with ALH than ADH in the Nashville and Nurses cohorts, recent results from the Mayo Clinic cohort do not show a difference in risk between ALH and ADH. However, an increasing number of atypical foci, the presence of calcifications in the histological material, and the combination of ADH and ALH, all raise risk significantly over that observed in the absence of these findings (Fig. 19-2).

Despite the consistently increased risk seen with typical and atypical epithelial proliferation in the breast, most women with these findings do not, in fact, develop breast cancer (e.g., 80% of the 330 women with atypical hyperplasia in the Mayo cohort remained free of breast cancer over a mean follow-up period of almost 14 years). A number of authors have attempted to identify molecular factors which might improve the specificity of risk assessment, so that preventive interventions can be targeted to a more purified high risk group. Despite a number of potential risk biomarkers, there has been little progress in prospective validation of these. The more obvious immunohistochemical markers estrogen receptor, p53, and HER-2/neu demonstrate risk increases of two- to threefold but have not been validated and are not in clinical use. Expression of cyclooxygenase-2 (COX-2) has been examined in atypical lesions from women in the Mayo cohort, with an observed increase in breast cancer risk with increasing COX-2 expression. Thus, if expression was weak or absent, RR was 2.63 (95% CI 3.0,7.4); with

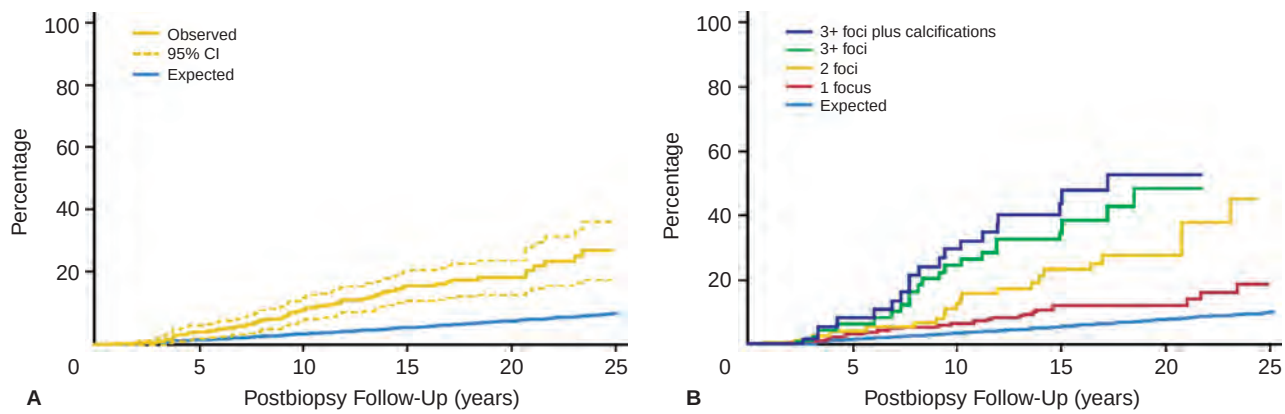


FIGURE 19-2 **(A)** Cumulative risk of breast cancer over time. Observed cumulative breast cancer incidence among women with atypical hyperplasia, with 95% represented by stippled lines. Expected breast cancer events were calculated by applying age- and calendar period-stratified person-years of observation to corresponding lows Surveillance, Epidemiology, and End Results breast cancer incidence rates. Observed and expected events cumulated after accounting for death as a competing. **(B)** Observed and expected cumulative breast cancer incidence among women with atypical hyperplasia, stratified by number of foci of atypia and histologic presence of calcifications. (From Degnim AC, Visscher DW, Berman HK, et al., Stratification of breast cancer risk in women with atypia: a Mayo cohort. *J Clin Oncol* 2007;1;25(19):2671–2677. Epub 2007Jun 11. (A is Fig 2; B is Fig 3, both on page 2675.))

moderate COX-2 expression, RR was 3.56 (95% CI, 1.94, 5.97) and with strong expression, RR was 5.66 (95% CI, 2.59, 10.75). Although these findings have not been replicated, the fact that COX-2 expression is also a marker of increased recurrence risk in DCIS lesions strengthens the possibility that the findings are biologically significant. Nevertheless, at the moment there are no validated risk biomarkers in breast epithelial lesions, and the morphologic diagnosis of atypical hyperplasia and lobular carcinoma *in situ* remains the strongest tissue-based marker of breast cancer risk.

An additional aspect of breast histology that has been investigated recently by Hartmann and colleagues in the Mayo Clinic cohort is the appearance of age-related lobular involution, described as physiological atrophy of the breast, with a decrease in the number and size of acini per lobule. These investigators hypothesized that absence of involution may be a risk factor for breast cancer, and classified benign biopsy sections into three categories: no involution where 0% lobules were involuted, partial involution with 1% to 74% lobules involuted, or complete involution with ≥75% lobules involuted. Involuted terminal duct lobular units (TDLUs) contain only a few to several small acini and flattened, inconspicuous acinar epithelium with fibrosis or fatty replacement of specialized intralobular stroma. They found a significant increase in relative risk in women displaying complete absence of involution. On further analysis, in a study that included mammographic density data, it appears that lobular involution is inversely associated with breast density (61% of women with extremely dense breasts displayed no involution); it remains independently associated with breast cancer risk following adjustment for mammographic density. Thus, the highest risk was observed in women with no involution and dense breasts (adjusted HR = 4.08, 95% CI = 1.72–9.68) (13). The mechanism of increased risk related to failure of lobular involution remains to be defined, but it is clearly plausible that involution is related to attrition of cytokine and hormonal signals that both maintain parenchymal volume, and support tumorigenesis in breast epithelium.

BREAST EPITHELIAL SAMPLING IN ASYMPTOMATIC, HIGH RISK WOMEN

Until recently, atypical hyperplasia has been identified only in women who developed breast lumps or mammographic findings that required biopsy. In such populations, the prevalence of atypical hyperplasia in an older series of open surgical biopsies was 3.5% (10) but more recent estimates in series of core needle biopsies of image-detected lesions range up to 9%. Autopsy studies suggest that the prevalence of occult atypical IEN could be as high 26%, depending on the detail of the sampling. There is good evidence, therefore, that the prevalence of occult breast IEN is significantly higher than that suggested by surgical biopsy data.

The recent interest in techniques for the sampling of epithelium from clinically normal breasts is motivated by the expectation that an improved ability to identify occult IEN would lead to improvements in our ability to assess individual risk. Noninvasive methods of breast epithelial sampling have another important application: the potential for the development of surrogate endpoints for the occurrence of malignancy, which are notably lacking in the field of breast cancer prevention at the moment. Although there has been significant progress in this area over the last decade or so, breast epithelial sampling of asymptomatic women remains a research tool, with no specific application in the clinical management of high risk women; available methods are briefly summarized below.

Methods of Non-Invasive, Minimal Sampling of the Healthy High Risk Breast

The techniques available include two, which obtain fluid and cells from ductal lumina (nipple aspiration fluid and ductal lavage) and two, which obtain epithelial and stromal cells via random fine or core needle biopsy.

Nipple Aspiration Fluid (NAF): Nipple fluid contains cells that are exfoliated into the ductal lumen and can be collected at the duct orifice by suction-aspiration. It is well tolerated, inexpensive, and produces samples that are paucicellular (or acellular) but rich in proteins, hormones, and possibly nucleic acids. It was first evaluated by Papanicolaou in the 1950s, with the goal of breast cancer detection, and was subsequently furthered by Sartorius, who developed a breast pump device designed to improve nipple fluid yield from asymptomatic women. The method in use today involves breast massage, dekeratinization of the nipple, and suction-aspiration with commercially available devices (Atossa Genetics, Halo Healthcare). Analyses of cells or protein in NAF samples obtained with these devices are also commercially available. However, the validation of protein assays is lacking, and reproducibility of cytologic analyses has long been a problem. A significant limitation of NAF as a biosample is the great variability in the fraction of women who yield of nipple fluid in various studies; a recent report from the Netherlands by van Diest and colleagues describes the successful use of oxytocin nasal spray to induce NAF production but the absence of a comparison group, or a within-person comparison before and after oxytocin use renders it difficult to interpret these results. Oxytocin nasal spray currently has no FDA approved uses in the United States, is difficult to obtain, and expensive. An added concern in the interpretation of studies of NAF-based biomarkers is the inability to extend these to women who do not yield NAF, and recent data suggest that non-yielders of NAF have significantly lower serum prolactin levels than yielders (Khan et al., manuscript under review).

Ductal Lavage (DL): DL is an extension of NAF, designed to overcome the problems of scant cellularity in NAF samples, and to sample the entire length of the ductal tree (14). The procedure involves application of a topical anesthetic or periareolar infiltration with lidocaine; the elicitation of nipple fluid as described above, cannulation of each fluid-yielding duct (non-fluid yielding ducts can also be cannulated) with a single lumen catheter and lavage with normal saline. The lavage effluent is fixed, centrifuged to recover a cell pellet, and cytological smears prepared. Ductal lavage was introduced with the expectation that it would perform better than NAF in the identification of occult IEN. When compared to NAF, DL samples consistently provide a higher cell yield, but at significantly greater cost in supplies, time, and patient discomfort. Although some investigations continue, this technique has not proven useful for early diagnosis of breast cancer, risk evaluation, or for monitoring of biomarkers in prevention trials (15).

Random Fine-Needle Aspiration (rFNA): The rRNA method is performed in the clinically and radiologically normal breast in healthy, high risk women. It is based on the concept of field change in the high risk breast and does not provide site-specific sampling. First tested by Marshall in Utah in the late 1980s, major work in this area has subsequently been reported from University of Kansas by Fabian and colleagues, who have modified the original technique (16). After local anesthesia with buffered lidocaine with

epinephrine, eight to ten passes are made per breast with a 21 gauge needle introduced at two locations (periareolar, upper outer and upper inner quadrants). Samples from both breasts are pooled. With the prophylactic use of Vitamin K, use of buffered lidocaine, post-procedure cold packs, and tight-fitting sports bras, hematomas are rare, and the procedure is generally well tolerated.

Random Core Needle Biopsy (rCNB): With the availability of spring-loaded core needle biopsy devices, rCNB has become a possible approach to breast epithelial sampling. Some data exist in terms of the utility of this approach for tissue acquisition for biomarker studies (17), but there is no published information as to its use in risk assessment. In one biomarker study, up to seven cores were obtained from each subject, through the same skin incision. On average, 3 of the 6–7 cores per subject contained epithelium, the rest being fatty. The investigators were able to count 3,000 cells per case after Ki-67 labeling, by combining a mean of 11 core-cut sections per subject. They did not find any significant difference in pre- and posttreatment Ki-67 labeling indices (17).

OCCULT IEN AND BREAST CANCER RISK

The concept of epithelial sampling to define breast cancer risk was pioneered by Petrakis and colleagues, who published a series of reports through the 1970s to the present, characterizing nipple fluid yield and cytologic findings in healthy women. In two cohorts studied by this group, NAF yield varied considerably (85% for the first cohort and 40% for the second) (18). In the first cohort, women who produced NAF and had cytological evidence of hyperplasia developed breast cancer at a 2.5-fold higher rate (95% CI, 1.1–5.5), which increased to 4.9-fold (95% CI, 1.7–13.9) when cytologic atypia was present (Fig. 19-3). Women who did not produce NAF were the reference group. In the second cohort, accrued between 1981 and 1991, the relative risk was 2.0 (95% CI, 1.3–3.3) for the hyperplasia and atypical hyperplasia groups combined, as no cancers occurred in the 22 women with atypical hyperplasia. There are no long-term follow-up studies of women who have undergone ductal lavage.

The notion that occult IEN exists in high risk women and can be identified through random needle sampling techniques was substantiated by findings from a study of rFNA performed by Fabian et al., in 486 high risk women (median 5-year Gail model estimate of 4%), followed for a median of 45 months after rFNA, showed that evidence of hyperplasia with atypia on random FNA equates with an increased short-term risk of breast cancer (see Fig. 19-3). Hyperplasia with atypia was present in the initial FNA in 21% of women, and was predictive of the probability of developing breast cancer independent of a 10-year Gail risk. Good separation of cumulative 3-year breast cancer incidence rates was achieved by using a combination of Gail risk and rFNA atypia: women with both an above-median Gail risk and hyperplasia with atypia on rFNA had an incidence rate of 15%, those with only an above-median Gail risk had a 3-year incidence of 4%, and those with a below-median Gail risk had no cancers detected in the first 3 years of follow-up. These findings have yet to be validated in a multi-institutional setting.

Practical Utility of Identifying IEN

The identification of occult IEN remains, for the moment, in the realm of clinical research, as both of the long-term studies demonstrating the value of occult IEN for breast cancer risk prediction (NAF and rFNA) came from single institutions and have not been replicated. Further, these institutions have the benefit of highly developed cytological expertise, an important issue because the reproducibility of cytological assessment of these minimal samples is problematic. For women whose risk estimate would be changed by a finding of occult atypia, data regarding the decision-making value of this information are beginning to appear. Although several studies have reported that a low fraction of risk-eligible women accept tamoxifen therapy, an analysis of accrual patterns to the Breast Cancer Prevention Trial and the STAR trial (Study of Tamoxifen and Raloxifene) show that 36% of women with a history of atypical IEN were willing to participate, compared to 21% of those without a history of breast IEN. Data from Northwestern University shows a similar trend for acceptance of prophylactic tamoxifen, in that the acceptance rate in 68 high risk women who were offered tamoxifen because of a history of atypical IEN was 53%, compared to 29% of 65 women who were high risk for other reasons. (p = .008). Furthermore, among 99 high risk women who underwent rFNA, 50% of those with atypical findings accepted tamoxifen therapy (19).

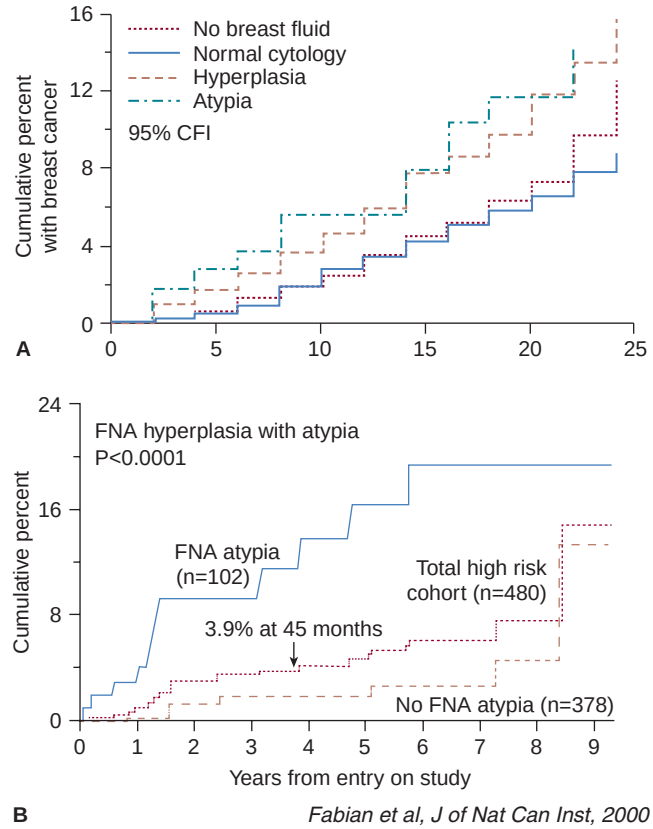


FIGURE 19-3 Breast cancer incidence rates in women undergoing NAF in two study cohorts from the University of California, San Francisco. **(A)** Group 1, 1973–1999. **(B)** Group 2, 1981–1999. (From Wrensch et al. Breast cancer risk in women with abnormal cytology in nipple aspirates of breast fluid. Dec 5, Vol. 93. *J Natl Cancer Inst* 2002, reproduced with permission.) **(C)** Breast cancer incidence rates in high risk women with and without evidence of atypical hyperplasia in random FNA samples at the Kansas University Medical Center. (From Fabian et. al. Short-term breast cancer prediction by random periareolar fine-needle aspiration cytology and the gail risk model. Aug 2, Vol. 92. *J Natl Cancer Inst* 2000, reproduced with permission.)

BIOMARKER EVALUATION IN BREAST EPITHELIAL SAMPLES

Biomarker assessment in breast epithelial samples can potentially add precision to risk estimation as discussed-earlier; however, the validation of potential risk biomarkers has proved challenging. Molecular markers of risk that have been evaluated in rFNA studies range from immunocytochemistry of proteins (such as EGFR, ER, p53), to methylation of promoter regions of tumor suppressor genes. Although these biomarkers are significantly related to features such as epithelial atypia and obesity, there is no validated biomarker panel that can be used to improve precision of risk estimation beyond what is achieved with the identification of IEN.

The reversibility of biomarkers in short-term Phase 2/3 studies of chemopreventive intervention has not been demonstrated so far, although attempts have been made, using surrogate endpoints related to cell morphology and biomarker expression in rFNA samples (16). In single arm studies with letrozole as the intervention in postmenopausal women, and flaxseed isoflavones in premenopausal women, Ki-67 labeling did decrease significantly in the posttreatment samples, but the lack of an untreated control arm renders interpretation difficult (20). Nevertheless, Ki-67 labeling is a promising intermediate endpoint based on its validation in neoadjuvant breast cancer therapy trials, where posttreatment Ki-67 is a strong independent predictor of clinical outcomes.

ESTIMATION OF RISK FOR SPORADIC BREAST CANCER

Breast cancer risk estimation has acquired a practical importance with the availability of proven methods of surveillance and risk reduction, which are logically targeted to high risk women. As discussed earlier, epidemiological investigations over the past half-century defined a number of breast cancer risk factors, and numerical estimation of group or individual breast cancer risk has become possible through the development of statistical models which incorporate these risk factors. The first of these was developed by Gail and colleagues, who used data collected during the Breast Cancer Detection and Demonstration Project, and combined several known risk factors: age at menarche, age at first full-term pregnancy, number of first degree relatives with breast cancer, number of surgical breast biopsies, and whether or not the biopsy showed atypical hyperplasia. Specific probability estimates were then calculated using age- and race-specific frequencies of breast cancer in the population, recognizing that uncertainty was greater in non-European women because baseline data were not as robust. This model (available at http://www.cancer.gov/bcrisktool/) has been validated prospectively (21), and risk assessment using statistical models has been adopted as a standard clinical tool.

Although use of the Gail model has led to precise prediction of rates of breast cancer occurrence in groups of women (3) (i.e., it is well calibrated for populations), the ability to identify individual women who will develop breast cancer (i.e., its discriminatory ability) remains poor. The discriminatory ability of a model is measured by the concordance statistic, which is equivalent to the area under the curve (AUC) in a receiver-operator curve (ROC) analysis, and examines the sensitivity and specificity of a given test at different thresholds. Thus, the concordance statistic, or AUC, measures the overall accuracy of the model, and for a perfect model should approach 1.0, whereas for a useful model should be 0.8 or greater. A concordance statistic of 0.5 would imply a model that predicts as well as chance (e.g., flipping a coin). The concordance statistic for the Gail model in the Nurses Health Study was 0.58 (95% CI, 0.56–0.60). Only 3.3% of women who developed breast cancer in the Nurses cohort had a risk above the threshold recommended for preventive intervention with tamoxifen (22). In addition, the model overestimates risk in young, unscreened women and underestimates risk in women over 59 years of age. Well established sources of risk, such as mammographic density, body mass index, and use of hormone replacement therapy are not included. Finally, it is a model that is well calibrated for sporadic breast cancer risk but does not address important attributes of family history associated with inherited susceptibility syndromes, (age at onset, bilaterality of cancer, affected second degree relatives, and history of ovarian cancer).

More recently, several other models have been developed that attempt to incorporate features of breast cancer risk applicable to both the genetic and the environmental/endocrine components. The Tyrer-Cusick model (4) incorporates a number of endocrine risk factors including age at menopause and use of hormones for postmenopausal women, height, weight, and a family history that includes information on extended family, age at onset, and ovarian cancer information (available at http://www.ems-trials.org/riskevaluator/). The model calculates personal risk over 10 years and life-time (presented in comparison to population risk); and computes the probability of BRCA 1 and 2 mutations. In the IBIS-I trial, the number of observed cancers did not differ significantly from the number predicted (23); and in a separate high risk cohort studied by Amir et al. in Manchester, the model had a discriminatory accuracy of 0.762, compared to 0.735 for the Gail model. Prospective validation is expected from the IBIS-II trial, where high risk postmenopausal women are being randomized to anastrozole or placebo, but existing data suggest that the model performs better than the Gail in populations with strong familial risk, where the IBIS model showed better discrimination (AUC = 69.5%, CI = 63.8%–75.2%) than did the Gail model (AUC = 63.2%, CI = 57.6%–68.9%) (24). However, among women with atypical hyperplasia or lobular carcinoma *in situ*, the IBIS model performs poorly, with significant overestimation of breast cancer risk (25).

Adding Mammographic Density

Given the strong impact of mammographic density on breast cancer risk, efforts are under way to incorporate this important risk factor into predictive models. Gail et al. have incorporated mammographic density data on 7,500 women from the national cancer detection demonstration project (NCDDP) into the GAIL-2 model, and have found that their new model remains well calibrated in a set of 1,744 white women, with a modest increase in discriminatory power. The average age-specific concordance was 0.643 for the new model, in comparison with 0.596, for Gail model 2 (26). A second model including mammographic density has been developed by Barlow and colleagues using data from the Breast Cancer Surveillance Consortium. For premenopausal women, significant risk factors included age, breast density, a positive family history of breast cancer, and a prior breast procedure. The fitted model had a concordance statistic of 0.631 (95% CI = 0.618–0.644), compared to 0.607 (95% CI = 0.592–0.621) when breast density was excluded. For postmenopausal women, the c statistic for the overall model was 0.624 (95% CI = 0.619–0.630). When breast density was

excluded, the c statistic decreased to 0.605 (95% CI = 0.600–0.611). Mammographic density has also been added to the Gail model in a post-hoc analysis of the Study of Tamoxifen and Raloxifene (STAR) and resulted in minimal improvement in prediction accuracy (27). The addition of mammographic density, therefore, seems to improve risk estimation modestly at best, suggesting that mammographic density has substantial overlap with risk factors that are largely already included in the Gail model.

Risk Estimation for African American Women

The Gail model/NCI risk assessment tool underestimates risk in women of African ancestry. A modification of the Gail model has been developed by Gail et al. using 1,600 AA case-control pairs from the Women's Contraceptive and Reproductive Experiences (CARE) Study (28). Five-year breast cancer risk estimates from the CARE model and the NCI Breast Cancer Risk Assessment Tool show good agreement in younger women, but estimates for older women (over 45 years) are higher with the CARE model. The calibration of the CARE model was tested in the 14,059 African American women who entered womens' health initiative (WHI) without a prior history of breast cancer, 350 of whom developed invasive breast cancer over a mean 7-year follow-up period. The number of women predicted to develop breast cancer with the CARE model (323) was not significantly different from the number observed, with an observed-to-predicted ratio of O/E = 1.08 (95% CI = 0.97–1.20). This held up for most categories, with the exception of women with a prior history of benign breast biopsy, where the O/E was significantly lower than observed, indicating underestimation of the breast cancer risk. For women who had one benign breast biopsy and for those who had two or more biopsy examinations the rates were 1.51 (95% CI =1.20–1.92) and 1.65 (95% CI = 1.16–2.35), respectively. Among screenees for the STAR trial, the models agreed for 83% of the AA women screened, but 14.5% of women were risk eligible for the trial when screened with the NCI Breast Cancer Risk Assessment Tool, compared to 30.3% with the CARE model.

Estimation of Risk by Hormone Receptor Status

For the implementation of targeted risk reduction with selective estrogen receptor modulators (SERMs) such as tamoxifen, which are effective only in the prevention of estrogen receptor (ER) positive breast cancer, the identification of women specifically at risk for ER positive disease is highly desirable. For women with a prior history of breast cancer, the hormone receptor status of the first primary tumor may predict that of a future second primary, as evidenced in a pooled analysis of contralateral breast cancers observed in national surgical breast & bowel project (NSABP) treatment trials (29). Among women who had not received tamoxifen, there was strong concordance between the ER status of the first and second primary cancers: 89% of those with an ER positive primary cancer had an ER positive contralateral breast cancer and 70% with an ER negative primary breast cancer had an ER-negative contralateral breast cancer (or, for the association between primary and contralateral ER status = 14.8, 95% CI 3.8–74.3). In a subsequent study by Arpino and colleagues from the Baylor College of Medicine, the ER concordance between first and second primaries was 88% when the first primary was ER positive; but when the first primary was ER negative, only 25% of women developed an ER negative second primary. Among patients who received tamoxifen, both studies showed that the ER status of the second primary was not predicted by that of the first primary. A subsequent study based on surveillance, epidemiology and end-Results (SEER) data provides further confirmation of the similarity in hormone receptor status of first and second breast primary tumors, which is particularly strong among young women with ER negative index primaries, possibly reflecting the inclusion of women with BRCA1 mutations (30).

Among unaffected women, there are modest positive associations between the risk for ER positive disease and European ancestry, postmenopausal obesity, and post menopausal hormone therapy. High serum hormone levels have also been associated with the risk of ER positive breast cancer in several studies, but in a nested case-control study within the EPIC (European Prospective Investigation into Cancer and Nutrition) cohort, sex steroid hormones were associated with increased risks of hormone receptor positive and hormone receptor negative breast cancer. The risk of ER+PR+ breast cancer was significantly increased by about threefold for highest versus lowest tertile of estradiol and twofold for similar categories of testosterone. The risk of ER-PR- breast cancer was similarly significantly increased, twofold for both estradiol and testosterone (31). In the Women's Health Initiative cohort the discriminatory accuracy of the Gail model was 0.58 overall (95% CI, 0.56–0.60), but was slightly better for women who developed ER positive breast cancer (0.60, 95% CI, 0.58–0.62). For the prediction of ER negative breast cancer, the model performed no better than chance (32). The AUC for the Gail model in the WHI is seen in Figure 19-4. Thus, with the possible exception of an ER positive first primary tumor, there is no indicator of risk for ER positive breast cancer that is specific enough to select women for endocrine prevention strategies on this basis.

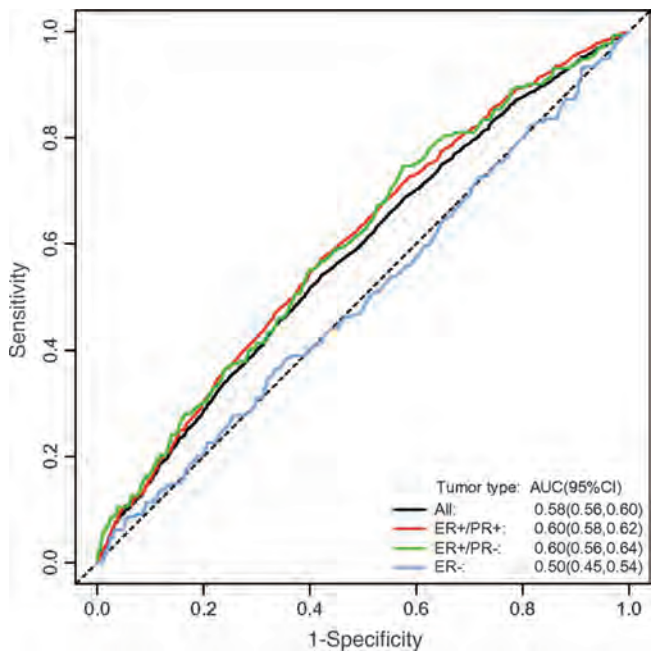


FIGURE 19-4 Receiver operating characteristic analysis and corresponding area under the curve (AUC) statistics for Gail model of prediction of invasive breast cancer risk by receptor status evaluated on the Women's Health Initiative clinical trial cohort. ER, estrogen receptor; PR, progesterone receptor; CI, confidence interval. (From Chlebowski RT, Anderson GL, Lane DS, et al. Predicting risk of breast cancer in postmenopausal women by hormone receptor status. *J Natl Cancer Inst* 2007;99(22):1695–1705, Oxford University Press.)

MANAGEMENT OF WOMEN AT HIGHER THAN AVERAGE RISK

Once a woman has been determined to be at high risk but is not a mutation carrier, the management issues to be considered include counseling regarding life-style factors that may modify risk, surveillance for early detection of breast cancer, and pharmacologic interventions to reduce risk. The discussion of prophylactic mastectomy in the non-mutation carrier should be undertaken with women who wish to explore this option, but this is best initiated by the patient rather than the physician.

Surveillance

Physical examination is the most basic form of breast cancer surveillance and remains an important part of the surveillance plan. It is generally recommended twice or thrice a year in high risk women, and can be shared between her various physicians (e.g., gynecologist, breast surgeon, internist) or may be performed by the same practitioner. In many offices, experienced physician extenders can provide this service with a high level of competence. Self examination should be encouraged, although it is of uncertain utility in the early detection of breast cancer. However, women should be encouraged to learn the topography of their own breasts so that a change is easily noted.

Annual mammography remains the mainstay of breast surveillance, although its relatively poor performance in young, high risk women has led to the evaluation of other imaging modalities: whole breast ultrasound (WBUS) and magnetic resonance imaging (MRI). The evidence for WBUS utility in surveillance of women with dense breasts is accumulating, and several studies have shown that screening with WBUS increases cancer yield by 3–4 per 1,000 screens in women with dense breasts. The American College of Radiology Imaging Network (ACRIN) 6666 protocol randomized 2,659 women with dense breasts and at least one other risk factor to either WBUS first or mammogram first, performed by different study radiologists who were blinded to the results of the other test. WBUS detected 4.3 cancers per 1,000 screens that were not seen on mammogram, 80% of which were invasive. Among incidence screens in years two and three, the sensitivity of mammography plus ultrasound was 0.76 (95% CI, 0.65–0.85), significantly higher than for mammography alone (0.52; 95% CI, 0.40–0.64), but with significantly lower specificity (0.84; versus 0.91) (33).

The addition of breast MRI to mammography and US in the surveillance of high risk women has been evaluated in several studies and there is good consensus that it adds to the effectiveness of breast surveillance for women with BRCA mutations and those with a high probability of being mutation carriers (see Chapters 13 and 17). In 2007, the American Cancer Society published guidelines for the incorporation of breast MRI in the surveillance regimen of women at increased risk of breast cancer *based on family history* (34), recommending surveillance MRI for women who have a life-time breast cancer risk of 20% to 25% as estimated with BRCAPRO or other models that largely utilize family history (i.e., *not* the Gail model). In a study of 687 women with high risk family history (1/3 mutation carriers and 2/3 with BRCAPRO lifetime risk of >20%) Kuhl et al. have compared the yield of MRI, mammography, and ultrasound. They document a cancer yield of about 15 per 1,000 screens for MRI, compared to 5 to 6 for mammography alone and ultrasonography alone (35). Of note, there were no interval cancers in the 2.5 years of follow-up, and MRI alone performed as well as MRI in combination with other modalities, raising the question of whether other screening tests can be dropped when MRI is used in this population.

However, the addition of MRI to the surveillance regimen of women at risk for sporadic breast cancer is still controversial. The expense of MRI and the burden of multiple repeat imaging examinations and biopsies generated needs to be considered along with the lack of evidence that MRI utilization in these populations improves survival or other cancer-related outcomes. The American Cancer Society and the national comprehensive cancer network (NCCN) guidelines are in agreement that there is not sufficient evidence to recommend use of MRI in women with high risk epithelial lesions.

RISK REDUCING INTERVENTIONS

Modifiable Breast Cancer Risk Factors

Despite the vast amount of information available on features that may increase the risk of developing breast cancer, few of these are modifiable, and, therefore, most cannot be exploited for breast cancer risk reduction. Of those that are modifiable, high life-time physical activity is associated with a lower risk of breast cancer; during adolescence, physical activity is associated with delayed menarche and delay in the establishment of regular ovulatory cycles. Later in life, a beneficial effect of physical activity has been observed in several recent studies. Postmenopausal obesity, too, should be modifiable, and high risk women who are obese should be directed toward weight control, as the combination of increased physical activity and caloric restriction are likely to have salutary effects not only on breast cancer risk, but on overall health. Among the reproductive risk factors, lactation appears to be protective against breast cancer. Women who accumulate a life-time exposure to lactation of at least 15 months have a lower risk for breast cancer after adjusting for other risk factors. Every 12-month period of lactation decreases risk by 4.3%, as estimated in a meta-analysis of over 50,000 breast cancer cases and 100,000 controls from 30 countries. The relative benefit of lactation was homogeneous across countries. Women of child-bearing age should, therefore, be encouraged to nurse their children for as long a period as feasible.

Alcohol use is clearly modifiable, although there does not appear to be any difference in risk according to timing of alcohol consumption during early, middle or late adulthood, and there is no clear evidence that a decrease in alcohol use later in life will reduce breast cancer risk. Nevertheless, as in recommendations for diet, weight control, and physical activity, advice regarding moderation of alcohol use is generally well placed. There is evidence for an interaction between menopausal hormone use and alcohol use, so that women who consume two or more drinks daily and also use hormones are at higher risk than those exposed to either factor alone (36). Thus, women on postmenopausal hormones should be particularly cautioned against regular alcohol use.

It is not clear whether mammographic density is modifiable through life-style changes. There is clearly a large genetic component to the determinants of mammographic density, as discussed previously. In contrast, the impact of dietary restriction or physical activity has been difficult to demonstrate conclusively. In a study of a low fat dietary intervention, no change in breast density was observed (37), and there are no specific dietary patterns associated with high density. A recent systemic review of 20 studies did not identify a significant association between physical activity and mammographic density (38). However, breast density decrease with pharmacologic intervention (tamoxifen) was

associated with tamoxifen benefit in the IBIS trial (9), suggesting that with some preventive interventions, this may be a useful surrogate endpoint of benefit.

Current users of combination postmenopausal hormone therapy clearly experience an increased risk of breast cancer (39). The risk elevation appears to dissipate once hormone use is discontinued, and, therefore, high risk women should be advised to abstain from use of combination hormone therapy except for the control of menopausal symptoms, and then to use these in the lowest effective dose for the shortest possible time. In addition, it is reasonable to target hormone replacement to specific symptoms: for example, for vaginal dryness, low dose vaginal estrogen replacement results in a far lower systemic exposure than oral therapy. Data from the WHI suggest that use of estradiol alone in hysterectomized women does not increase risk (40); this hypothesis needs further testing and is somewhat at odds with the results of cohort studies which showed a lower risk for estradiol alone than combination therapy, but risk was still higher than among non-users of postmenopausal hormones. Therefore, symptomatic postmenopausal women may use estradiol alone if they have undergone hysterectomy, but use in the absence of symptoms should still be discouraged.

Pharmacological Intervention

The clinical trials of breast cancer prevention are discussed fully, and referenced, in Chapter 20; the following discussion focuses on selection criteria that may guide use of specific medications based on risk profile and patient characteristics. Strong Level I evidence now supports the use of SERMs, and aromatase inhibitors (AIs) for primary prevention in healthy, high risk women. The landmark Breast Cancer Prevention Trial (BCPT) of the NSABP study led to the establishment of tamoxifen, the prototypic SERM, as a method to reduce risk of breast cancer in women, a finding confirmed by the IBIS-I trial. The equivalence of tamoxifen to the second generation SERM raloxifene (in postmenopausal women only) was established in the STAR (P-2) trial of the NSABP. The third generation of breast cancer prevention trials in postmenopausal women has demonstrated that two newer SERMs (lasofoxifene and arzoxifene) offer similar breast cancer risk reduction in postmenopausal women, with beneficial effects on bone, and for arzoxifene, similar thromboembolic risk (see Chapter 20 for full discussion). Finally, aromatase inhibitors have entered the primary prevention arena, with publication of early results of exemestane therapy in the MAP.3 trial. Recruitment to the IBIS-II trial (testing anastrozole against placebo) is now closed, and follow-up is ongoing.

SERMs

Tamoxifen remains the standard of care for premenopausal women who are risk eligible for pharmacologic prevention, with a low risk of significant adverse effects. It should also be considered in hysterectomized postmenopausal women because of the slightly greater efficacy seen in the 8-year follow-up publication of the STAR trial (41). The benefits of tamoxifen, therefore, include a one-half to one-third reduction in the risk of invasive breast cancer; a similar reduction in the risk of non-invasive breast cancer; a one-third reduction in the risk of new benign breast biopsies; a reduction in mammographic density; and a reduction in osteoporotic fractures (seen in the BCPT only with a significant 32% reduction in osteoporotic fractures) (41). Women who are high risk because of a history of atypical hyperplasia appear to derive a larger benefit from tamoxifen therapy, with a risk reduction of 46% (41). These women also seem to be more willing to accept recommendations for preventive medication; therefore, this discussion should be included in the management plan for all women with a biopsy diagnosis of atypical hyperplasia. At-risk women can also be reassured that the benefit of tamoxifen is long-lived, judging from the overview data reported by the Early Breast Cancer Trialists' Group, where incidence rates remain lower in women who used five years of tamoxifen therapy, going out to 15 years and confirmed by the long-term results of the IBIS-I trial, where the reduction in breast cancer incidence in the tamoxifen arm is maintained to the same degree or better in the second five-year period following cessation of tamoxifen therapy (42).

The possibility that the standard 20 mg dose of tamoxifen is not required for therapeutic efficacy has been considered by Decensi and colleagues in a series of studies (43) designed to examine the effect of dose reductions of tamoxifen. In a pre-surgical study of women with ER positive invasive breast cancer, a daily dose of 20 mg was compared to doses of 5 mg and 1 mg. There was equivalent reduction in tumor cell proliferation in all three groups, and serum biomarkers such as sex hormone binding globulin, fibrinogen, anti-thrombin III, and decreases in insulin-like growth factor showed a significant dose-response relationship, suggesting potentially lower for toxicity at lower doses. A Phase III trial in healthy postmenopausal women has completed accrual.

Post-menopausal women with an intact uterus should be offered raloxifene because the uterine toxicity of tamoxifen seen in the BCPT has not been observed with raloxifene. An apparently lower protective benefit against DCIS in the initial publication was less evident on longer follow-up (44). For the hysterectomized postmenopausal woman, the decision between tamoxifen and raloxifene would be a trade-off between the generally better tolerability of raloxifene and the somewhat better efficacy of tamoxifen.

Although it would be desirable to select women who are specifically at high risk for ER positive breast cancer for SERM therapy, at this time there is no basis for denying a woman tamoxifen therapy because of a predicted risk of ER negative disease, with the possible exception of breast cancer survivors with ER negative index primaries. Data from a subset analysis of the multiple outcomes for raloxifene (MORE) trial suggested that women with the highest quartile of serum estradiol levels were at highest risk and also derived the greatest benefit from raloxifene therapy (45). But a similar subset analysis by NSABP investigators showed no difference in breast cancer risk of BCPT participants by estradiol levels, and no differential benefit of tamoxifen therapy (46).

Toxicity of SERMS: The uptake of tamoxifen therapy among high risk women has been highly variable, with concerns about toxicity being widely discussed and publicized. Because tamoxifen is now being mainly used in premenopausal women, it should be noted that the risk of tamoxifen-induced uterine neoplasia increases with age, with prior use of postmenopausal hormone therapy, with BMI, and with increasing duration of tamoxifen use (particularly over 5 years). In the BCPT, women aged 49 years or younger experienced a non-significant excess of uterine cancer (RR = 1.42, 95% CI = 0.55–3.81); uterine safety is, therefore, a relatively minor concern in this age group. In contrast, there was a substantially higher frequency of uterine malignancy in older women (RR = 5.33, 95% CI = 2.47–13.17). Annual uterine surveillance with Papanicolaou smears and pelvic examination is, therefore, recommended for women with intact uteri who are using tamoxifen, with additional testing (transvaginal ultrasound, uterine biopsies) reserved for those with symptoms such as uterine bleeding or abnormalities on clinical surveillance.

The risk of thromboembolic disease (TED) associated with tamoxifen is increased approximately twofold, but, again, was observed mainly in older women (IBIS-I, NSABP P-1). With raloxifene, the risk of deep vein thrombosis and pulmonary embolism may be lower than with tamoxifen but the risk of stroke and transient ischemic attacks is similar. Subgroups of women who should not be offered SERM therapy include obese women, those with recent surgery, fracture, or immobilization who are at increased risk of thrombotic events. Data on the added risk associated with Factor V Leiden or prothrombin G20210→A (PT20210) mutations are mixed (47). Notably, thromboembolic events occur early in the course of treatment, and these predict a continued higher risk. Thus, increased risk of TED needs to be factored into the SERM therapy decision by women who have risk factors for it (i.e., overweight, smokers, wheelchair-confined), and it seems reasonable to advise women on tamoxifen therapy to discontinue use approximately two weeks prior to major surgery, but screening women who are SERM candidates for factor V Leiden or thrombin mutations is not warranted.

The risk-benefit balance of SERM therapy in postmenopausal women has been nicely synthesized by Freedman and colleagues in an analysis of pooled data from the BCPT, the STAR trial, and the Women's Health Initiative; this is presented in Figure 19-5. It is worth emphasizing that the toxicity of tamoxifen in women under 50 is low: the risk of uterine malignancy is essentially unchanged, and the risk of deep vein thrombosis is increased about twofold, but normalizes rapidly once the drug is discontinued (48).

The quality of life side effects such as hot flashes and vaginal symptoms as well as the perceived association of tamoxifen use with weight gain and depressive symptoms has resulted in low rates of tamoxifen acceptance by both pre- and postmenopausal women who are risk-eligible for tamoxifen. Discussion of the management options for these at the time when SERM use is recommended is helpful and can increase uptake of therapy. The use of low dose vaginal estradiol supplements (either estradiol coated rings, or low dose estradiol tablets) for vaginal symptoms has not been formally evaluated in relation to breast cancer risk, but is reasonable in women with vaginal symptoms as the systemic estrogen exposure with these preparations is extremely low and unlike estrogen-containing vaginal creams, serum estradiol levels are not affected. The alleviation of hot flashes with selective serotonin uptake inhibitors is helpful for many women on tamoxifen therapy but recent data regarding the deleterious effects of some of these compounds on CYP2D6 activity and, therefore, the formation of the active tamoxifen metabolites endoxifen and 4-hydoxytamoxifen suggest that selective serotonin reuptake inhibitors (SSRI) agents should be selected based on lack of CYP2D6 antagonism. Gabapentin is an alternative agent in women with severe hot flashes. The concomitant use of postmenopausal hormone therapy does not appear to alleviate hot flashes and data from the Italian and Marsden trials where hormone therapy was allowed, suggests that this interferes with the benefit of tamoxifen therapy. Additionally (although there are no specific data to this effect) one would worry that the uterine and thromboembolic toxicity of SERMs would increase if SERMS were combined with estrogen with or without progestins.

Aromatase Inhibitors

Aromatase inhibitors are the second group of breast cancer prevention agents, with data from therapy trials suggesting an improved benefit over tamoxifen in risk reduction for contralateral breast cancer, and early results from the MAP3 trial showing efficacy of exemestane for primary prevention of breast cancer in high risk postmenopausal women. Results from the IBIS II trial (testing anastrozole) should be available in the next several years, and additional data regarding the impact of anastrozole on contralateral breast events in women with DCIS is anticipated from the NSABP B-35 and IBIS II trials. For postmenopausal women with an intact uterus, or those with a history of (or risk factors for) thromboembolic disease, aromatase inhibitors are clearly an option. Although they are generally well tolerated, the musculoskeletal morbidity can be significant, and SERM therapy may be a better choice for women with musculoskeletal pain syndromes or osteopenia/osteoporosis. Longer follow-up of MAP.3 and maturation of IBIS II data will provide better information regarding the risk-benefit balance of these agents in healthy women (particularly the frequency of arthralgias, bone loss, fractures, loss of libido, vaginal dryness, and cardiovascular safety). At present, the use of AIs for primary prevention should be restricted to those women who are at significant risk (e.g., those with a history of LCIS) and have a contraindication to SERM therapy (e.g., a history of deep vein thrombosis). AIs may also be considered for primary prevention in women who have completed SERM therapy for breast cancer prophylaxi but continue to develop new atypical lesions of the breast.

Risk-Reducing Mastectomy

For selected women at high risk for breast cancer who are either not good candidates for pharmacologic risk reduction, or are highly motivated to reduce risk to the lowest level possible, prophylactic mastectomy may be a reasonable consideration. Indications for risk-reducing mastectomy have been outlined by the Society of Surgical Oncology (49), and include i) mutations in BRCA 1 and 2 or other genetic susceptibility genes; ii) strong family history with no demonstrable mutation; iii) histological risk factors; and iv) difficult surveillance. In the setting of a strong family history, genetic evaluation should be strongly encouraged; the identification of a cancer-causing mutation in the family will mean that individuals who test negative can be reassured that they are population risk. If a mutation cannot be identified following testing of the appropriate affected individuals in the family, mutations in as yet unidentified genes may be responsible and, after appropriate counseling, prophylactic mastectomy can be undertaken. The family history pattern in this setting would be similar to BRCA mutation families (early age of onset, at least two generations involved). Women with histological risk factors (atypical hyperplasia, LCIS) should first be given a full explanation of the risks and benefits of SERM therapy for chemoprevention as this subset derives a particularly large benefit from it. Prophylactic mastectomy in this setting should be reserved for women who have contraindications to SERM therapy, or are unwilling to take it and yet seek a substantial reduction in breast cancer risk. With the advent of MRI and ultrasound imaging, difficult surveillance should be an unusual indication for prophylactic mastectomy.

The option of risk-reducing mastectomy with nipple preservation has received attention recently, with several reported series showing that the procedure is feasible, with survival of the nipple-areolar complex in about 95% of women. However, the long-term safety of this procedure is not fully established, and bearing in mind the known possibility of new primary breast cancer following subcutaneous mastectomy (50), meticulous attention needs to be paid to complete resection of breast tissue (including the axillary tail) if this procedure is undertaken for risk reduction.

Women with intact uterus

Hysterectomized women

European Women

A

5-year projected Risk of IBC (%)	Tamoxifen *v* Placebo (with uterus) 50–59	60–69	70–79	Raloxifen *v* Placebo (with uterus) 50–59	60–69	70–79
1.5	–133	–310	–325	21	–11	–15
2.0	–105	–283	–298	43	11	7
2.5	–78	–255	–271	65	33	29
3.0	–51	–228	–244	86	55	51
3.5	–25	–202	–217	108	76	71
4.0	3	–175	–190	128	97	93
4.5	29	–148	–164	150	119	115
5.0	56	–121	–137	172	140	136
5.5	83	–95	–111	193	161	157
6.0	109	–69	–84	214	183	179
6.5	135	–42	–58	236	204	199
7.0	162	–15	–32	256	225	221

5-year projected risk of IBC is °1.67% — Using BCPT data WHI baseline rates — Combining RR form BCPT and STAR using WHI baseline rate

B

5-year projected Risk of IBC (%)	Tamoxifen *v* Placebo (with uterus) 50–59	60–69	70–79	Raloxifen *v* Placebo (with uterus) 50–59	60–69	70–79
1.5	3	–53	–93	27	2	–4
2.0	31	–26	–66	49	23	18
2.5	57	2	–39	71	45	40
3.0	84	29	–12	92	67	62
3.5	111	56	15	114	88	82
4.0	138	83	42	134	109	104
4.5	164	109	69	156	131	126
5.0	191	136	96	178	152	147
5.5	218	163	121	199	173	168
6.0	244	189	148	220	195	190
6.5	270	215	175	242	216	210
7.0	297	242	201	262	237	232

5-year projected risk of IBC is °1.67% — Using BCPT data WHI baseline rates — Combining RR form BCPT and STAR using WHI baseline rate

African American Women

C

5-year projected Risk of IBC (%)	Tamoxifen *v* Placebo (with uterus) 50–59	60–69	70–79	Raloxifen *v* Placebo (with uterus) 50–59	60–69	70–79
1.5	–144	–319	–349	–25	–68	–108
2.0	–117	–292	–322	–3	–46	–86
2.5	–89	–264	–294	19	–24	–64
3.0	–62	–237	–267	41	–3	–43
3.5	–36	–211	–241	62	19	–21
4.0	–9	–184	–214	83	40	–1
4.5	18	–157	–187	105	62	22
5.0	45	–130	–160	126	83	43
5.5	72	–105	–135	147	104	64
6.0	98	–78	–108	169	126	86
6.5	124	–51	–81	190	146	106
7.0	151	–25	–55	211	168	128

5-year projected risk of IBC is °1.67% — Using BCPT data WHI baseline rates — Combining RR form BCPT and STAR using WHI baseline rate

D

5-year projected Risk of IBC (%)	Tamoxifen *v* Placebo (with uterus) 50–59	60–69	70–79	Raloxifen *v* Placebo (with uterus) 50–59	60–69	70–79
1.5	–67	–111	–200	–21	–58	–101
2.0	–40	–84	–173	1	–36	–79
2.5	–12	–56	–145	23	–14	–57
3.0	15	–29	–118	45	8	–36
3.5	42	–3	–92	66	29	–14
4.0	69	25	–65	87	50	7
4.5	95	51	–38	109	72	29
5.0	122	78	–11	130	93	50
5.5	149	104	15	151	114	71
6.0	175	131	42	173	136	93
6.5	201	157	68	194	156	113
7.0	228	183	94	215	178	135

5-year projected risk of IBC is °1.67% — Using BCPT data WHI baseline rates — Combining RR form BCPT and STAR using WHI baseline rate

Blue: strong evidence of benefits outweighing risks **Yellow: moderate evidence of benefits outweighing risks**
Grey: benefits do not outweigh risks

FIGURE 19-5 Benefit/risk indices for tamoxifen and raloxifene chemoprevention by level of 5-year projected risk for invasive breast cancer (IBC) by age group. The upper panels show estimates for white, non-Hispanic women (**A:** uterus intact and **B:** without uterus); the lower panels show estimates for African American women (**C:** uterus intact, **D:** without uterus). Based on a woman's risk factors (age, ethnicity, breast cancer risk, and whether she has a uterus), one can calculate her probability of having a health event in 5 years in the absence or presence of preventive therapy. To summarize risks and benefits in a single index, Vogel et al. assigned weights of 1.0 for life-threatening events (IBC, hip fracture, endometrial cancer, stroke, and pulmonary embolism) and 0.5 for severe events (*in situ* breast cancer and deep vein thrombosis). The net benefit index is the expected number of life-threatening equivalent events in 5 years without SERM therapy in 10,000 such women minus the expected number of life-threatening equivalent events if SERM therapy is used. (A severe event is regarded as equivalent to half a life-threatening event). For example, in Panel A, among 10,000 non-Hispanic, white women with a uterus, age 50 to 59 years, and with a 5-year IBC risk of 3.5%, one expects that 108 life-threatening equivalent events would be prevented in 5 years by taking raloxifene instead of placebo, and there is strong evidence (*P* .9; blue) that the benefits of taking raloxifene outweigh the risks. If tamoxifen were used instead, we estimate chemoprevention would result in 25 excess life-threatening events (*P* .6, gray). BCPT, Breast Cancer Prevention Trial; WHI, Women's Health Initiative; RR, relative risk; STAR, Study of Tamoxifen and Raloxifene.

MANAGEMENT SUMMARY

- Women at risk for sporadic breast cancer are a heterogeneous population and include those with endocrine and life-style risk factors, proliferative breast disease, and lesser degrees of family history.
- Breast cancer risk can be quantitated using a variety of statistical models, which perform well in general for groups of women but lack discriminatory power for individuals.
- The degree of improved precision resulting from the addition of mammographic density measurements to existing models is modest.
- Minimally invasive techniques to sample breast epithelium and identify occult epithelial atypia remain investigational at present.
- Women at increased risk should be counseled about modifiable risk factors: long-term lactation by women in child-bearing age, regular physical activity, the avoidance of more than light alcohol use, avoidance of postmenopausal weight gain, the limitation of postmenopausal hormone use to the alleviation of symptoms with lowest possible dose for the shortest possible time.
- Surveillance for this group of patients includes annual mammography, directed ultrasound, and magnetic resonance imaging for those with lifetime risk of 20% or greater, calculated using models based on family history (after a full discussion of risks and benefits, including the likely need for additional imaging and biopsies). Data regarding potential benefits of MRI surveillance for women with mammographically dense breasts and atypical epithelial lesions is being accumulated in ongoing trials.
- Pharmacologic intervention to reduce breast cancer risk consists of tamoxifen for premenopausal women, and raloxifene or exemestane for postmenopausal women. Hysterectomized, postmenopausal women, particularly those with musculoskeletal concerns, should be given the option of tamoxifen therapy, with a discussion of the marginally better preventive efficacy of tamoxifen compared to raloxifene.
- Prophylactic mastectomy should be reserved for those at markedly increased life-time risk (e.g., 30% or greater) who are unable or unwilling to take risk-reducing medication, and seek prophylactic mastectomy as a way to manage their risk.

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CHAPTER 20

Chemoprevention

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CHAPTER CONTENTS

INTRODUCTION

Breast cancers represent the highest proportion of noncutaneous cancer in women in the United States. Current estimates predict more than 226,000 diagnoses of breast cancer in these women, resulting in 39,000 deaths in 2012 alone (1). Critical insights have been and continue to be established in breast carcinogenesis, resulting in strategies enabling more effective screening, risk assessment, risk reduction, and intervention.

Screening methods, such as digital mammography and breast MRI scans, are now routine, with standard practice including annual mammographic screening for all women beginning at age 40 (2) and annual MRI scans gaining in use for women at very high risk. Other tests not yet routine but gaining in use include breast ultrasound and tomography analyses.

Effective prevention of breast cancer is critically dependent upon the identification of high-risk patients and has been more thoroughly developed than other cancers. Classification of individuals at high risk based upon known risk factors and biomarkers specific for breast cancer (e.g., obesity, alcohol consumption, *BRCA1/2, TP53, PTEN*, mammographic breast density, family history, and endocrine-related risks, such as lack of children and early menarche) facilitates the identification of women most likely to benefit from early intervention. This enables targeted chemoprevention specifically within higher risk populations, maximizing the potential for effective prevention. To this end, models aimed at assessing risk have been developed and continue to be the focus of studies seeking to further improve their effectiveness at predicting breast cancer risk. These include the Gail, Tyrer-Cuzick ("IBIS"), Berry-Parmigiani-Aguilar (*BRCA*-Pro), Claus, and Couch models as well as the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) (3,4). Each of these models was developed to facilitate stratification of the population into categories of predictable risk, defining individuals at low, average, moderate, high and very high risk, thereby enabling the identification of those most likely to benefit from preventive therapies.

In addition to screening and risk assessment, recent advances in breast carcinogenesis research have led to more effective strategies for risk reduction. Prophylactic bilateral mastectomies, which have demonstrated a 90% reduction of breast cancer risk, are currently used as an aggressive strategy for primary breast cancer prevention among extremely high-risk women (e.g., *BRCA1/2* carriers) (5). However, breast cancer prevention incorporates both less aggressive strategies designed for the general population (e.g., behavioral approaches reducing exposure to carcinogens such as medical radiation, limiting alcohol consumption, and maintaining a healthy weight) as well as the more aggressive risk-based approaches (e.g., preventive therapeutics, bilateral mastectomy, and possibly vaccines). Today, primary breast cancer prevention efforts integrate these strategies, centering on reducing exposure to known carcinogens and exogenous estrogen in combination with behavioral strategies to reduce risk. The remaining prevention strategies are used in high-risk groups, including preventive therapies approved by the FDA (e.g., tamoxifen and raloxifene), surgical strategies (bilateral mastectomies), and additional interventions, such as novel drugs and vaccines currently being tested in clinical trials.

Chemoprevention provides the means to reduce breast cancer incidence and is the current focus of a broad range of studies investigating the therapeutic potential of natural and synthetic agents for the prevention of breast cancer. However, as breast cancer encompasses both estrogen receptor (ER)-positive and ER-negative subtypes, distinct chemopreventive strategies may be required for effective intervention. This requires the evaluation of both short- and long-term toxicities of preventive agents to establish the individualized risk–benefit ratios.

In this chapter, we will outline the results of landmark clinical studies testing the selective estrogen receptor modulators (SERMs) tamoxifen and raloxifene that demonstrated the effectiveness of chemoprevention in breast cancer. We will also review additional studies targeting the ER for breast cancer prevention as well as strategies focused

on decreasing risk of ER-negative breast cancer. Finally, we will summarize current recommendations for management of women at increased risk of both ER-positive and ER-negative breast cancer. Strategies incorporating multiple aspects of prevention carry the highest potential for effective reduction of breast cancer incidence and mortality. Furthermore, those strategies addressing the individual patient as a whole, combining risk assessment, screening, and preventive strategies, will lay the foundation for breast cancer prevention in the future.

BREAST CANCER CHEMOPREVENTION

Antiestrogen drugs are highly effective for the treatment of breast cancer and have been shown to reduce the incidence of second primary breast cancers in women with early stage breast cancer (6,7). These results led to testing selective estrogen receptor modulators (SERMs), as well as other hormonal agents, for primary prevention of breast cancer in high-risk women.

Selective Estrogen Receptor Modulators (SERMs)

Five antiestrogen SERMs have been tested in clinical trials over the past two decades, including tamoxifen, raloxifene, idoxifene, arzoxifene, and lasofoxifene. The first-generation SERM, tamoxifen, was the first FDA-approved endocrine preventive therapy in high-risk women; the four large Phase III cancer prevention trials testing tamoxifen are outlined in Table 20-1. In addition, three Phase III studies have been conducted to determine the preventive effects of the second generation SERM, raloxifene, on breast cancer, followed by a fourth study comparing treatment with raloxifene versus tamoxifen. More recently, two Phase III studies have tested the third generation SERMs lasofoxifene and arzoxifene.

Tamoxifen

Endocrine treatment has been shown to reduce recurrence and mortality rates of ER-positive breast cancer and is able to do so in a manner independent of chemotherapy (6). The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) recently reported an updated meta-analyses for women in trials that examined the 10- to 15-year follow-up effects of 5 years of adjuvant tamoxifen (6,7). This report demonstrated that second primary breast cancers were reduced by 50% in women using tamoxifen. These studies laid the foundation for investigations focused on the development of breast cancer preventive drugs and resulted in a series of Phase III tamoxifen prevention trials in moderate-to-high-risk women with no diagnosis of breast cancer (Table 20-1). These four Phase III studies follow in chronological order and form the initial timeline for SERM-based therapeutic breast cancer prevention.

Royal Marsden Trial: Recruitment for the Royal Marsden Tamoxifen Breast Cancer Prevention Trial extended from 1986 to 1996 (8). Initially designed as a pilot trial, the primary goal was to determine the preventive effects of tamoxifen in 2,494 high-risk undiagnosed women. 20-year follow-up results identified a non-statistically significant decrease in overall (hazard ratio [HR] = 0.84, CI 0.64–1.10, p = .2) and invasive (HR = 0.78, CI 0.58–1.04, p = .005) breast cancer incidence following tamoxifen treatment (8). In addition, this study demonstrated a significant effect of tamoxifen on ER-positive (HR = 0.61, CI 0.43–0.864) but not ER-negative breast cancers.

NSABP P-1 (BCPT) Trial: The largest of the SERM breast cancer prevention trials, the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT) P-1, recruited 13,388 women from 1992–1996 (9). The effect of 5 years of tamoxifen treatment (20 mg/day, n = 6,681) on the incidence of invasive breast cancer was investigated in pre- and postmenopausal women at increased risk of breast cancer. A 49% decrease in invasive breast cancer was seen with tamoxifen versus placebo (relative risk [RR] = 0.51, CI 0.39–0.66). These initial results were reported in 1998 and led to early termination of the trial, followed by FDA approval of tamoxifen for treatment of women at high risk of breast cancer. The 7-year follow-up results confirmed the initial study findings, demonstrating reductions in invasive (RR = 0.57, CI 0.46–0.70), noninvasive (RR = 0.63, CI 0.45–0.89), ER-positive (RR = 0.38, CI 0.28–0.50), and ductal carcinoma *in situ* (DCIS) (HR = 0.54, CI 0.36–0.80) breast cancers, but no decrease in ER-negative tumor incidence (9). Although the NSABP P-1 trial also identified toxicity associated with tamoxifen, including increased hot flushes, vaginal discharge, and increased risk of endometrial cancer and thromboembolic events, the study established tamoxifen as the most effective treatment strategy for the prevention of breast cancer, particularly, ER-positive breast cancer.

Italian Tamoxifen Prevention Study: The Italian Randomized Tamoxifen Prevention Trial recruited 5,408 women at normal risk of breast cancer (10). However, to avoid the undesired side effect of increased incidence of endometrial cancer, the Italian trial limited the study population to healthy women who had previously undergone a hysterectomy. Importantly, many of these women took postmenopausal hormones after their hysterectomy. An unanticipated high subject dropout rate (26%) resulted in early termination of recruitment, but follow-up was continued with the previously enrolled subjects. While no statistically significant reduction in breast cancer incidence was initially observed, the 11-year follow-up report demonstrated a 76% reduction in hormone receptor (HR)-positive breast cancers in high-risk patients previously treated with a bilateral oophorectomy (RR = 0.24, CI 0.10–0.59), suggesting a preventive effect associated with tamoxifen (10).

IBIS-I Trial: Recruitment for the International Breast Cancer Intervention Study I breast cancer prevention trial spanned from 1992 to 2001 and resulted in the accrual of 7,154 women at high risk for breast cancer (11). With the primary objective of identifying whether the risk–benefit ratio associated with tamoxifen treatment was sufficient to support its use for the prevention of breast cancer, this study measured breast cancer incidence following 5 years of treatment with tamoxifen (20 mg/day, n = 3,578) versus placebo (n = 3,566). The 96-month follow-up report demonstrated a reduction of risk in subjects not receiving hormone replacement therapy (HRT) while on treatment that was limited to all (RR = 0.62, CI 0.46–0.83), ER-positive (RR = 0.49, CI 0.32–0.74), and DCIS (HR = 0.52, CI 0.27–0.99) breast cancer, although a non-statistically significant decrease in ER-negative breast cancer was reported. In addition, 5 years of tamoxifen treatment was associated with an improved long-term risk–benefit ratio characterized by a cancer preventive benefit persisting for 10 years and a reduction in toxicity after stopping treatment (11).

Adverse Events Associated with Tamoxifen Treatment: Across the four large-scale Phase III tamoxifen cancer prevention trials (all treating with 20 mg/day for 5 years, except the Royal Marsden Trial, which included 8 years of treatment), endometrial/uterine cancer and thromboembolic

TABLE 20-1

Selective Estrogen-Receptor Modulator (SERM) Breast Cancer Prevention Studies

	Trial	*Participants*	*Study Design*	*Reduction in Incidence*	*RR/HR (95%CI)*
TAMOXIFEN	Royal Marsden[1,2] (Recruitment: 1986–1996)	• 2,494 high-risk women • 30–70 y of age	1,238 tamoxifen (20 mg/d) and 1,233 placebo Treatment time: for 8 y	All breast cancers: 16% Invasive breast cancer: 22% Invasive ER-positive breast cancer: 39%	HR 0.84 (0.64–1.10) HR 0.78 (0.58–1.04) HR 0.61 (0.43–0.86)
	NOTE: No difference initially; longer follow-up showed reductions in invasive and ER-positive breast cancer incidence, but no significant change in ER-negative or overall breast cancer incidence				
	NSABP-P1(BCPT)[3,4] (Recruitment: 1992–1997)	• 13,388 high-risk women • >35 y of age	6,681 tamoxifen (20 mg/d) and 6,707 placebo Treatment time: 5 y Follow-up: 7 y	Invasive breast cancer: 43% Invasive ER-positive breast cancer: 62% Noninvasive DCIS/LCIS breast cancer: 37%	RR 0.57 (0.46–0.70) RR 0.38 (0.28–0.50) RR 0.63 (0.45–0.89)
	Italian[5,6] (Recruitment: 1992–1997)	• 5,408 normal-risk women with a hysterectomy • 35–70 y of age	2,700 tamoxifen (20 mg/d) and 2,708 placebo Treatment time: 5 y Follow-up: 11 y	All breast cancers: 16% Invasive breast cancer: 20% Invasive ER-positive breast cancer: –10% Noninvasive breast cancer: –50%	RR 0.84 (0.60–1.17) RR 0.80 (0.56–1.15) RR 1.10 (0.59–2.05) RR 1.50 (0.53–4.20)
	IBIS-I[7,8] (Recruitment: 1992–2001)	• 7,154 high-risk women • 35–70 y of age	3,579 tamoxifen (20 mg/d) and 3,575 placebo Treatment time: 5 y Follow-up: 96-mo	All breast cancers: 27% Invasive breast cancer: 26% Invasive ER-positive breast cancer: 34% Noninvasive DCIS breast cancer: 37%	RR 0.73 (0.58–0.91) RR 0.74 (0.58–0.94) RR 0.66 (0.50–0.87) RR 0.63 (0.32–1.20)
RALOXIFENE	MORE[9] (Recruitment: 1994–1998)	• 7,705 postmenopausal women with low BMD • <80 y of age	2,557 raloxifene (60 mg/d), 2,572 raloxifene (120 mg/d) and 2,576 placebo Treatment time: 4 y Follow-up: 40 mos avg.	All breast cancers: 65% Invasive breast cancer: 76% Invasive ER-positive breast cancer: 90%	RR 0.35 (0.21–0.58) RR 0.24 (0.13–0.44) RR 0.10 (0.04–0.24)
	CORE[10] (Recruitment: 1998–2002)	• 5,213 postmenopausal women with low BMD (reconsented from MORE trial) • <80 y of age	3,510 raloxifene (60 mg/d) and 1,703 placebo Treatment time: an additional 4 years after 4 y of raloxifene on MORE trial	All breast cancers: 50% Invasive breast cancer: 59% Invasive ER-positive breast cancer: 66% Noninvasive breast cancer: –78%	HR 0.50 (0.30–0.82) HR 0.41 (0.24–0.71) HR 0.34 (0.18–0.66) HR 1.78 (0.37–8.61)
	RUTH[11] (Recruitment: 1998–2000)	• 10,101 postmenopausal women with CHD • >35 y of age	5,044 raloxifene (60 mg/d) and 5,057 placebo Treatment time: median 5.6 y	All breast cancers: 33% Invasive breast cancer: 44% Invasive ER-positive breast cancer: 55% Noninvasive breast cancer: –117% Reduction in invasive ER-positive tumors	HR 0.67 (0.47–0.96) HR 0.56 (0.38–0.83) HR 0.45 (0.28–0.72) HR 2.17 (0.75–6.24)

TAM VS RALOX	NSABP-P2[12,13] (STAR) (Recruitment: 1999–2004)	• 19,490 high-risk, post-menopausal women • >35 y of age	9,736 tamoxifen (20 mg/d) and 9,754 raloxifene (60 mg/d) Treatment time: 5 y Follow-up: median 81-mo	*Raloxifene vs. tamoxifen:* Invasive breast cancer: –24% Noninvasive DCIS breast cancer: –22% Noninvasive DCIS/LCIS breast cancer: –2%	 RR 1.24 (1.05–1.47) RR 1.22 (0.88–1.69) RR 1.02 (0.61–1.70)
	NOTE: Accrual figures as represented on 81-mo follow-up report			*Extrapolated data for raloxifene vs. placebo:* Invasive breast cancer: 38% Noninvasive breast cancer: 39%	
LASOFOXIFENE	PEARL[14,15] (Recruitment: 2001–2007)	• 8,556 women with low BMD • 59–80 y of age	2,852 lasofoxifene (0.25 mg/d), 2,852 lasofoxifene (0.5 mg/d) and 2,852 placebo Treatment time: 5 y	*0.5 mg lasofoxifene vs. placebo:* All breast cancers: 79% Invasive ER-positive breast cancer: 83% Noninvasive DCIS breast cancer: 50%	 HR 0.21 (0.08–0.55) HR 0.17 (0.05–0.57) HR 0.50 (0.09–2.73)
ARZOXIFENE	GENERATIONS[16,17] (Recruitment: 2004–2009)	• 9,354 women with low BMD • 60-85 y of age	4,676 arzoxifene (20 mg/d) and 4,678 placebo Treatment time: ≤60 mo (Results reported are at 48 mo follow-up)	All breast cancers: 59% Invasive ER-positive breast cancer: 70% Noninvasive breast cancer: 70% Noninvasive DCIS breast cancer: 62%	HR 0.41 (0.25–0.68) HR 0.30 (0.14–0.63) HR 0.30 (0.08–1.09) HR 0.38 (0.10–1.42)

bone mineral density (BMD); continued outcomes of raloxifene evaluation (CORE); coronary heart disease (CHD); International Breast Intervention Study (IBIS-I); Italian Randomized Tamoxifen Prevention Trial (Italian); Multiple Outcomes of Raloxifene Evaluation (MORE); National Surgical Adjuvant Breast and Bowel Project Breast Cancer Prevention Trial (BCPT) P1 (NSABP-P1); National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P2 (NSABP-P2); Postmenopausal Evaluation and Risk-Reduction with Lasofoxifene (PEARL) Trial; Raloxifene Use for the Heart (RUTH) Trial; Royal Marsden Tamoxifen Prevention Trial (Royal Marsden).

Data from: [1,2]Powles TJ, et al. *J Natl Cancer Inst* 2007; 99(4):283–290 and *Br J Cancer* 1989; 60(1):126–131; [3,4]Fisher B, et al. *J Natl Cancer Inst* 2005; 97(22):1652–1662 and 1998; 90(18): 1371–1388; [5,6]Veronesi U, et al. *J Natl Cancer Inst* 2007; 99(9):727–737 and 2003; 95(2):160–5; [7,8]Cuzick J, et al. *Lancet* 2002; 360(9336):817–824 and *J Natl Cancer Inst* 2007; 99(4):272–282; [9]Cauley JA, et al. *Breast Cancer Res Treat* 2001; 65(2):125–134; [10]Vogel VG, et al. *Clin Breast Cancer* 2009; 9(1):45–50; [11]Grady D, et al. *J Natl Cancer Inst* 2008; 100(12):854–61; [12,13]Vogel VG, et al. *JAMA* 2006; 295(23):2727–2741 and *Cancer Prev Res* (Phila) 2010; 3(6):696–706; [14,15]Cummings SR, et al. *N Engl J Med* 2010; 362(8):686–696 and LaCroix AZ, et al. *J Natl Cancer Inst* 2010; 102(22):1706–1715; [16,17]Powles TJ, et al. *Breast Cancer Res Treat* 2012; 134(1):299–306 and Cummings SR, et al. *J Bone Miner Res* 2011; 26(2):397–404.

and cardiovascular events constituted the most common adverse events (8–11). Other negative side effects most consistently reported within these studies included cerebrovascular events, vaginal symptoms, and hot flushes or cold/night sweats (Table 20-2). In addition, an increase in risk of cataracts was observed in subjects receiving tamoxifen versus placebo in the NSABP P-1 (21%) and IBIS-I (0.4%, not statistically significant) trials. Most negative effects related to tamoxifen treatment did not persist beyond the active treatment period, and while long-term follow-up reports demonstrate no significant increase in total or cause-specific death, neither do they demonstrate a significant improvement in survival among subjects taking tamoxifen versus placebo (Tables 20-2 and 20-3).

Endometrial/Uterine Cancer Increased risk of endometrial cancer following treatment with tamoxifen was reported in the Royal Marsden, NSABP P-1, and IBIS-1 Trials. The first published evidence of this was in the 1998 interim analysis of the Royal Marsden study that, by the 20-year follow-up, identified a 2.5-fold increase in endometrial cancer for subjects who had received tamoxifen versus placebo (8). The NSABP P-1 and IBIS-1 Trials have also reported a 1.5- to 3.4-fold elevated risk of endometrial cancer associated with tamoxifen therapy in participants ≥50 years of age (9). The majority of all endometrial cancer cases (53 in the tamoxifen arm, 17 in the placebo arm) were classified as International Federation of Gynecology and Obstetrics (FIGO) (12) stage I.

Thromboembolic and Cardiovascular Events Primary incidences of thromboembolic and cardiovascular events consistently reported in the four trials were in increased rates of stroke and venous thromboembolic events. Strokes were 25% lower for subjects in the tamoxifen arm of the Royal Marsden Trial (8); however, the NSABP P-1 (9), IBIS-I (11), and Italian (10) trials reported non-statistically significant increased rates of stroke/cerebrovascular accidents in the tamoxifen study arm. Increased incidence of deep vein thrombosis and overall thromboembolic events was reported in the tamoxifen arms of the Royal Marsden (8), IBIS-I (11), and NSABP P-1 (9) trials.

Risk vs. Benefit: In an analysis of the risks and benefits associated with tamoxifen treatment for the prevention of breast cancer, Gail and coworkers concluded that these are dependent on the age, race, and breast cancer risk level of the individual (13). They described the increased risk for deep vein thrombosis, endometrial cancer, pulmonary embolism, and stroke, predicting 15, 16, 15, and 13, respectively, additional cases per 1,000 women following 5 years of tamoxifen treatment. In addition, differential efficacy of tamoxifen was age and race dependent, with the overall benefit defined as 97, 53, and 1 fewer cases for invasive breast cancer, *in situ* breast cancer, and hip fractures, respectively, per 1,000 women treated with tamoxifen for 5 years.

Due to the variation in risk–benefit effects and ratios for African American women versus white women, the Gail model, originally developed to predict risk in white women using the NCI's Breast Cancer Risk Assessment Tool (www.cancer.gov/bcrisktool), has been updated specifically for African American women. This risk assessment model, known as the Women's Contraceptive and Reproductive Experiences (CARE) model, more accurately predicts risk of breast cancer within this population. Finally, while tamoxifen has been shown to significantly reduce risk of invasive breast cancer by 49%, a greatly increased benefit is seen in women with prior atypical ductal hyperplasia (ADH) and lobular carcinoma *in situ* (LCIS) lesions, which exhibit relative reductions of 86% and 56%, respectively (14).

Preventive Therapy is Now Standard of Care: Collectively, the results of the tamoxifen trials, particularly the dramatic results of the NSABP P-1 breast cancer prevention trial, led to FDA approval of the SERM tamoxifen as a viable therapeutic strategy for breast cancer risk reduction. This decision, representing the first approval of a preventive agent for breast cancer risk reduction by the FDA, has led to the acceptance of tamoxifen as the standard premenopausal endocrine therapy for the prevention of breast cancer, especially ER-positive breast cancer.

In 1999, based upon the collective results of these four Phase III randomized clinical trials investigating the effects of tamoxifen in the prevention of breast cancer, the American Society of Clinical Oncology (ASCO) published a review of the data with recommendations for its use as a cancer preventive therapy (15). The most recent ASCO guidelines include tamoxifen therapy (20 mg/d for 5 years) as a treatment option for long-term (≥10 years) risk reduction of invasive ER-positive breast cancer in premenopausal women ≥35 years of age with LCIS or a 5-year projected absolute risk of breast cancer ≥1.66% (16). However, tamoxifen should not be used in women with a history or at high risk of deep venous thrombosis, pulmonary embolism, or cerebral vascular accidents. In addition, ASCO guidelines recommend avoiding tamoxifen use in individuals who are immobilized, pregnant, nursing, or receiving HRT. Despite FDA approval and consensus recommendations by ASCO and other professional organizations, tamoxifen is very rarely used for breast cancer prevention due to patient concerns about side effects and a lack of demonstrated survival benefit from tamoxifen use in this setting.

Raloxifene

Raloxifene was initially developed as a potential therapeutic agent for osteoporosis for the prevention of bone fractures. Three large-scale Phase III raloxifene clinical trials have since investigated the effects of the drug versus placebo as a preventive therapy for breast cancer, bone fractures, and heart disease (the Multiple Outcomes of Raloxifene Evaluation [MORE], Continuing Outcomes Relevant to Evista [CORE], and Raloxifene Use for the Heart [RUTH] trials) (Table 20-1). In addition, the NSABP Study of Tamoxifen and Raloxifene (STAR) P-2 Trial compared raloxifene to tamoxifen. The consecutive nature of the information provided by the MORE/CORE trials has enabled the comparison of incidence rates among women treated for 4 years (duration of treatment in the MORE trial) versus 8 years (duration of treatment in both the MORE and CORE trials).

Multiple Outcomes of Raloxifene Evaluation: In the 1990s, the MORE trial was conducted to determine the effectiveness of raloxifene in reducing bone fractures in 7,705 postmenopausal women 80 years of age or younger with osteoporosis, but also investigated the secondary endpoints of breast cancer and heart disease (17). Participants were treated for 3 years with low-dose raloxifene (60 mg/day), high-dose raloxifene (120 mg/day), or placebo, and all participants received both calcium and Vitamin D (cholecalciferol) supplements. This trial demonstrated that postmenopausal raloxifene treatment was associated with a dose-dependent reduction in vertebral bone fractures (60 mg/d: RR = 0.7, CI 0.5–0.8; 120 mg/d: RR = 0.5, CI 0.4–0.7) (17). In addition, dose-independent reductions were observed in all (RR = 0.35, CI 0.21–0.58) and invasive breast cancers (RR = 0.24, CI 0.13–0.44). However, as with tamoxifen, the study results demonstrated a decrease in risk of ER-positive (RR = 0.10, CI 0.04–0.24), but not ER-negative breast cancer.

TABLE 20-2

Select Adverse Events and Side Effects Associated with Tamoxifen

	Royal Marsden Trial[1,2] *(events on treatment or for entire follow-up; participant figures at 20-year follow-up)*			*NSABP P-1 Trial (BCPT)*[3,4] *(participant figures at 7-year follow-up)*				*Italian Study*[5,6] *(events during active treatment; participant figures at baseline)*				*IBIS-1 Trial*[7,8] *(entire period; participant figures at 96-month follow-up)*			
Reported Event	*Tamoxifen n = 1079*	*Placebo n = 1034*	*p-value*	*Tamoxifen n = 6681, rate*[b]	*Placebo n = 6707, rate*[b]	*RR*[a]	*95% CI*	*Tamoxifen n = 2700, rate*[b]	*Placebo n = 2708, rate*[b]	*RR*[a]	*95% CI*	*Tamoxifen %; n = 3579*	*Placebo %, n = 3575*	*RR*[a]	*95% CI*
Osteoporotic fractures	19	22	0.6	80, 1.97	116, 2.88	0.68	0.51–0.92	—	—	—	—	91, 2.5	76, 2.1	1.19	0.89–1.62
Cancer:	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Endometrial/ uterine	13	5	0.06	—	—	—	—	—	—	—	—	17	11	1.55	0.68–3.65
Invasive	—	—	—	53, 2.24	17, 0.68	3.28	1.87–6.03	—	—	—	—	—	—	—	—
in situ	—	—	—	1, 0.04	3, 0.12	0.35	0.01–13.17	—	—	—	—	—	—	—	—
Other than breast and/or endometrial/ uterine	64[e]	70[e]	0.8[e]	178[e]	155[e]	—	—	106, 4.37[d]	91, 3.73[d]	1.17[d]	0.88-1.55[d]	—	—	—	—
Cerebrovascular event	—	—	—	—	—	—	—	12, 1.19	7, 0.67	1.78	0.70–4.52	32, 1.12	34, 1.19	0.94	0.56–1.57
Cardiovascular problems (vascular-related):	10	12	0.2	—	—	—	—	5, 0.49	5, 0.48	1.04	0.30–3.58	—	—	—	—
Stroke	7	9	0.6	71, 1.75	50, 1.23	1.24	0.97–2.08	6, 0.59	2, 0.19	3.11	0.63–15.4	—	—	—	—
Stroke/cerebrovascular accident	—	—	—	—	—	—	—	—	—	—	—	15, 0.53	12, 0.42	1.25	0.55–2.93
Transient ischemic attack (TIA)	—	—	—	31, 0.76	34, 0.84	0.91	0.54–1.52	6, 0.59	5, 0.48	1.24	0.38–4.08	17, 0.60	22, 0.77	0.77	0.39–1.52
Pulmonary embolism (PE)	—	—	—	28, 0.69	13, 0.32	2.15	1.08–4.51	—	—	—	—	—	—	—	—
Venous thromboembolic event	8	3	0.2	—	—	—	—	44, 4.45	28, 2.72	1.63	1.02–2.62	—	—	—	—

(Continued)

TABLE 20-2 *(Continued)*

Select Adverse Events and Side Effects Associated with Tamoxifen

	Royal Marsden Trial[1,2] *(events on treatment or for entire follow-up; participant figures at 20-year follow-up)*			*NSABP P-1 Trial (BCPT)*[3,4] *(participant figures at 7-year follow-up)*				*Italian Study*[5,6] *(events during active treatment; participant figures at baseline)*				*IBIS-1 Trial*[7,8] *(entire period; participant figures at 96-month follow-up)*			
Reported Event	*Tamoxifen n = 1079*	*Placebo n = 1034*	*p-value*	*Tamoxifen n = 6681, rate*[b]	*Placebo n = 6707, rate*[b]	*RR*[a]	*95% CI*	*Tamoxifen n = 2700, rate*[b]	*Placebo n = 2708, rate*[b]	*RR*[a]	*95% CI*	*Tamoxifen %; n = 3579*	*Placebo %, n = 3575*	*RR*[a]	*95% CI*
Superficial thrombophlebitis	—	—	—	—	—	—	—	—	—	—	—	23, 0.81	8, 0.28	2.88	1.24–7.44
Deep vein thrombosis (DVT)	4[c]	2[c]	—	49, 1.21	34, 0.84	1.44	0.91–2.30	—	—	—	—	—	—	—	—
DVT/PE	—	—	—	—	—	—	—	—	—	—	—	23, 0.81	8, 0.28	1.84	1.21–2.82
Gynecological problems	37	13	0.001	—	—	—	—	—	—	—	—	—	—	—	—
Hysterectomy	177	96	<0.001	—	—	—	—	—	—	—	—	—	—	—	—
Vaginal symptoms:	37	17	0.008	—	—	—	—	—	—	—	—	—	—	—	—
Discharge	321	167	<0.001	54.77	34.13	1.60	—	505, 60.60	173, 17.59	3.44	2.90–4.09	—	—	—	—
Dryness	—	—	—	—	—	—	—	295, 34.09	269, 29.93	1.14	0.97–1.34	—	—	—	—
Genital itching	—	—	—	47.13	38.29	1.23	—	—	—	—	—	—	—	—	—
Bleeding	—	—	—	21.96	21.26	1.03	—	—	—	—	—	—	—	—	—
Hot flashes	598	394	<0.001	77.66	65.04	1.19	—	635, 119.29	446, 67.20	1.78	1.57–2.00	81.8	67.7		*p* value <.0001
Cold sweats	—	—	—	21.40	14.77	1.45	—	—	—	—	—	—	—	—	—
Night sweats	—	—	—	66.80	54.92	1.22	—	—	—	—	—	—	—	—	—

[a]Relative risk (tamoxifen vs. placebo); [b]Per 1,000 women; [c]Results identified in interim report; [d]Other than breast cancer; [e]Other than breast or endometrial/uterine cancer.
Data from: [1,2]Powles TJ, et al. *J Natl Cancer Inst* 2007;99(4):283–290 and *Br J Cancer* 1989;60(1):126–131; [3,4]Fisher B, et al. *J Natl Cancer Inst* 2005;97(22):1652–1662 and 1998;90(18):1371–1388; [5,6]Veronesi U, et al. *J Natl Cancer Inst* 2007;99(9):727–737 and 2003;95(2):160–165; [7,8]Cuzick J, et al. *Lancet* 2002;360(9336):817–824 and *J Natl Cancer Inst* 2007;99(4):272–282.

TABLE 20-3

Select Causes of Death in Tamoxifen Trials

	Royal Marsden Trial[1,2] *(events on treatment or for entire follow-up; participant figures at 20-year follow-up)*				*NSABP P-1 Trial (BCPT)*[3,4] *(participant figures at 7-year follow-up)*				*Italian Study*[5,6] *(events during active treatment; participant figures at baseline)*				*IBIS-1 Trial*[7,8] *(entire period; participant figures at 96-month follow-up)*			
Cause of Death	*Tamoxifen n = 1079*	*Placebo n = 1034*	*HR*[a]	*95% CI; p-value*	*Tamoxifen n = 6681, rate*[c]	*Placebo n = 6707, rate*[c]	*RR*[b]	*95% CI*	*Tamoxifen n = 2700, rate*[c]	*Placebo n = 2708, rate*[c]	*RR*[b]	*95% CI*	*Tamoxifen %; n = 3579*	*Placebo %, n = 3575*	*RR*[b]	*95% CI*
Total Deaths:	54	54	0.99	0.95	126, 3.08	114, 2.80	1.10	0.85–1.43	36, 1.46	38, 1.54	0.95	0.60–1.49	65	55	—	—
Cancer:	42	33	—	—	57	71	—	—	22	25	—	—	36	34	—	—
Breast	—	—	—	—	12	11	—	—	2	2	—	—	11	13	—	—
Endometrial/ uterine	—	—	—	—	0	1	—	—	—	—	—	—	1	0	—	—
Other	—	—	—	—	45	59	—	—	20	23	—	—	53	42	—	—
Cardiac & vascular disease	—	—	—	—												
Stroke	1	2	—	—	35	22	—	—	3	5	—	—	6	2	—	—
Heart Condition	6	2	—	—												
Other	5	17	—	—	33	21	—	—	11	8	—	—	19	16	—	—

[a]Hazard ratio; [b]Relative risk (tamoxifen vs. placebo); [c]Per 1000 women)

Data from: [1,2]Powles TJ, et al. *J Natl Cancer Inst* 2007;99(4):283–290 and *Br J Cancer* 1989;60(1):126–131; [3,4]Fisher B, et al. *J Natl Cancer Inst* 2005;97(22):1652–1662 and 1998;90(18): 1371–1388; [5,6]Veronesi U, et al. *J Natl Cancer Inst* 2007;99(9):727–737 and 2003;95(2):160–165; [7,8]Cuzick J, et al. *Lancet* 2002;360(9336):817–824 and *J Natl Cancer Inst* 2007;99(4):272–282.

Continuing outcomes relevant to evista trial: The CORE Trial was designed to enable an additional 4 years of raloxifene therapy in participants of the MORE trial to better ascertain the preventive efficacy of raloxifene in reduction of bone fracture incidence, with a secondary endpoint of ER-positive breast cancer incidence (18). Participants from the placebo arm of the MORE Trial were treated with placebo in the CORE Trial (n = 1,703), while subjects from either treatment arm received raloxifene (60 mg/day, n = 3,510) for an additional 4 years. While both the 4-year CORE results and 8-year MORE/CORE results demonstrated reduced incidence of invasive and ER-positive breast cancers, extended treatment resulted in increased levels of prevention. Incidence rates after 4-years versus 8-years of raloxifene therapy identified decreases in invasive breast cancer incidence of 31% (HR = 0.69, CI 0.23–2.01) and 59% (HR = 0.41, CI 0.21–0.81), respectively (18). These results suggest persistence of the preventive effects of raloxifene following discontinuation of therapy as well as increased prevention with 8 years of treatment. Decreased incidence of ER-positive breast cancer also improved with extended treatment, rising from 66% (HR = 0.34, CI 0.18–0.66) to 76% (HR = 0.24, CI 0.15–0.40); however, no significant decrease in ER-negative breast cancer was observed with either treatment regimen (17,18).

Raloxifene Use for the Heart (RUTH) Trial: The Raloxifene Use for the Heart (RUTH) Trial investigated the incidence of both invasive breast cancer and coronary events associated with 5 years of raloxifene treatment (60 mg/day) (19). Between 1998 and 2000, a total of 10,101 women were randomized to the study (raloxifene: n = 5,044; placebo: n = 5,057). Reductions of 44% in invasive (HR = 0.56, CI 0.38–0.83) and 55% in ER-positive (HR = 0.45, CI 0.28–0.72) breast cancer incidence were identified in subjects receiving raloxifene treatment for a median of 5.6 years, while no significant reductions were found in ER-negative or noninvasive breast cancers. This confirmed the results of the MORE and CORE trials (19).

Other Beneficial Effects: The MORE and CORE trials studied the effects of raloxifene in women with osteoporosis. Consequently, data included vertebral and nonvertebral fractures as well as changes in bone mineral density and bone turnover. 36 months of raloxifene treatment resulted in a 30% to 50% reduction in vertebral fractures (low-dose arm: RR = 0.7, CI 0.5–0.8; high-dose arm: RR = 0.5, CI 0.4–0.7) and a 2% to 3% increase in bone mineral density of both the spine and hip ($p < .001$) compared to the placebo (17). Statistically significant reductions of nonvertebral fractures were limited to ankle fractures, which decreased by 40% in the pooled raloxifene arms (RR = 0.6, CI 0.4–1.0). These results demonstrate that raloxifene treatment of postmenopausal women with osteoporosis leads to preservation of bone density and reductions of both bone turnover and risk of vertebral fractures. The RUTH trial confirmed this, reporting 35% fewer vertebral fractures in raloxifene patients (HR = 0.65, CI 0.47–0.89) (19).

Adverse Events Associated With Raloxifene Treatment: Raloxifene therapy has been shown to result in adverse thromboembolic/cardiovascular events as well as other negative side effects, including hot flushes, leg cramps, hypertension, peripheral edema, and vaginal discharge and bleeding.

Endometrial/Uterine Cancer No significant difference was observed in incidence of endometrial cancer in the raloxifene or placebo arms of the MORE or CORE trials (17). Likewise, the RUTH study found no significant change in risk of endometrial cancer between treatment arms (19). Collectively, these results demonstrate that treatment with raloxifene, unlike tamoxifen, does not increase risk of endometrial cancer.

Thromboembolic and Cardiovascular Events 36 to 40 months of raloxifene therapy produced increased risk of venous thromboembolic events in the MORE trial (17). These events, including deep vein thrombophlebitis and pulmonary embolism, were significant for both low- and high-dose treatment groups compared to placebo (pooled treatment arms: RR = 3.1, CI 1.5–6.2). The RUTH trial confirmed this, reporting a 44% increase in venous thromboembolic events in participants of the raloxifene arm (HR = 1.44, CI 1.06–1.95) (19). In addition, the RUTH trial reported a 49% increased risk of fatal cerebrovascular stroke following raloxifene treatment (HR = 1.49, CI 1.00–2.24).

Coronary Heart Disease The RUTH trial was designed specifically to determine whether treatment with raloxifene affected coronary heart disease (CHD). However, results from the RUTH trial identified no effect on the risk of CHD associated with raloxifene treatment in women with CHD or at increased risk for CHD (19).

Study of Tamoxifen and Raloxifene (Star) / NSABP P-2 Trial: Following the initial report of the NSABP P-1 (BCPT) and the other tamoxifen and raloxifene prevention trials (17,18), the NSABP STAR P-2 Trial was developed (Table 20-1) (20). The primary objective of this study was to compare the effects, beneficial and toxicity-related, of the two SERMs tamoxifen and raloxifene. This two-arm trial investigated the effects of 5 years of treatment with tamoxifen (20 mg/day) versus raloxifene (60 mg/day). While the initial results showed equal efficacy of tamoxifen and raloxifene in reduction of breast cancer risk, the 81-month follow-up results demonstrated that raloxifene was 76% as effective as tamoxifen in preventing invasive breast cancer (RR = 1.24, CI 1.05–1.47), and 78% as effective as tamoxifen in preventing both noninvasive breast cancer (RR = 1.22, CI 0.95–1.59) and DCIS (RR = 1.22, CI 0.88–1.69) (Fig. 20-1) (20). Furthermore, after stopping treatment, persistence of the cancer-preventive effect of tamoxifen was observed, while that of raloxifene began to diminish (Fig. 20-1). Conversely, decreased toxicity was observed with raloxifene, with subjects characterized by significantly fewer invasive endometrial/uterine cancers (RR = 0.55, CI 0.36–0.83), uterine hyperplasia (RR = 0.19, CI 0.12–0.29), thromboembolic events (RR = 0.75, CI 0.60–0.93), and cataracts developed during follow-up (RR = 0.80, CI 0.72–0.89). No differences in the frequency of ischemic heart disease events or strokes or in the number of deaths were observed (Fig. 20-2) (20).

Ultimately, this study demonstrated the effectiveness of both tamoxifen and raloxifene in reducing risk of breast cancer in high-risk postmenopausal women. More specifically, the NSABP P-2 results identify both subject- and SERM-specific risk–benefit ratios associated with treatment (21). These findings support either agent for breast cancer prevention in high-risk postmenopausal women. Raloxifene preventive therapy may be particularly effective for a high-risk postmenopausal woman who has an intact uterus and is concerned about risk of hot flushes and thromboembolic side effects, while tamoxifen preventive therapy may be preferred in a high-risk postmenopausal woman without a uterus (21).

Recommendations for the Use of Raloxifene for Breast Cancer Risk Reduction: In 2007, following the MORE, CORE, and RUTH clinical trials, the FDA approved raloxifene hydrochloride as a preventive therapy for postmenopausal women with

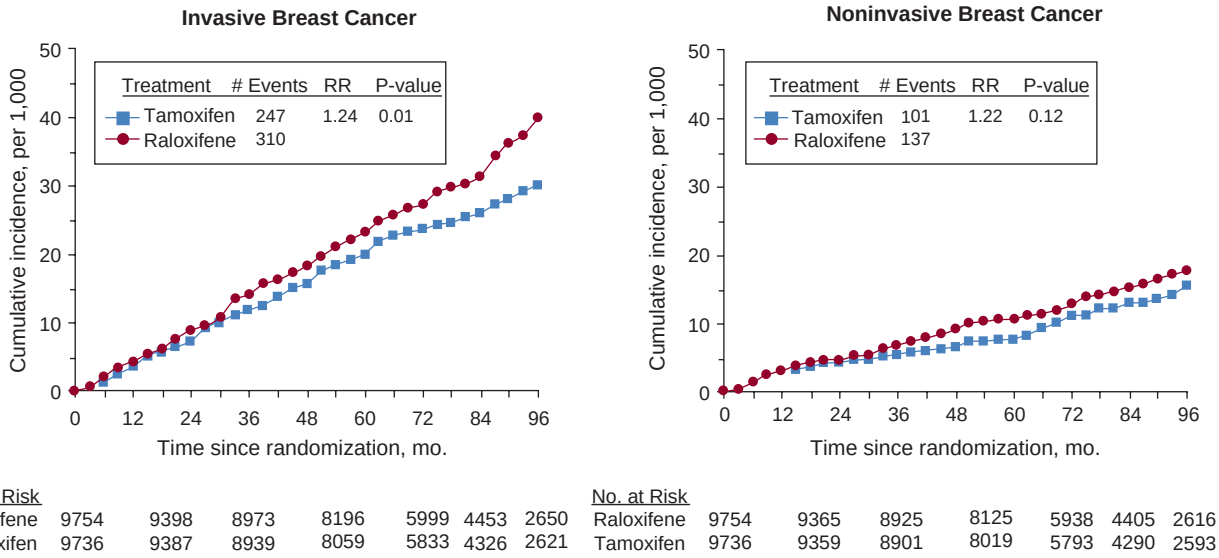


FIGURE 20-1 **NSABP STAR P-2 Trial: Updated results.** 81-month follow-up incidence rates for invasive and noninvasive breast cancer following treatment with tamoxifen or raloxifene. (From Vogel V, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: preventing breast cancer. *Cancer Prev Res* 2010;3(6):696–706, with permission.)

osteoporosis or at high risk for invasive breast cancer. In 2009, ASCO published its first clinical practice recommendation of raloxifene (20 mg/day for 5 years) for the prevention of ER-positive breast cancer in postmenopausal women without a history or at risk of thromboembolic events, a recommendation retained in the 2013 update (16).

Other SERMs

While no SERMs aside from tamoxifen and raloxifene have been approved by the FDA, several have been and continue to be the focus of recent/current clinical trials. Among these are the third-generation SERMs lasofoxifene and arzoxifene.

Lasofoxifene

Several studies have investigated the third-generation SERM lasofoxifene in postmenopausal women, including the Postmenopausal Evaluation and Risk Reduction with Lasofoxifene (PEARL) (22) and Comparison of Raloxifene and Lasofoxifene (CORAL) (23) trials. The PEARL trial, a 5-year Phase III study investigating lasofoxifene versus placebo, demonstrated a 79% decrease in breast cancer following treatment with lasofoxifene (0.5 mg/day) (Table 20-1) and was associated with fewer adverse events (including major coronary events, vertebral and nonvertebral fractures, and stroke) than previously studied SERMs (22). The 2-year Phase III CORAL trial compared the effects of raloxifene, lasofoxifene, and placebo on bone mineral density; it identified similar adverse effect profiles associated with both SERMs, but a more profound decrease in low-density lipoprotein cholesterol levels and improved bone mineral density of the lumbar spine in subjects treated with lasofoxifene (23).

Arzoxifene

Another third-generation SERM, arzoxifene, was the focus of the GENERATIONS trial, which accrued a total of 9,354 postmenopausal women with osteoporosis or low bone mass (osteopenia) (Table 20-1) (2). The objective of the study was to determine the effects of 60 months of arzoxifene (20 mg/day; n = 4,676) or placebo (n = 4,678) on vertebral fracture in osteoporotic women and to evaluate its ability to prevent

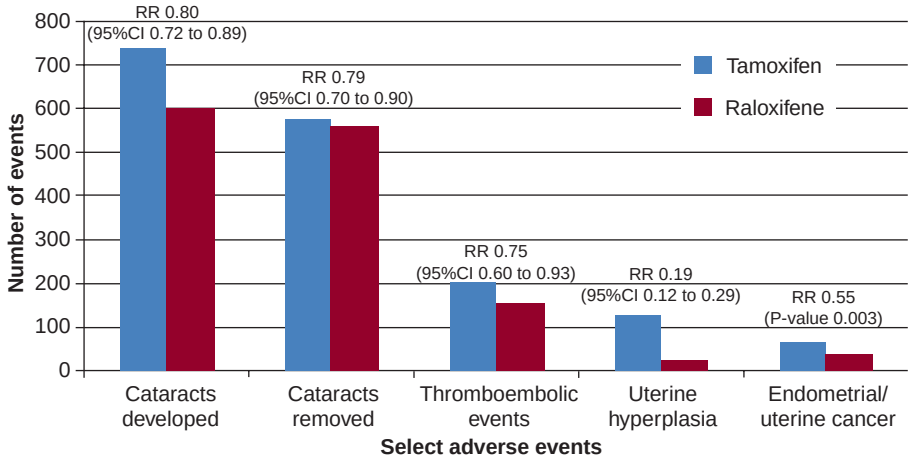


FIGURE 20-2 **NSABP STAR P-2 Trial: Updated results.** Comparison of select adverse events following treatment with tamoxifen versus raloxifene. (Adapted from Vogel V, et al. Update of the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) P-2 Trial: Preventing Breast Cancer. *Cancer Prev Res* 2010;3(6):696–706.)

invasive breast cancer in all subjects. The 48-month follow-up reported reduced risk of both invasive (HR = 0.30, CI 0.08–1.09) and ER-positive (HR = 0.30, CI 0.14–0.63) breast cancer in arzoxifene subjects (2). In addition, subjects with osteoporosis had a 41% reduction in risk of vertebral fractures (RR = 0.58, 95% CI 0.45–0.77). Non-statistically significant increases in incidence of endometrial cancer and endometrial hyperplasia occurred in participants treated with arzoxifene. Arzoxifene was also associated with increased risk of venous thromboembolic events (63 of the 90 events, 95% CI 1.5–3.7), and other side effects, including vaginal symptoms, hot flushes, and muscle cramps.

Next-Generation SERMs

To improve upon the risk–benefit profiles of tamoxifen and raloxifene, other SERMs developed and investigated include toremifene, acolbifene, idoxifene, droloxifene, levomeloxifene, bazedoxifene, and ospemifene. Although tamoxifen and raloxifene are FDA approved as drugs for breast cancer risk reduction, newer SERMs have demonstrated potential as preventive alternatives with high tolerability for postmenopausal osteoporotic women. Dr. Jack Cuzick and collaborators recently published an updated meta-analysis comparing the effects of SERMs reported in 9 large-scale prevention trials (Fig. 20-3) (24). As demonstrated within the individual trials, treatment with SERMs decreases incidence of overall and ER-positive breast cancer, but not ER-negative breast cancer. Furthermore, all SERMs, with the singular exception of raloxifene, reduce incidence of DCIS; the next-generation SERMs, particularly lasofoxifene (0.5 mg/d), reduce incidence of vertebral fractures but increase incidence of venous thromboembolic events. Continued development of third-generation SERMs for cancer preventive indications is needed and will require substantial support from pharmaceutical companies. However, these companies have become increasingly reluctant to develop preventive agents due to liability concerns focused on rare toxicities of drugs given to cancer-free women.

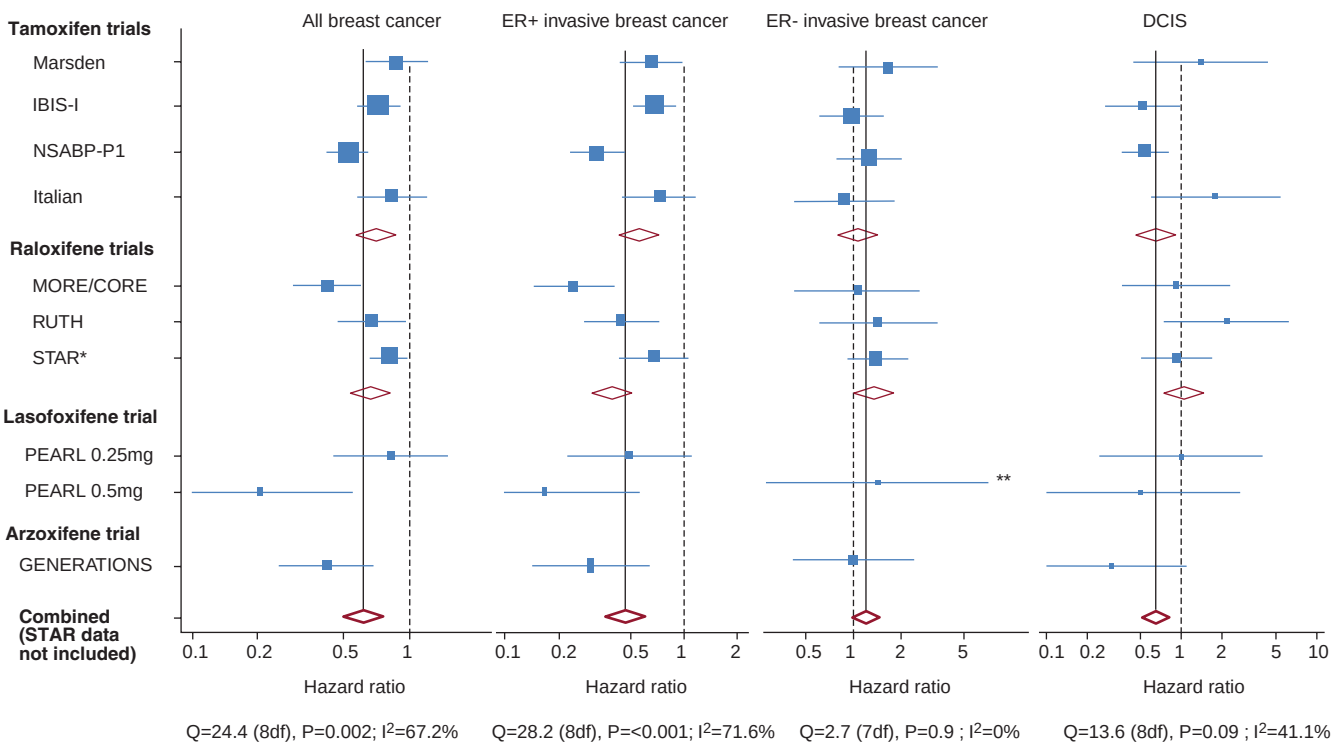
SERMs as Standard of Care for Breast Cancer Prevention

Due to the lack of long-term evaluation of the next generation SERMs in large-scale Phase III prevention trials, tamoxifen and raloxifene remain the only SERMs currently used for the clinical prevention of breast cancer. Of three drugs recommended by ASCO for the prevention of breast cancer, these two SERMs are the only FDA-approved drugs for breast cancer risk reduction (16).

Aromatase Inhibitors (AIs)

Effect of AIs on Second Primary Tumors from Treatment Trials

Multiple clinical studies have investigated aromatase inhibitors (AIs), which inhibit the conversion of peripheral androgens to estrogens, for the treatment of women with hormone receptor positive breast cancer. AIs tested include the reversible, nonsteroidal inhibitors anastrozole and letrozole as well as the irreversible steroidal inhibitor exemestane. The cancer preventive potential of AIs was discovered by investigating the development of second primary contralateral tumors in women with early breast cancer



*Adjusted by overall tamoxifen effect to give raloxifene vs. placebo comparison, STAR data not included in overall effect ** Pooled data

FIGURE 20-3 **Preventive impact of SERMs.** (From Cuzick J, et al. Selective oestrogen receptor modulators in prevention of breast cancer: an updated meta-analysis of individual participant data. *Lancet* 2013;381(9880):1827–1834, with permission.)

who were treated with AIs as adjuvant therapy. These trials have demonstrated significant reductions in both contralateral and ER-positive breast cancer following treatment with anastrozole (25–28) as well as lower incidence of uterine cancers, hot flushes, and venous thromboembolic events but higher incidence of bone fractures (25). In addition, the effectiveness of the AIs letrozole (29,30) and exemestane (8,31–33) versus tamoxifen for the treatment of early breast cancer have demonstrated reduced risk of both recurrence and contralateral breast cancers associated with AI versus tamoxifen therapy (8,32). These findings have stimulated the development of several prevention trials testing AIs in women with DCIS or at high risk of breast cancer.

Prevention Trials

Trials of AIs in Women with DCIS Breast Cancer: Two Phase III trials are currently comparing the cancer preventive effect of anastrozole versus tamoxifen in women with DCIS. These studies, the NSABP B-35 and IBIS-II (DCIS) trials, are discussed in Chapter 23 (DCIS and Microinvasion), and summarized in Table 20-4. Results from these two studies, collectively encompassing over 7,000 women with DCIS (target accrual), are anticipated within the upcoming years and will help define incidence of breast cancer (DCIS recurrence, invasive and contralateral breast cancer) following 5 years of treatment with anastrozole (1 mg/day) versus tamoxifen (20 mg/day).

Trials of AIs in Women at High Risk of Breast Cancer: Two other Phase III breast cancer prevention trials have or are testing AIs in postmenopausal women at high risk of breast cancer, the NCIC-MAP.3 trial testing exemestane (34) and the second component of the IBIS-II trial, known as the IBIS-II Prevention trial, testing anastrozole (35) (Table 20-4). Initial results of the NCIC-MAP.3 trial (34) were recently reported and demonstrate that exemestane reduces the incidence of invasive breast cancer by 65% (HR = 0.35; 95% CI 0.18–0.70) and ER-positive breast cancer by 73% (HR = 0.27; 95% CI 0.12–0.60) (34) (Fig. 20-4). Furthermore, these results showed a favorable risk-to-benefit ratio supported by no significant change in quality of life or serious toxicities (Table 20-5). Adverse events reported include arthritis and hot flushes, but do not include osteoporosis or the endometrial cancers and thromboembolic events associated with tamoxifen. In a recent review by DeCensi et al. (36), the significant improvement in breast cancer preventive efficacy of exemestane as compared to SERMs was noted; however, the question of whether serious exemestane-induced toxicities occur, particularly bone-related toxicities, will depend upon extended follow-up results of the MAP.3 trial.

AIs as Standard of Care for Breast Cancer Prevention

Based upon the NCIC-MAP.3 trial results, the most recent ASCO consensus statement includes the recommendation to include exemestane (25 mg/d for 5 years) as a therapeutic alternative to tamoxifen and/or raloxifene in postmenopausal women ≥35 years of age with atypical hyperplasia, LCIS, or ER-positive breast cancer (16). While exemestane has not yet received approval by the FDA beyond use as an adjuvant treatment for breast cancer, ASCO's updated guidelines represent the first instance of a non-SERM drug being recommended for the prevention of breast cancer. The IBIS-II anastrozole trial results are anticipated in the near future and should clarify whether anastrozole will also be useful for breast cancer prevention.

PREVENTION OF ER-NEGATIVE BREAST CANCER

While Phase III clinical trials demonstrate the effectiveness of SERMs and AIs in preventing ER-positive breast cancer, there is a clear need for drugs that can prevent ER-negative breast cancer (Fig. 20-5) (37). Promising approaches include preventive therapy with retinoids, inhibitors of the HER2 family of receptor kinases, COX-2 inhibitors, PARP inhibitors, and metformin as well as vaccine approaches.

HER2/EGFR-*Tyrosine Kinase Inhibitors*

Overexpression of members of the *ErbB* family of growth factor receptors, particularly *ErbB2* (HER2, *neu*) (overexpressed in 20% to 25% of human breast cancers), can induce breast cell transformation (38). HER2 inhibitors, such as trastuzumab (Herceptin), pertuzumab, and lapatinib (an oral dual kinase inhibitor of HER2 and *EGFR*), are useful drugs for the treatment of HER2-positive breast cancer (38). Given the activity of these drugs in the treatment setting, they are now being tested in pre-clinical and early clinical trials as breast cancer preventive drugs (Table 20-6). Clinical trials testing trastuzumab for the treatment of HER2-positive DCIS include the Phase II trial reported by Kuerer et al. (39) and the ongoing Phase III NSABP B-43 trial. In the Phase II trial, an immunologic response (increased antibody-dependent cell mediated cytotoxicity), but no pathologic response or antiproliferative activity was noted following a single dose preoperative trastuzumab treatment (39). In the Phase III NSABP B-43 trial, women who have already had excisional surgery are being treated with radiation or radiation plus two doses of trastuzumab. The primary endpoint of this study is the cumulative incidence of ipsilateral invasive breast cancer, ipsilateral skin cancer recurrence, and ipsilateral DCIS.

Several pre-clinical and clinical studies of oral HER2 and *EGFR* receptor tyrosine kinase inhibitors have also been conducted, including studies of the *EGFR* inhibitor gefitinib and the dual *EGFR*/HER2 kinase inhibitor lapatinib. These studies have demonstrated a significant delay in time-to-tumor development of ER-negative, HER2-positive mammary tumors in *ErbB2*/HER2-transgenic mice with 9 months of treatment (40,41) and have provided the rationale to test lapatinib in early cancer prevention clinical trials (Table 20-6). Two Phase II trials have been developed testing the effects of lapatinib therapy prior to tumor excision on Ki67 immunohistochemical staining in DCIS cells in women with HER2-positive DCIS. In the DeCensi study, recent results identify that treatment with lapatinib (1,500 mg/day) reduces cell proliferation in breast cancer tissue, adjacent ductal intraepithelial neoplasia, and distant ductal hyperplasias (42). These results indicate an antiproliferative effect of lapatinib on both cancer and pre-cancerous cells. The second Phase II trial testing a lower dose of lapatinib (1,000 mg/day) is ongoing.

Other Cancer Prevention Agents

Retinoids: Derivatives of vitamin A, retinoids, regulate development, differentiation, and homeostasis in most cells by binding retinoic acid receptors (RARs) (43) and include the naturally occurring RAR ligands, such as all-trans retinoic acid (ATRA), alitretinoin (9-*cis*-RA), and isotretinoin (13-*cis*-RA). These agents have been shown to affect a number of mechanisms, including the down-regulation of expression of COX-2 and cyclin D1 (44), inhibition of AP-1 transcription factor activity (45), induction of cell cycle arrest at G1 (46), and overexpression of IGF binding proteins (IGF-BPs) 3 and 6 (45), RAR-beta (45), and TGF-beta (47). In addition, various

TABLE 20-4

Select Aromatase Inhibitor (AI) Breast Cancer Prevention Studies

Trial	*Participants*	*Study design*	*Primary endpoint(s) &/or reduction in Incidence*	*HR(95%CI)*	*p value*
DCIS TRIALS					
NSABP B-35 (Recruitment: 2003–2006)	• Planned: 3,000 women • Enrollment (Jan 2013): 3,104 women • Postmenopausal • With ER+/PR+ DCIS	anastrozole (1 mg/d) vs. tamoxifen (20 mg/d) Treatment time: 5 y	• Time to first event of breast cancer	Ongoing, estimated date of 1st report: March 2016	
IBIS-II (DCIS)[1,2] (Recruitment: 2003–2012)	• Planned: 4,000 women • Enrollment (May 2012): 2,980 women • Postmenopausal • With DCIS • 40–70 y of age	anastrozole (1 mg/d) vs. tamoxifen (20 mg/d) Treatment time: 5 y Follow-up: 5 y	• Development of invasive and non-invasive breast cancer with median 5-year follow- up	Ongoing, estimated date of 1st report: 2013–2014	
PREVENTION TRIALS					
NCIC-MAP.3[3] (Recruitment: 2004–2010)	• 4,560 women accrued • Postmenopausal • High risk of breast cancer • ≥35 y of age	2,285 exemestane (25 mg/d) and 2,275 placebo Treatment time: 5 y Follow-up: median 35 mo (at initial report)	Invasive breast cancer incidence. Invasive breast cancer: 65% Invasive ER-positive breast cancer: 73% Invasive PR-positive breast cancer: 74% Invasive breast cancer and DCIS: 53%	HR 0.35 (0.18–0.70) HR 0.27 (0.12–0.60) HR 0.26 (0.10–0.69) HR 0.47 (0.27–0.79)	 .002 <.001 .004 .004
IBIS-II (Recruitment: 2004–2012)	• Planned: 6,000 women • Enrollment (April 2012): 3,864 women • Postmenopausal • High risk of breast cancer • 40–70 y of age	anastrozole (1 mg/d) vs. placebo Treatment time: 5 y Follow-up: 5 y	• Development of invasive and non-invasive breast cancer with median 5-y follow- up	Ongoing, estimated date of 1st report: 2016	

Hazard ratio (HR); The Second International Breast Cancer Intervention Study (IBIS-II) Ductal carcinoma *in situ* (DCIS); National Surgical Adjuvant Breast and Bowel Project B-35 (NSABP B-35); The National Institute of Canada Clinical Trials Group Mammary Prevention.3 trial (NCIC CTG MAP.3, or NCIC-MAP.3).
Data from: [1,2]Cuzick J. *Expert Rev Anticancer Ther* 2008; 8(9):1377–1385 and Cuzick J. et al. *Lancet* 2003;361(9354):296–300; [3]Goss PE, et al. *N Engl J Med* 2011;364(25):2381–2391.

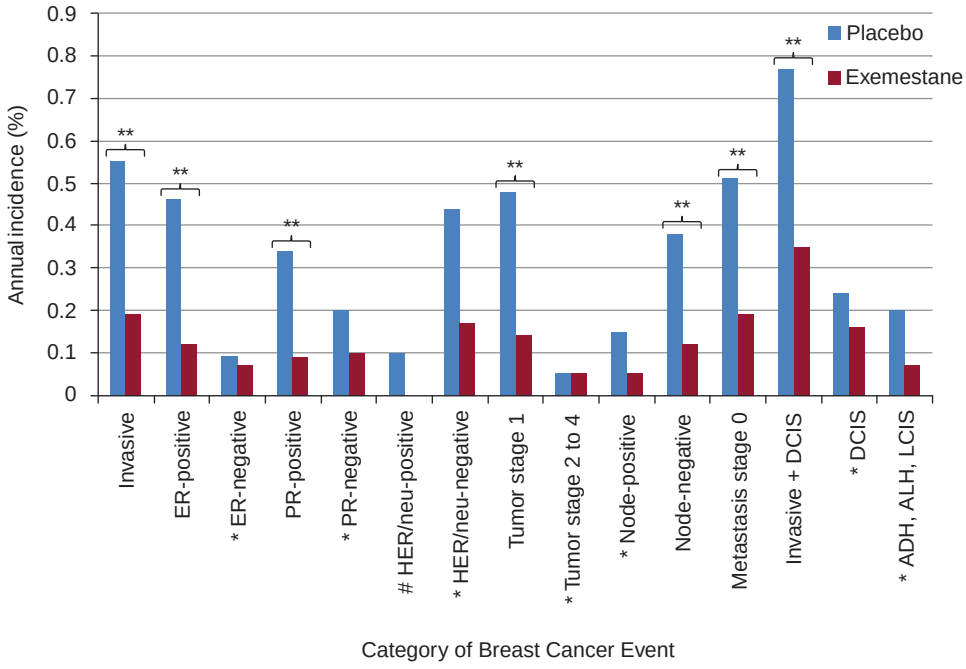


FIGURE 20-4 NCIC-MAP.3 Annual incidence rates of invasive and preinvasive breast cancer events by treatment group. (Adapted from Goss P, et al. Exemestane for breast cancer prevention in postmenopausal women. *N Engl J Med* 2011;364(25):2381–2391.) **Result is statistically significant; *Result not statistically significant; #Statistical significance not reported.

animal models have established the cancer preventive effects of 13-*cis*- and 9-*cis*-RA in mammary tumorigenesis in mice and rats (48,49), and second primary head and neck tumors in humans (50). However, toxicities associated with these retinoids have prevented either agent from being used as standard of care in the clinical setting (49,50).

In 2006, Veronesi and colleagues presented the 15-year results of a multicenter Phase III clinical trial investigating the effects of the synthetic retinoid fenretinide on the prevention of contralateral or second ipsilateral breast cancer (Table 20-7) (51). This study identified a reduction in risk of second primary breast tumors in premenopausal women. Furthermore, the preventive efficacy of fenretinide persisted for several years following cessation of treatment and was associated with minimal adverse events. This agent remains a promising prevention strategy, although formulation and drug supply have presented challenges to its further development.

TABLE 20-5

NCIC-MAP.3: Select Adverse Events and Side Effects Associated with Exemestane

	Exemestane (n = 2,240)		*Placebo (n = 2,248)*		
Reported Event (Grades 1–4[a])	*Number*	*Percent*	*Number*	*Percent*	*p-value*
Total events		88.0		85.0	0.003
Osteoporotic Events:					
Osteoporosis (new diagnosis)	37	1.7	30	1.3	0.39
Skeletal fracture	149	6.7	143	6.4	0.72
Cancer:					
Other than breast	50	2.2	44	2.0	—
Other solid tumors or hematologic malignant lesions	43	1.9	38	1.7	0.58
Cardiovascular problems	106	4.7	111	4.9	0.78
Vaginal symptoms					
Dryness	352	16	343	15	0.68
Hot flashes	900	40	718	32	<0.001
Sweating	486	22	433	19	0.046
Joint Pain	665	30	660	27	0.04

Adverse events and side effects include reflect issues reported with the SERM trials and/or events with ≥3% difference between exemestane and placebo.
[a]According to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.
Data adapted from Goss P, et al. Exemestane for breast cancer prevention in postmenopausal women. *N Engl J Med* 2011;364(25): 2381–2391.

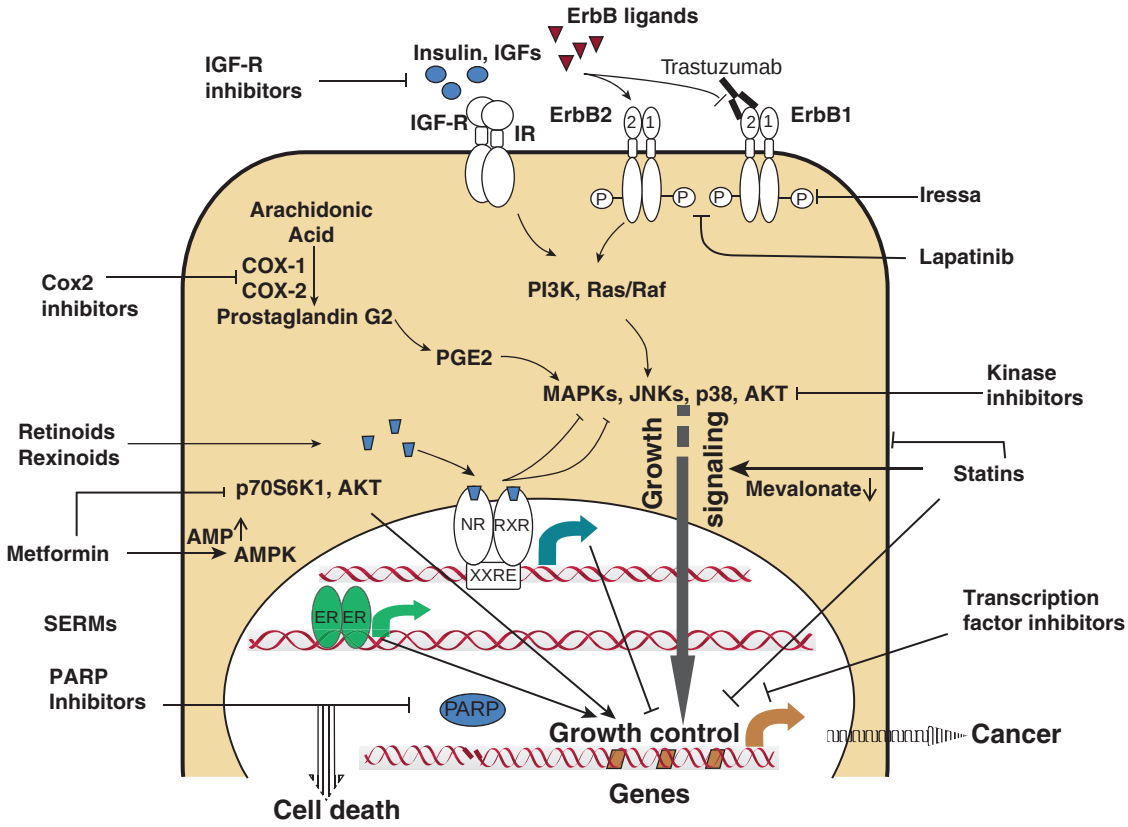


FIGURE 20-5 **Oncogenic pathways in the cell.** (Adapted from Uray I, Brown P. Chemoprevention of hormone receptor-negative breast cancer: new approaches needed; recent results. *Cancer Res* 2011;188:147–162.)

While retinoids bind RARs, rexinoids preferentially activate retinoid X receptors (RXRs), which are dimeric partners of RARs. Rexinoids, including bexarotene (LG1069) and the newer third-generation rexinoid LG100268, bind RXRs and activate the RAR:RXR dimeric transcription factor. A number of animal studies have already shown increased preventive efficacy as well as decreased toxicity following treatment with rexinoids versus retinoids (52–54). Results from studies in transgenic mice demonstrate prevention of ER-negative mammary tumorigenesis with either bexarotene or LG100268 (Fig. 20-6) (41,55), while combined LG100268-tamoxifen treatment has been shown to be more effective at suppressing mammary tumorigenesis than either drug alone (56). Moreover, toxicity resulting from treatment with LG100268 is significantly lower than that associated with bexarotene or naturally occurring retinoids. While results from a recently conducted Phase II clinical trial demonstrate that rexinoid treatment is associated with significant down-regulation of cyclin D1 and decreased cellular proliferation in breast tissue of postmenopausal women at high risk of breast cancer (57), it also caused toxicity (elevated serum triglycerides and subclinical hypothyroidism) and thus may be limited in use to high-risk women willing to tolerate moderate toxicity. The future of retinoids and rexinoids as cancer preventive agents depends upon upcoming results from pre-clinical and clinical studies currently testing the efficacy and toxicity of these agents in the preventive setting.

COX-2 Inhibitors: In 1988, Kune et al. demonstrated that prevention of colorectal cancer was possible through the use of nonsteroidal anti-inflammatory drugs (NSAIDs), which inhibit the eicosanoid pathway (58). Aspirin and other NSAIDs have been shown to inhibit cyclooxygenase (COX), for which two isoforms, COX-1 and COX-2, have been described. COX-1 is constitutively expressed in most cells, while inducible COX-2 expression is limited by location, state of inflammation, and/or mitogenic stimulation. The COX-2 inhibitor celecoxib has received FDA approval for use in reducing colonic polyps in individuals with familial adenomatous polyposis (FAP) (59).

Numerous epidemiological (60–64) studies have identified reduced cancer risk (e.g., lung, colon, breast) associated with long-term use of the irreversible COX-1 and COX-2 inhibitor, aspirin (63,64), and ongoing studies with extended follow-up periods will help to further establish the long-term prophylactic benefit of aspirin use (64). In addition, the preventive effects of NSAIDs and selective COX-2 inhibitors have been the focus of a variety of pre-clinical studies. Among these, dietary treatment with celecoxib has been shown to significantly reduce mammary tumors in MMTV-erbB2 transgenic mice (65) as well as breast tumor incidence (68%), multiplicity (86%), and volume (81%) in Sprague Dawley rats (66).

The preventive activity of NSAIDs and COX-2 inhibitors has also been the focus of a number of clinical studies; five such studies investigating the COX-2 inhibitor celecoxib on breast cancer are listed in Table 20-8. However, cardiovascular toxicities associated with COX-2 inhibitors discovered in large Phase III colon polyp prevention trials (67–71) have halted the development of celecoxib for chemoprevention, with several Phase II breast cancer prevention trials having been stopped due to concerns about rare but serious toxicities. Given the importance of COX-2 in carcinogenesis,

TABLE 20-6

Pre-clinical and Clinical Studies Testing *EGFR* and Her2 Inhibitors for the Prevention of Breast Cancer

Trial	*Phase/Participants*	*Study Design*	*Primary End Points*(S)/ *Results*	*HR (95%CI)*	*p value*
TRASTUZUMAB					
H.Kuerer/	Phase II	trastuzumab single dose therapy (8 mg/kg) vs. placebo	No significant pathologic response (size of DCIS lesions)		
W.Symmans[1]	• 24 women	Treatment was followed by surgery 14–28 d later	No significant change in proliferation (Ki-67 staining) or apoptosis (cleaved caspase-3 staining) Immunologic responses seen		
(Recruitment: 2005–2009)	• With HER2-positive DCIS				
M.Cobleigh	Phase III (Ongoing)	trastuzumab (2 doses at wk 1 and wk 4 plus radiation therapy (at 6 wks) versus radiation therapy alone (at 6 wks)	*Primary Endpoints (Ongoing):* Time from randomization to IIBCR-SCR-DCIS Time to IIBCR-SCR-DCIS compared across treatment arms		
NSABP B-43	• Planned: 2,000 women				
NCT00769379	• With HER2-positive DCIS (mixed DCIS/LCIS allowed)				
GEFITINIB					
C Lu /P Brown[2]	Pre-clinical Study	gefitinib (10 mg/kg) and gefitinib (100 mg/kg body) versus placebo	Delay in median time-to-tumor:		
	• 49 *MMTV-ErbB2* transgenic mice	Treatment time: 9 mo (3–12 mo of age) prior to developing tumors	High dose gefitinib: 310 d Control: 230 d		<.001
LAPATINIB					
T Strecker/	Pre-clinical Study	lapatinib (30 mg/kg) and lapatinib (75 mg/kg) versus placebo	Reduction in tumor development (high dose lapatinib vs. placebo at 418 d old): 69%		
P. Brown[3]	• 49 MMTV-ErbB2 transgenic mice	Treatment time: 12 mo (3–12 mo of age) prior to developing tumors			<.001
A DeCensi/	Phase IIb	lapatinib (1,500 mg/d) versus placebo	Reduction in cell proliferation (Ki-67) in:		
B Bonanni[4]	• 60 women	Treatment time: 3 wks, followed by resection	-breast cancer tissue		.008
(Recruitment: 2006–2009)	• With HER2-positive breast cancer		-adjacent ductal intraepithelial neoplasia (DIN)		.067
			-distant ductal hyperplasia without atypia (DH)		.006
P.Brown	Phase II (Ongoing)	lapatinib (1000 mg/d) versus placebo	*Primary Endpoints (Ongoing):*		
LAPIS Trial	• Planned: 60 women	Treatment time: 2–6 wks	Proliferation (Ki-67 staining)		
NCT0055152	• With HER2- or EGFR-positive DCIS		Toxicity Profile		

Abbreviations: Confidence interval CI, Conf: (DCIS) ductal carcinoma *in situ*; (HR) Hazard ratio; (IIBCR-SCR-DCIS) Ipsilateral invasive breast cancer recurrence, ipsilateral skin cancer recurrence, or ipsilateral DCIS; (NSABP43) National Surgical Breast and Bowel Project 43.

Data gathered from: [1]Kuerer HM, et al., *Cancer* 2011; 117(1):39–47; [2]Lu C, et al., *J Natl Cancer Inst* 2003; 95(24):1825–1833; [3]Strecker, T.E., et al., *J Natl Cancer Inst* 2009; 101(2):107–113; [4]De Censi, A., et al., *Cancer Prev Res (Phila)* 2011; 4(8):1181–1189.

TABLE 20-7

Phase III Clinical Breast Cancer Prevention Trial Results of Fenretinide in the Prevention of Second Primary Tumors in Women (30–70 years of age)

Event	*Treatment arm (fenretinide, n = 872)*	*Control arm (n = 867)*	*HR (95% CI)*
All Breast Cancer (contra- and ipsilateral)			
Premenopausal	83	126	0.62 (0.46–0.83)
Postmenopausal	85	64	1.23 (0.63–2.40)
Total	168	190	0.83 (0.67–1.03)
Contralateral Breast Cancer			
Premenopausal	26	43	0.63 (0.38–1.04)
Postmenopausal	45	34	1.23 (0.41–3.71)
Total	71	77	0.90 (0.65–1.26)
Ipsilateral Breast Cancer			
Premenopausal	57	83	0.61 (0.43–0.87)
Postmenopausal	40	32	1.16 (0.49–2.74)
Total	97	115	0.77 (0.58–1.02)

Both HR and CI were adjusted for menopausal status at time of randomization, type of primary tumor surgery, tumor size, and histology. As some subjects had both contra- and ipsilateral tumors as first recurrence events, these figures do not necessarily add up. CI, confidence interval; HR, hazard ratio. Data adapted from Veronesi, et al. Fifteen-year results of a randomized phase III trial of fenretinide to prevent second breast cancer. *Annals Oncol* 2006;17(7):1065–1071, with permission.

current research is focused on identifying alternative targetable molecules within this pathway, enabling safer, more effective preventive interventions.

Metformin: Metformin activates AMP-activated protein kinase (AMPK) and has become the first-line therapy of choice for type 2 diabetes mellitus as well as a treatment strategy for polycystic ovary syndrome (PCOS). A review of epidemiologic studies by Xue and Michels identified an association between type 2 diabetes and breast cancer risk, particularly apparent in postmenopausal women (72). In addition, treatment with metformin has been shown to inhibit breast cancer cell growth (73) and mammary tumor growth in *HER-2/neu* transgenic mice (74). Likewise, epidemiological studies investigating risk of breast cancer in patients being treated with metformin for diabetes have recently demonstrated significant reductions in risk of breast cancer following treatment with metformin versus other antidiabetic therapies (75–82). Following these studies, several early phase clinical trials showed reduced proliferation of breast cancer cells following metformin treatment (Table 20-9) (83).

Several additional clinical trials studying metformin are currently in progress or have yet to release results (Table 20-9), including the Phase III NCIC-MA.32 trial, in which women with early stage breast cancer are being treated with metformin. This trial will examine the effect of metformin on invasive disease-free survival, overall survival, and contralateral breast cancer incidence. Although study results are not expected for several years, the results of a window of opportunity study have been recently published, demonstrating decreased Ki67 staining and increased TUNEL staining (markers for proliferation and apoptosis, respectively), following treatment with metformin (83).

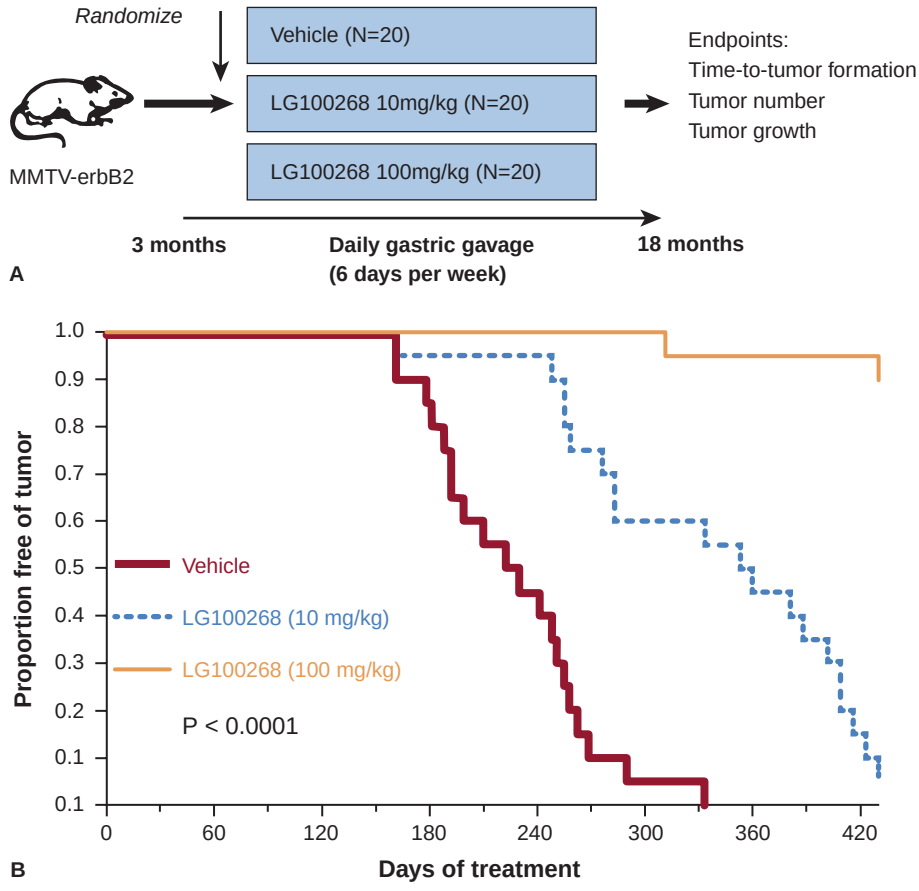


FIGURE 20-6 Inhibition of mammary tumor development in MMTV-erbB2 mice treated with LG100268 versus placebo. (From Li Y, et al. The rexinoid LG100268 prevents the development of preinvasive and invasive estrogen receptor-negative tumors in MMTV-erbB2 mice. *Clin Cancer Res* 2007;13(20):6224–6231, with permission.)

TABLE 20-8

Select Celecoxib (COX-2) Breast Cancer Prevention Studies

Trial, Pi & Site #	*Study Phase and Participants*	*Study Design*	*Primary Endpoint(S)*
NCT00328432 C Fabian University of Kansas (KU)	Phase IB (Completed) • Planned: 100 women • Pre-/postmenopausal • With newly diagnosed breast cancer	Arm 1: celecoxib (400 mg bid) Arm 2: placebo Treatment time: 10–42 d	Proliferation (Ki-67 IHC staining)
NCT00056082 C Fabian University of Kansas (KU)	Phase II (Completed) • Planned: 110 women • 18–55 y of age • Premenopausal • With high risk for ER-negative breast cancer	Arm 1: celecoxib (400 mg bid) Treatment time: 12 mo	Proliferation (Ki-67 IHC staining)
NCT00291694 C Fabian University of Kansas (KU)	Phase II (Completed) • Planned: 72 women • Pre-/postmenopausal • With hyperplasia of the breast	Arm 1: celecoxib (400 mg bid) Arm 2: placebo Treatment time: 12 mo	Proliferation (Ki-67 IHC staining)
N01-CA-9757 B Arun MD Anderson Cancer Center (MDACC)	Phase II (Completed) • Planned: 44 women • Pre-/postmenopausal • High risk	Arm 1: celecoxib (400 mg bid) Treatment time: 6 mo	Proliferation (Ki-67 IHC staining)
NCI-04-C-0044 J Eng-Wong National Cancer Institute (NCI)	Phase II (Ongoing) • Planned: 72 women • Postmenopausal • High risk	Arm 1: exemestane + celecoxib (400 mg bid) Arm 2: exemestane Treatment time: 5 y	Mammographic breast density

COX-2, ccyclo-oxygenase-2; ECOG, Eastern Cooperative Oncology Group; 15-PGDH, 15-hydroxyprostaglandin dehydrogenase; NCIC CTG, National Cancer Institute of Canada Clinical Trials Group; PG, prostaglandin; PGE2, prostaglandin E2; SWOG, Southwest Oncology Group.

Statins: Statins inhibit the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, which leads to reduced cellular biosynthesis of cholesterol, improved endothelial function, and modulation of the membrane microdomain (84). Epidemiologic studies of individuals taking lipid-lowering drugs (e.g., atorvastatin, cerivastatin, fluvastatin, lovastatin, simvastatin, pravastatin) have shown reduced risk of breast, prostate, and colorectal cancers (85–88). Furthermore, statins cause inhibition of proliferation in ER-negative breast cancer cell lines (89) and in ER-negative mouse models (90). However, epidemiological studies have produced mixed results: a meta-analysis of breast cancer studies failed to report a significant decrease in risk of breast cancer (91), while other studies have demonstrated reductions in risk approaching 50% (92). Furthermore, treatment with lipophilic statins has been shown to influence tumor phenotype (e.g., fewer ER/PR-negative tumors, lower tumor grade/stage), with increased effects from ≥1 year treatment before diagnosis of cancer (92).

A number of Phase II prevention trials investigating the biologic impact of statins in breast cancer prevention are currently in progress. Garwood et al. have reported increased apoptosis and reduced proliferation with short-term fluvastatin treatment (3 weeks of 20 or 80 mg/day) in subjects with high-grade breast cancer (93). In addition, positive results from other statin studies evaluating simvastatin as a preventive strategy for women at increased risk of breast cancer (a biomarker modulation study) (94) and for risk of recurrence (a large population-based cohort study) (95) have been reported recently. Overall, despite the somewhat controversial nature of the efficacy of statins, current findings support further investigation of these agents as potential breast cancer chemopreventive alternatives.

PARP Inhibitors: Inhibition of poly (ADP-ribose) polymerase (PARP), particularly of PARP-1 and -2, provides yet another approach for targeted prevention of breast cancer (96). In PARP1-deficient cells, which are associated with loss-of-function *BRCA* mutations, homologous recombination is impaired through inhibition of single-strand break recombination, resulting in cellular lethality (97). Because PARP inhibitors require *BRCA1/2* mutations in order to be effective, they provide a novel synthetic lethal preventive strategy that is highly and preferentially toxic to *BCRA1/2* mutant tumor cells versus normal cells (37). Pre-clinical studies investigating the efficacy and tolerability of PARP inhibitors (e.g., iniparib, olaparib, rucaparib, velparib) have led to Phase I and II clinical trials of these drugs alone and in combination with cisplatin and gemcitabine, two chemotherapeutic agents that induce DNA-damage (98–100). However, while PARP inhibitors such as olaparib have shown high efficacy and tolerability with few negative side effects (98,101),

TABLE 20-9

Select Metformin Breast Cancer Prevention Studies (completed or with preliminary results)

Trial	*Participants*	*Study Design*	*Results*	*OR/HR (95%CI)*	*p value*
COMPLETED OR WITH PRELIMINARY RESULTS					
Hadad[1]	55 women	Preoperative, window of opportunity study:	Reduction in Ki-67 staining in:		
Ninewells Hospital and Medical School, UK	Non-diabetic With operable invasive breast cancer	metformin (500 mg q.d. 1st wk, and 1 g bid 2nd wk vs. non-metformin	Metformin pilot cohort: 5% Metformin group: 3.4%	— —	.041 .027
Bonanni[2]	200 women	Preoperative, window of opportunity study:	Change in Ki-67 staining:		
European Institute of Oncology, IT	Non-diabetic With operable invasive breast cancer	metformin (850 mg q.d. 1st 3 days, and 850 mg bid next 25 d) vs. placebob Treatment time: 28 d	Overall: 4.0% HOMA[d] ≤ 2.8 (n = 142): 11.1% HOMA[d] > 2.8 (n = 53): −10.5% Altered effect of metformin according to HOMA index[d] in luminal B tumors	−5.6 to +14.4 −0.6 to +24.2 −26.1 to +8.4	.4 .045 .05
P Goodwin[3]	39 women	Prospective window of opportunity, single-arm, neoadjuvant study:	Decreased Ki67 staining: 2.97 ± 9.78%	—	.016
NCT00897884	<70 years of age	metformin (500 mg q.d. 1st 2 days, 500 mg bid days 3–4, and 500 mg tid until surgery)	Increased TUNEL staining: 0.49 ± 1.0%	—	.004
Mount Sinai Hospital (MSH), Toronto, CA	With newly diagnosed, untreated, early-stage breast cancer at Mount Sinai and Princess Margaret Hospitals, Toronto, CA 2009–2011		Short-term preoperative metformin was well tolerated		
CURRENTLY ONGOING					
Trial	*Participants*	*Study Design*	*Primary Endpoint(S)*		
P Goodwin NCT01310231 Mount Sinai Hospital (MSH), Toronto, CA	Phase II Planned: 78 women 18–75 y of age With invasive breast cancer histologically diagnosed within 12 mo	metformin (850 mg q.i.d. + standard chemotherapy (anthracycline, taxane, platinum or capecitabine based regimens) vs. placebo Treatment time: 3 y, or until progression, unacceptable toxicity, or death	Progression-free survival		
R Patterson NCT01302379 University of California, San Diego, USA (UCSD)	Planned: 340 women Diagnosed with stage I/II/III breast cancer within past 5 years	Lifestyle intervention and standard dietary guidelines arms with: metformin (500 mg q.d. 1st wk, 1,000 q.d. 2nd–4th wk, 1,500 mg q.d. 5th wk) vs. placebo	Biomarkers associated with breast cancer survival		

D Hershman	Phase II	Metformin (1,500 mg q.d.) single-arm) study	Measurement of effects of metformin on AMPK/ mTOR signaling pathway
NCT00930579 Columbia University, USA	Planned: 35 women ≥25 y of age With operable early invasive breast cancer or DCIS	Treatment time: ≥2 wks prior to surgery	Reduction of fasting serum insulin levels
A Harris NCT01266486 The University of Oxford, UK	Phase II Planned: 40 subjects ≥18 y of age With locally advanced breast cancer (LABC)	Metformin (1,500 mg q.d.) single-arm study Treatment time: 14–21 d	Immunohistochemical analysis of effects of metformin on phosphorylation of S6K, 4E-BP-1 and AMPK
W Han NCT01589367 Seoul National University Hospital (SNUH), S Korea (KR)	Phase II Planned: 208 women 18–80 y of age Postmenopausal Stage I/II ER-positive breast cancer	Letrozole and no letrozole arms for: metformin (500 mg bid week 1, 1,500 mg q.d. week 2, 1,000 mg bid weeks 3–24) vs. placebo	Clinical response rate after 24 wks; and Comparison with RECIST 1.1 (baseline to 24 wks)
P Goodwin[4] NCIC-MA.32 NCT01101438 Mount Sinai Hospital (MSH), Toronto, CA	Phase III adjuvant trial Planned: 3,582 subjects 18–74 y of age Stage I and II node-positive or high-risk node-negative breast cancer Non-diabetic	metformin (850 mg bid, with 1 mo dose ramp up) versus placebo Treatment time: 5 y	Invasive disease-free survival (IDFS)

CI, confidence interval; DCIS, ductal carcinoma *in situ*; HR, hazard ratio; HOMA, homeostasis model assessment; NMSC, non-melanoma skin cancer; q.d., once per day; b.i.d., twice per day.
[a]HR is relative to metformin monotherapy; [b]Summary RR (SRR); [c]For heterogeneity; [d]Insulin resistance: HOMA index > 2.8, fasting glucose (mmol/L) × insulin (mU/L)/22.5; [e]*p:* versus non-metformin; [f]*p:* versus metformin.
Data from: [1]Hadad S, et al. *Breast Cancer Res Treat* 2011;128(3):783–794; [2]Bonanni B, et al. *J Clin Oncol* 2012;30(21):2593–2600; [3]Niraula S, et al. *Breast Cancer Res Treat* 2012;135(3): 821–830; [4]Goodwin PJ, et al. *Breast Cancer Res Treat* 2011;126(1):215–220.

additional clinical data further defining their effectiveness and tolerability as chemopreventive agents for *BRCA1/2* carriers will determine their place in the future of breast cancer prevention.

Natural Products: In addition to pharmacologic approaches, current advances in the understanding of the association between diet and tumorigenesis have led to a wide range of natural products becoming the focus of breast and other cancer prevention studies, particularly as cancer is considered by many to be a disease that is largely preventable. These alternative strategies include specific diets, dietary and medicinal botanicals, and biologically active food components (BFCs) that have been found to both prevent disease and promote health. While over a hundred natural compounds are currently in clinical use (102), among those that have been shown to be inversely associated with an increased risk of breast cancer in pre-clinical, early clinical, and population-based studies are catechins (e.g., epigallocatechin gallate [EGCG], green tea extract); curcumin (yellow pigment in the spice turmeric of the ginger family); the flavonoids deguelin (a rotenoid in several plant species), luteolin (in vegetables including broccoli and cabbage), and those in pomegranate juice (cyanidin, delphinidin, and petunidin); indole-3-carbinol (I3C; in cruciferous vegetables); lycopene (red pigment of tomatoes, guava, pink grapefruit, and watermelon) and other carotenoids; omega-3-fatty acids (in marine and plant oils); resveratrol (antioxidant in the skins of red grapes, mulberries, and other plants); soy isoflavones (genistein, daidzein, and glycitein); and vitamin D.

Mechanistic analyses have demonstrated numerous, and in many cases multiple, signal transduction pathways targeted by these agents, including the activator protein-1 (AP-1), angiogenesis, antiviral, cytokine (e.g., osteoprotegerin), DNA methylation, growth factor (CSF, EGF, FGF, IGF, PDGF, and TGF), immunologic, nuclear factor-kappaB (NF-kappaB), p53, phase I and II enzymatic, and signal transducers and activators of transcription (STAT), ubiquitin-proteosome, pathways (103). While further clinical studies are needed, natural products offer promising alternative strategies for the prevention of breast cancer in the future.

Vaccine Approaches: Vaccination strategies targeting breast cancer include preventive treatments and therapeutic interventions for metastatic breast cancer. However, vaccine strategies in healthy individuals without cancer could enable the immune system to detect precancerous lesions otherwise undetectable by the immune system. For this reason, immunologic interventions are felt to be a particularly promising prevention strategy. Analysis of sera from breast cancer patients has been shown to contain serum antibodies against oncogenic proteins (e.g., carcinoembryonic antigen (CEA), cyclin B1, HER2*/neu,* and *p53*) at the time of treatment (104, 105). Furthermore, all but CEA antibody are present at diagnosis, and HER2 and *p53* antibodies are in prediagnostic sera (104). Peptide vaccines incorporate an immunoadjuvant into the treatment to stimulate the immune response of the subject (106). GP2, AE37, and E75 are three HER2*/neu* peptide vaccines currently in Phase I, II, or III clinical breast cancer trials. Both GP2 and E75 are major histocompatibility complex (MHC) class I peptides and stimulate tumor cell-destroying CD8-positive T cells (107), thereby limiting their effectivity to human leucocyte antigen A2-positive (HLA-$A2^+$) and HLA-$A3^+$patients (106). Conversely, AE37 is an MHC class II peptide and stimulates CD4-positive T cells (107), enabling induction of higher antitumor responses and encompassing a larger number of HLA types (106).

A successful Phase I dose escalation trial of the GP2 vaccine (108), has led to a Phase II prevention trial studying recurrence in node-positive or high-risk node-negative breast cancer patients, currently in progress. Likewise, potency of the AE37 vaccine in the absence of an immunoadjuvant has been demonstrated in a Phase Ib trial (109), which has resulted in an ongoing Phase II trial comparing the efficacy and tolerance of the GP2 and AE37 vaccines. This study has already demonstrated AE37 vaccination-mediated reductions in risk of 49% for all subjects and 68% for patients with low HER2 expression and patients with triple-negative breast cancer (109). However, E75 is the most studied of the HER2-derived cytotoxic T-lymphocyte peptide vaccines and the focus of a number of clinical trials. Phase I and II studies of E75 induced immunity in HLA-$A2^+$ and HLA-$A3^+$ disease-free, node-positive breast cancer patients have identified peptide-specific immune responses *in vivo* and improved disease-free survival (DFS) that persists over time, with highest clinical benefit in low-HER2/*neu* expressing patients (110). A booster program to prevent decreased immunity over time has now been initiated. In addition, recruitment is underway for the first Phase III clinical trial of a breast cancer vaccine, the Prevention of Recurrence in Early-Stage, Node-Positive Breast Cancer with Low to Intermediate HER2 Expression with NeuVax Treatment (PRESENT) study, which is investigating the effects of the E75 vaccination on 3-year DFS in 700 early-stage node-positive breast cancer patients. Positive trial results could lay the foundation necessary for the translation of the E75 vaccine into the clinical prevention setting.

Other Promising Agents

Other agents being tested in pre-clinical studies include insulin-like growth factor receptor (IGF1R) inhibitors, mammalian target of rapamycin (mTOR) inhibitors, phosphatidylinositol 3-kinase (PI3K) inhibitors, and synthetic oleanane triterpenoids, including 2-cyano-3,12-dioxooleana-1,9(11)-dien-28-oic acid (CDDO), CDDO-methyl ester (CDDO-Me), and CDDO-imidazolide (CDDO-Im).

Inhibitors of the IGF-1 pathway, which has been shown to be critical in mammary gland differentiation and development, provide one such option. These inhibitors, including agents such as cixutumumab, figitumumab, pasireotide, and R1507, have the potential of being useful for the prevention of both ER-positive and ER-negative breast cancer (111).

Likewise, mTOR inhibitors (e.g., rapamycin and the rapalogs deforolimus, everolimus, sirolimus, and temsirolimus) may be useful as cancer prevention agents. PI3K/AKT/mTOR signaling is critical for tumorigenesis and angiogenesis (112). mTOR functions as a downstream effector of the PI3K/AKT signaling pathway, participates in the phosphorylation of multiple kinases (e.g., 40S ribosomal S6 kinase [S6K], a marker associated with aging) (113) and interacts with growth factors in regulating cell cycle progression, among other things (114). While clinical results for these agents have been encouraging and demonstrate acceptable toxicity, further research is needed to assess the cancer preventive potential of these agents.

Finally, CDDO, CDDO-Im and CDDO-Me, which target the Nrf2 transcription factor, have been shown to delay mammary tumor formation and to synergistically enhance the effects of LG100268 in the suppression of ER-negative tumors (52,115). Based upon epidemiological, pre-clinical, and clinical results, alternative strategies, including IGF, mTOR, and PI3K inhibitors, as well as CDDO esters, may provide promising strategies for breast cancer prevention in the future.

TABLE 20-10

American Society of Clinical Oncology Recommendations for Pharmacologic Interventions for Breast Cancer Risk Reduction (from 2009 Update)

Agent	*Current Recommendation*					
	Population					
	Menopausal Status		*Individual Risk*	*Expected Benefit*	*Dosage*	*Follow-Up*
	Pre-	*Post-*				
SELECTIVE ESTROGEN RECEPTOR MODULATORS:						
Tamoxifen	Yes	Yes	Women with: • a 5-y projected absolute breast cancer risk ≥1.66%[a] OR diagnosis of LCIS • NO history of: - deep vein thrombosis - pulmonary embolus - stroke - transient ischemic attack • NO likelihood of pregnancy or nursing • NO concurrent treatment with hormone therapy	≥10-y risk reduction of invasive ER-positive breast cancer[b,c]	5 y at 20 mg/d	Timely analysis of any abnormal vaginal bleeding
Raloxifene	No	Yes	Postmenopausal women with: • a 5-y projected absolute breast cancer risk ≥1.66%[a], OR diagnosis of LCIS • NO history of: - deep vein thrombosis - pulmonary embolus - stroke - transient ischemic attack • NO concurrent treatment with hormone therapy	Risk reduction of invasive ER-positive breast cancer[b,c] Risk reduction of invasive ER-positive breast cancer in women with osteoporosis[b,c]	5 y at 60 mg/d ≥5 y at 60 mg/d	Annual gynecologic exams Timely analysis of any abnormal vaginal bleeding
AROMATASE INHIBITORS:						
Exemestane	No	Yes	Postmenopausal women with: • a 5-y projected risk ≥1.66%[a], OR diagnosis of LCIS, OR diagnosis of atypical hyperplasia	Risk reduction of invasive ER-positive breast cancer[b,c] Risk reduction of invasive ER-positive breast cancer in women with osteoporosis[b,c]	5 y at 25 mg/d	N/A
RETINOIDS:						
	No	No	No	NOT currently recommended outside the clinical trial setting	N/A	N/A

[a]Assessment of risk according to the NCI Breast Cancer Risk Assessment Tool, available at http://www.cancer.gov/bcrisktool.
[b]The effect of treatment on breast cancer morality is not currently known.
[c]Informed decision-making should include evaluation of patient-defined risk–benefit ratios.
Adapted from Visvanathan K, et al. Use of pharmacologic interventions for breast cancer risk reduction: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2013; Ahead of print, with permission.

SELECTION OF WHOM TO TREAT

Clinical trials have demonstrated that several drugs, including antiestrogen SERMs and aromatase inhibitors, can effectively prevent many breast cancers in women, especially ER-positive breast cancers. The current ASCO recommendations for reducing risk of breast cancer are outlined in Table 20-10 (16). Two drugs, tamoxifen and raloxifene, are currently FDA approved to treat women at increased risk of breast cancer. Of these, tamoxifen remains the only FDA-approved preventive therapy for high-risk premenopausal women, while both tamoxifen and raloxifene can be used in high-risk post-menopausal women. In addition, the aromatase inhibitor exemestane has recently been added to the ASCO clinical practice guidelines as an alternative preventive intervention for ER-positive breast cancers in post-menopausal women (16). However, the selection of which SERM or AI use in these post-menopausal women should be based on the individual's risk–benefit ratio. For example, for a high-risk post-menopausal woman without a uterus, the risk of tamoxifen is lessened; such a woman may thus prefer tamoxifen. On the other hand, a high-risk woman with an intact uterus and concerns about hot flushes and thromboembolic risks may be best treated with raloxifene (which does not increase the risk of uterine cancer and induces less hot flushing and thromboembolic events) or potentially with exemestane (which does not increase the risk of thromboembolic events). Conversely, for a high-risk postmenopausal women with a history of a deep venous thrombosis and normal bone mineral density, it is possible that exemestane could be used, pending FDA approval for breast cancer risk reduction. Finally, for women with atypical ductal hyperplasia premalignant lesions, tamoxifen preventive therapy should be considered, since tamoxifen reduced breast cancer risk in such women by 90% in the NSABP P-1 clinical trial (116). Other agents such as trastuzumab, lapatinib, retinoids, and vaccines are being investigated in clinical trials but are not yet being used clinically. Through the application of currently available drugs, it is now possible to significantly reduce the risk of ER-positive breast cancer in high-risk women. It is anticipated that ultimately, pre-clinical and clinical research will produce and/or identify drug-based preventive therapies capable of greatly reducing the incidence of ER-positive, HER2-positive, and ER-negative breast cancer.

MANAGEMENT SUMMARY

- Tamoxifen and raloxifene are now FDA-approved for breast cancer risk reduction in high-risk women. While raloxifene is slightly less effective at preventing breast cancer than tamoxifen, it is associated with fewer adverse events.
  - Tamoxifen (20mg/day for 5 years) can be used for pre- and postmenopausal women 35 years of age or older if they have been diagnosed with LCIS or have a 1.66% or higher 5-year projected risk of breast cancer according to the Gail risk model (http://www.cancer.gov/bcrisktool), and is expected to reduce risk of invasive ER-positive breast cancer by approximately 50%.
  - Raloxifene (60 mg/day for 5 years) can be used for postmenopausal women 35 years of age or older if they have been diagnosed with LCIS or have a 1.66% or higher 5-year projected risk of breast cancer according to the Gail risk model (http://www.cancer.gov/bcrisktool), and is expected to reduce risk of invasive ER-positive breast cancer by approximately 39%.
- Women with ADH premalignant lesions exhibit 85% reduction in breast cancer risk following treatment with tamoxifen.
- The most effective risk-benefit ratios for tamoxifen treatment are observed in premenopausal women at increased risk of breast cancer. This is due to the reduced risk of thromboembolic events and uterine cancer.
- Older, postmenopausal women have an age-related increased risk of deep-vein thrombosis and pulmonary embolisms and should be evaluated carefully prior to being offered tamoxifen as a preventive strategy for breast cancer.
- Neither tamoxifen nor raloxifene are recommended for breast cancer risk reduction in women: 1) with a history of deep vein thrombosis, pulmonary embolus, stroke, or transient ischemic attack; 2) currently nursing or likely to become pregnant; or 3) currently being treated with hormone therapy.
- Women with osteoporosis may receive increased benefit with more than 5 years of treatment with raloxifene.
- Exemestane (25mg/day for 5 years) is a potential therapeutic alternative to tamoxifen or raloxifene for breast cancer risk reduction in postmenopausal women if they have been diagnosed with ADH or LCIS or have a 1.66% or higher 5-year projected risk of breast cancer according to the Gail model. Treatment with exemestane is expected to reduce the risk of invasive ER-positive breast cancer by 65% in postmenopausal, high-risk women. Exemestane has not yet received FDA approval as a preventive treatment for breast cancer.
- Tamoxifen, raloxifene, and exemestane have not yet been approved by the European Medicines Authority for breast cancer prevention. However, guidelines from the National Institute for Health and Clinical Excellence (NICE) released in June of 2013 recommend offering high-risk (≥30% lifetime risk from age 20 or >8% risk between ages 40 and 50, determined by BOADICEA and/or the new Manchester scoring system), premenopausal women with no history of thromboembolic disease or endometrial cancer 5 years of tamoxifen treatment. NICE guidelines also recommend that high-risk, postmenopausal women with a uterus be offered tamoxifen or raloxifene, while high-risk, postmenopausal women without a uterus be offered tamoxifen for breast cancer prevention if they have no history of thromboembolic disease or endometrial cancer.

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SECTION V

In Situ Carcinoma

CHAPTER 21

Ductal Carcinoma *In Situ* and Other Intraductal Lesions: Pathology, Immunohistochemistry, and Molecular Alterations

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CHAPTER CONTENTS

Intraductal proliferative lesions are epithelial proliferations confined to the mammary ductal-lobular system. Based on architectural and cytologic features we classify these lesions as usual ductal hyperplasia (UDH), flat epithelial atypia (FEA), atypical ductal hyperplasia (ADH), and ductal carcinoma *in situ* (DCIS). DCIS, ADH, and FEA are established non-obligate morphologic precursors of breast carcinoma, albeit of very different biologic potential, whereas UDH is a benign proliferation that enters in the differential diagnosis of DCIS and ADH.

NORMAL BREAST

The mammary lobule is the milk-producing unit of the breast. It consists of a grape-like aggregate of acini surrounded by specialized mammary stroma. The acini drain into a terminal ductule, part of which is intralobular, and part extralobular. Few lobules and the terminal ductule that drains them form together the terminal duct lobular unit (TDLU) (Fig. 21-1A). Subgross pathology studies have shown that most of the epithelial changes occurring in the breast, including DCIS, originate in the TDLU (1).

The cellular lining of the mammary lobules and ducts consists of an inner (luminal) epithelial layer and an outer myoepithelial cell (MEC) layer. The luminal epithelium lining the glandular lumen has a polarized morphology, with the nucleus at one pole of the cell and an apical cytoplasmic compartment at the other end. Normal luminal epithelial cells show continuous linear membranous positivity for E-cadherin, a transmembrane adhesion molecule encoded by the *CDH1* gene, which is located at 16q22.1. Monostratified normal luminal cells usually are negative for CK5/6. A continuous layer of MECs surrounds the luminal epithelium. The morphology of MECs ranges from inconspicuous, with compressed nuclei and scant cytoplasm, to epithelioid with abundant clear cytoplasm. MECs can be readily demonstrated with immunohistochemical stains for cytoplasmic contractile proteins (i.e., calponin, smooth muscle actin, and smooth muscle myosin heavy chain) or p63—a p53 homologue that decorates the nucleus. E-cadherin reactivity in MECs has membranous linear distribution with a characteristic granular quality.

Estrogen and progesterone play a central role in regulating the growth and differentiation of normal breast tissue. Nuclear expression of estrogen receptor (ER)-α is present in normal ductal and lobular luminal cells, but it is limited to a small and sparse percentage of the cells, and varies with the phases of the menstrual cycle. ER-β is expressed more diffusely in normal breast tissue and is present in the epithelial cells of ducts and lobules, in MECs, endothelium, and stromal cells. The expression of ER-β does not vary during the menstrual cycle but is reduced in UDH, ADH, and DCIS. Some investigators have speculated that the

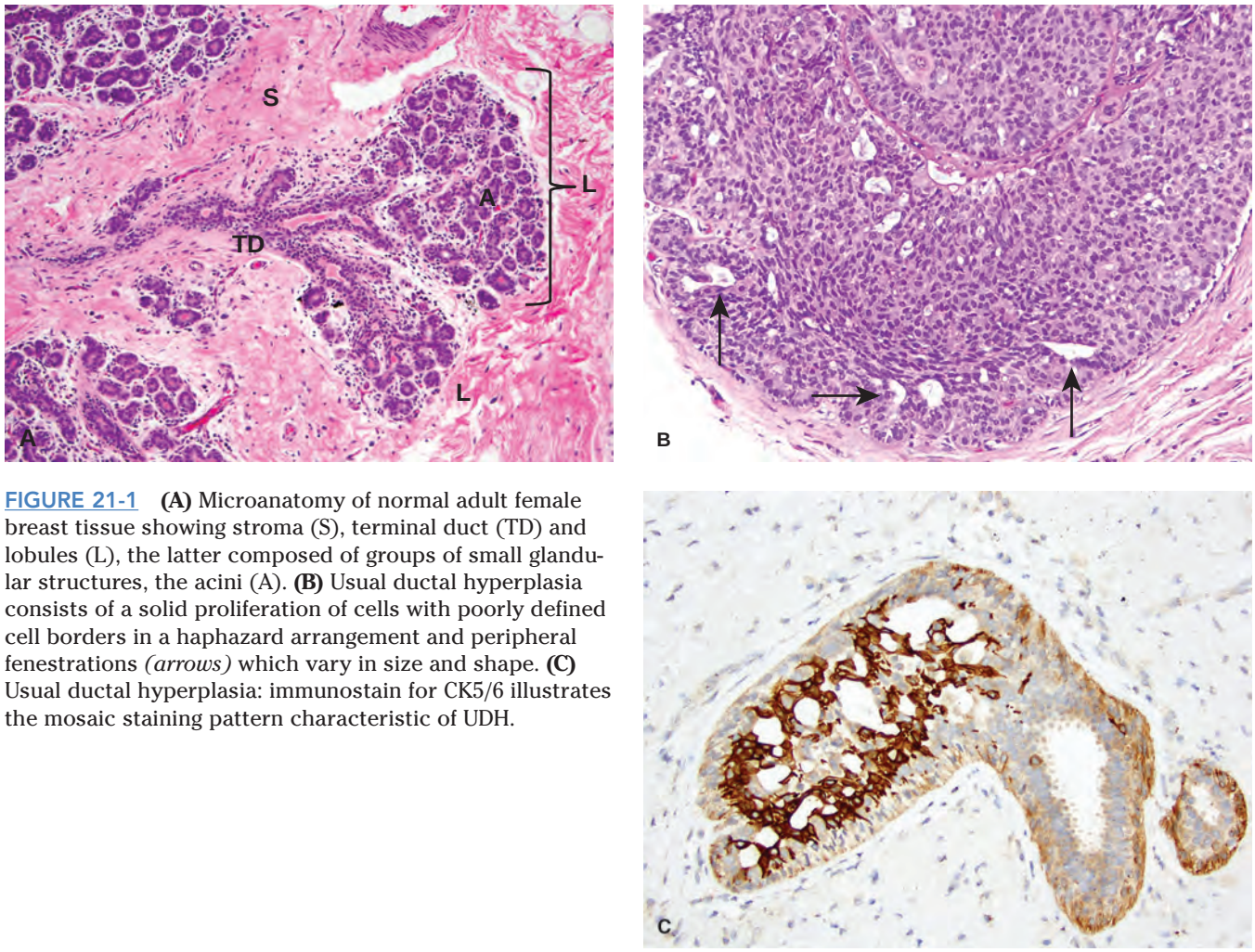


FIGURE 21-1 **(A)** Microanatomy of normal adult female breast tissue showing stroma (S), terminal duct (TD) and lobules (L), the latter composed of groups of small glandular structures, the acini (A). **(B)** Usual ductal hyperplasia consists of a solid proliferation of cells with poorly defined cell borders in a haphazard arrangement and peripheral fenestrations *(arrows)* which vary in size and shape. **(C)** Usual ductal hyperplasia: immunostain for CK5/6 illustrates the mosaic staining pattern characteristic of UDH.

relative levels of ER-β and ER-α may be important in determining the risk of breast cancer development and higher levels of ER-β relative to ER-α are protective against neoplastic progression. The expression of progesterone receptor (PR) in the ductal and lobular epithelium does not seem to vary with the menstrual cycle.

Carcinomas and its precursors are composed of transformed epithelial cells. Whether all breast epithelium has the potential to transform or this capability is limited to epithelial stem cells or progenitor cells is a topic of research and debate. Few authors have documented silent chromosomal alterations in morphologically normal epithelial cells, and suggested that they may predispose to premalignant or malignant transformation (2). However, these changes have low frequency and are more often seen in morphologically normal cells adjacent to carcinoma than away from it (2). Alterations affecting the p16 tumor suppressor gene increased epithelial proliferation and elevated expression of cyclooxygenase-2 (COX-2) have been documented in morphologically normal mammary epithelium, especially in women at high risk of breast carcinoma (3).

Usual Ductal Hyperplasia

The term *UDH* refers to a non-neoplastic epithelial proliferation. It can range from mild, consisting of just two to four cell layers, to florid, when it entirely fills and distends the ducts. UDH arising in a radial scar or in a papilloma can show focal necrosis, raising the differential diagnosis of DCIS. The cells comprising UDH are cytologically benign, vary in size, shape and orientation, have poorly defined borders, and are haphazardly arranged (Fig. 21-1B). Fenestrations lined by non-polarized cells are usually present within UDH, and often have circumferential distribution along the periphery of a duct.

Low and heterogenous expression of ER occurs in 30% to 40% of UDH cells, mainly at the periphery of the lesion. The proliferation rate is low (2%–5%). UDH shows a mosaic staining pattern for the basal keratins CK5/6 (see Fig. 21-1C) and 34BE12 (4). The pattern of immunoreactivity helps distinguish UDH from ADH and focal DCIS, as the latter two lesions are usually negative for these antigens with very few exceptions. Although some high-grade DCIS is CK5/6-positive, as discussed later in this chapter, nuclear atypia and pleomorphism distinguish it from UDH. UDH is associated with a 1.5- to 2-folds increase in the risk of breast cancer, which may occur in either breast. The risk is slightly higher in women with UDH who also have a first-degree relative with breast carcinoma (5).

Few and inconsistent genetic alterations have been documented in UDH, but no substantial shared genetic abnormalities with ADH, DCIS, or invasive breast cancer have been

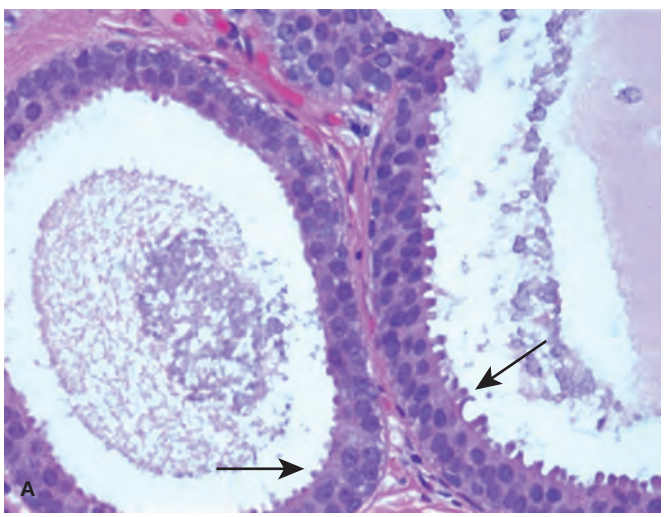
identified (6). Studies have shown that chromosomal loss of heterozygosity (LOH) is lower in UDH (4.5%–13%) than in ADH and low-grade DCIS (7). Comparative genomic hybridization (CGH) has identified few unbalanced chromosomal aberrations in UDH in some studies (8), but not in others (9). Some of the studies reporting chromosomal alterations in UDH used whole genome amplification methods (8) which may be more susceptible to artifacts. Overall, the chromosomal aberrations found in most UDH lesions are not similar to those observed in invasive carcinoma, effectively ruling out the possibility that UDH might represent a morphologic precursor of breast carcinoma (6).

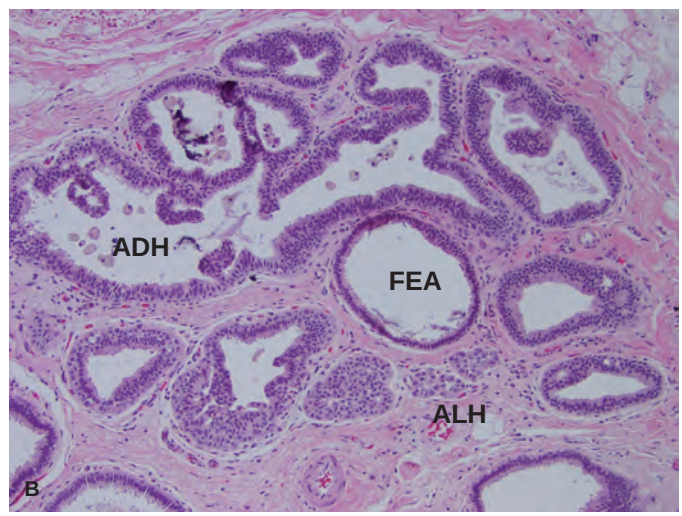
Flat Epithelial Atypia

FEA consists of enlarged TDLUs in which the native epithelial cells are replaced by "one to several layers of a single cell type showing low-grade (monomorphic) cytologic atypia" (10) (see Fig. 21-2A). The involved TDLUs have variably dilated acini with rounded contour. The nuclei of FEA cells are monomorphic, round to ovoid, and resemble those of ADH and low-grade DCIS. The proliferation is architecturally "flat" and devoid of any complex pattern (i.e., micropapillae, focal rigid bridges, bars and arcades, or sieve-like fenestrations) seen in ADH and low-grade DCIS. Lesions currently classified as FEA have been previously referred to by a wide range of terms, most notably "clinging carcinoma of the monomorphic type" and "columnar cell change with atypia." Columnar cell change, columnar cell hyperplasia, and FEA often coexist in adjacent lobules and even within the same TDLU. These diagnoses are not mutually exclusive, but only FEA has cytologic atypia.

The cells of FEA are positive for low-molecular-weight CKs, such as CK8, CK18, and CK19 (9). Even though FEA cells lack expression of high-molecular-weight CKs, such as CK5/6 (9,11), immunohistochemical stains for CK5/6 do not help to differentiate FEA from monostratified normal ductal epithelium, as the latter is also CK5/6 negative. In FEA strong positivity for ER is present in about 85% of the cells (9,12) and for PR in about 50% (9,12). The cells are characterized by strong cytoplasmic expression of bcl-2, and show minimal to no apoptosis (12). The proliferation index of FEA is significantly higher than in morphologically normal TDLUs (6% vs. 2%, respectively) (12).

FEA commonly coexists with ADH (see Fig. 21-2B), low-grade DCIS and tubular carcinoma, and shares close cytologic and immunophenotypic similarities with these lesions (1,13,14). Few investigators have also noted an association between columnar cell lesions/FEA and lobular carcinoma *in situ* (LCIS) and atypical lobular hyperplasia (ALH) (see Fig. 21-2B-C) (13,15).





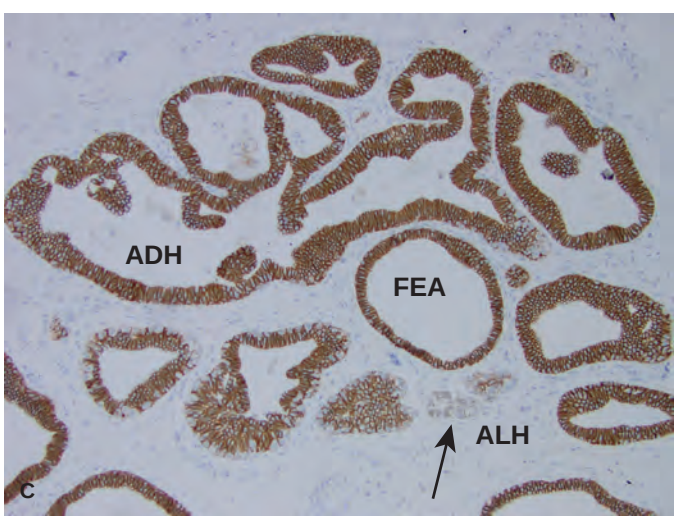
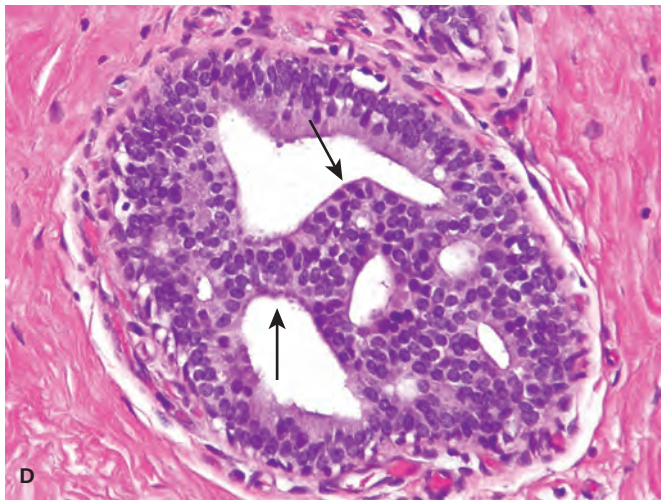


FIGURE 21-2 **(A)** Flat epithelial atypia (FEA): the lining epithelial cells have prominent apical cytoplasmic snouts *(arrows)* and round to oval nuclei, relatively uniform in appearance. Low-grade, monomorphic-type cytologic atypia characterizes FEA. **(B)** FEA, atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH). Some of the spaces in this TDLU show the characteristic features of FEA. One space shows a rigid bridge and cellular tufts composed by cells cytologically identical to those of FEA, however, because of the more complex architecture in this space, a diagnosis of ADH is warranted. ALH frequently coexists with FEA and ADH. **(C)** E-cadherin staining of the same area shown in **(B)**. Loss of membranous E-cadherin is appreciated in ALH *(arrow)*, whereas the epithelial cells of the normal TDLU, FEA, and ADH show strong membtranous positivity.



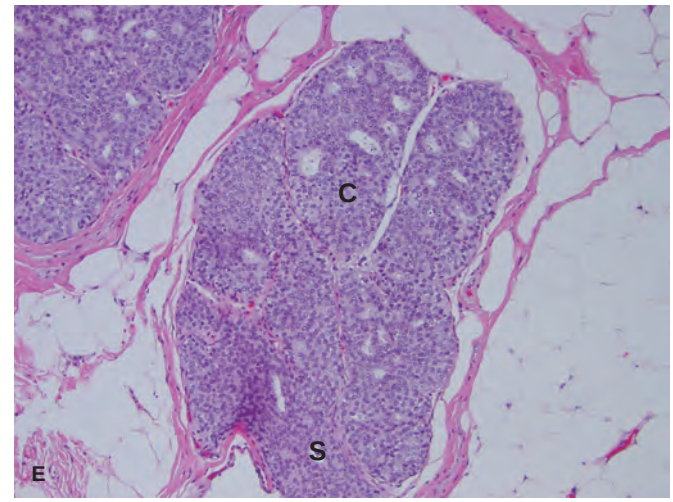


FIGURE 21-2 *(Continued)* **(D)** ADH comprising of uniform atypical cells in cellular rigid bridges *(arrows)*. The qualitative features of this lesion approach those of low-grade DCIS, but the lesion is limited in extent. **(E)** Low-grade DCIS with a solid (S) and cribriform (C) architectural pattern. The nuclei are small and uniform in appearance.

Molecular analysis shows that FEA has recurrent chromosomal alterations consistent with a clonal population (9,16). Recurrent copy number alterations include loss of 16q and gains of 15q, 16p, 17q, and 19q. Allelic imbalances are most frequently seen at 3p, 9q, 10q, 11q, 16q, 17p, and 17q (16).

Based on these findings FEA is part of the spectrum of low-grade mammary epithelial lesions (Fig. 21-3A), which include ADH, low-grade DCIS, tubular and tubulolobular carcinoma, invasive cribriform carcinoma, low-grade invasive ductal carcinoma, ALH, classic LCIS and invasive lobular carcinoma, classic type. It has been proposed that FEA represents the first morphologically recognizable precursor of low-grade mammary neoplasia (9,14). The risk of subsequent carcinoma associated with FEA has not been fully determined, but it is believed to be lower than for ADH (10). At present, no additional treatment or special screening modalities are recommended for patients with only FEA (10).

Atypical Ductal Hyperplasia

ADH is a very focal neoplastic epithelial proliferation confined to the mammary ductal-lobular system. The cells composing ADH are relatively small and monomorphic, with round to avoid nuclei, fine chromatin and inconspicuous nucleoli. They tend to be evenly spaced, show well-defined cell borders and focally form rigid arches and bridges (see Fig. 21-2D), trabecular bars of uniform thickness, or club-shaped micropapillae. They can also display solid foci or focal incomplete cribriform pattern, which results from the orderly arrangement of polarized cells around a neoformed glandular lumen. These cells are morphologically similar to those composing low-grade DCIS, but they are not as homogeneous. Extent of the lesion is an important criterion in differentiating ADH from low-grade DCIS, although there is no universally accepted size cutoff to distinguish between the two. Usually DCIS is diagnosed when the neoplastic proliferation involves at least two separate ducts or spans at least 2 mm, and any smaller lesion is classified as ADH. The diagnosis of ADH applies only to lesions for which the differential diagnosis of low-grade DCIS is considered, but that do not show the full range of diagnostic features. Despite undeniable limitations, the use of size criteria fosters interobserver reproducibility in the interpretation of small borderline ductal lesions.

The cells comprising ADH typically have strong and nearly uniform (90%–100%) positivity for ER and PR, but no cytoplasmic reactivity for CK5/6 (11) and 34BE12 (4). The use of these markers is of no practical value in the differential diagnosis with low-grade DCIS, but can be useful in the differential diagnosis with UDH, that is positive with a checkerboard pattern (see Fig. 21-1C). ADH has a low proliferative rate (4%–5%).

Recurrent chromosomal alterations including losses at 16q and 17p and gains at 1q (9) have been identified in ADH, similar to the changes found in low-grade DCIS as well as in the lesions part of the low-grade mammary epithelial neoplasia family (see Fig. 21-3A).

ADH is associated with a four to five-fold increase in the risk of subsequent breast cancer, with approximately equal frequency in both breasts.

Apocrine Lesions

The normal breast often shows apocrine metaplasia. Apocrine metaplastic cells are enlarged, have abundant finely granular, and eosinophilic cytoplasm, large round vesicular nuclei, prominent eosinophilic nucleoli and intracytoplasmic vacuoles (17). The degree of nuclear enlargement and prominence of the nucleoli can be worrisome and misleading, unless the apocrine nature of the process is recognized. Usually apocrine metaplasia is an incidental finding and coexists with benign or malignant lesions.

Apocrine atypical cells are characterized by enlarged nuclei with at least three-fold variation in size (17). The distinction between atypical apocrine adenosis and apocrine DCIS can be challenging, especially when the apocrine proliferation involves sclerosing adenosis or a sclerosing lesion. In equivocal cases a conservative diagnosis of atypical apocrine adenosis is usually preferable. Atypical apocrine adenosis in a core needle biopsy mandates excision.

When atypical apocrine epithelium is present in sclerosing adenosis, the combination of epithelial cells with enlarged nuclei and prominent nucleoli and glandular

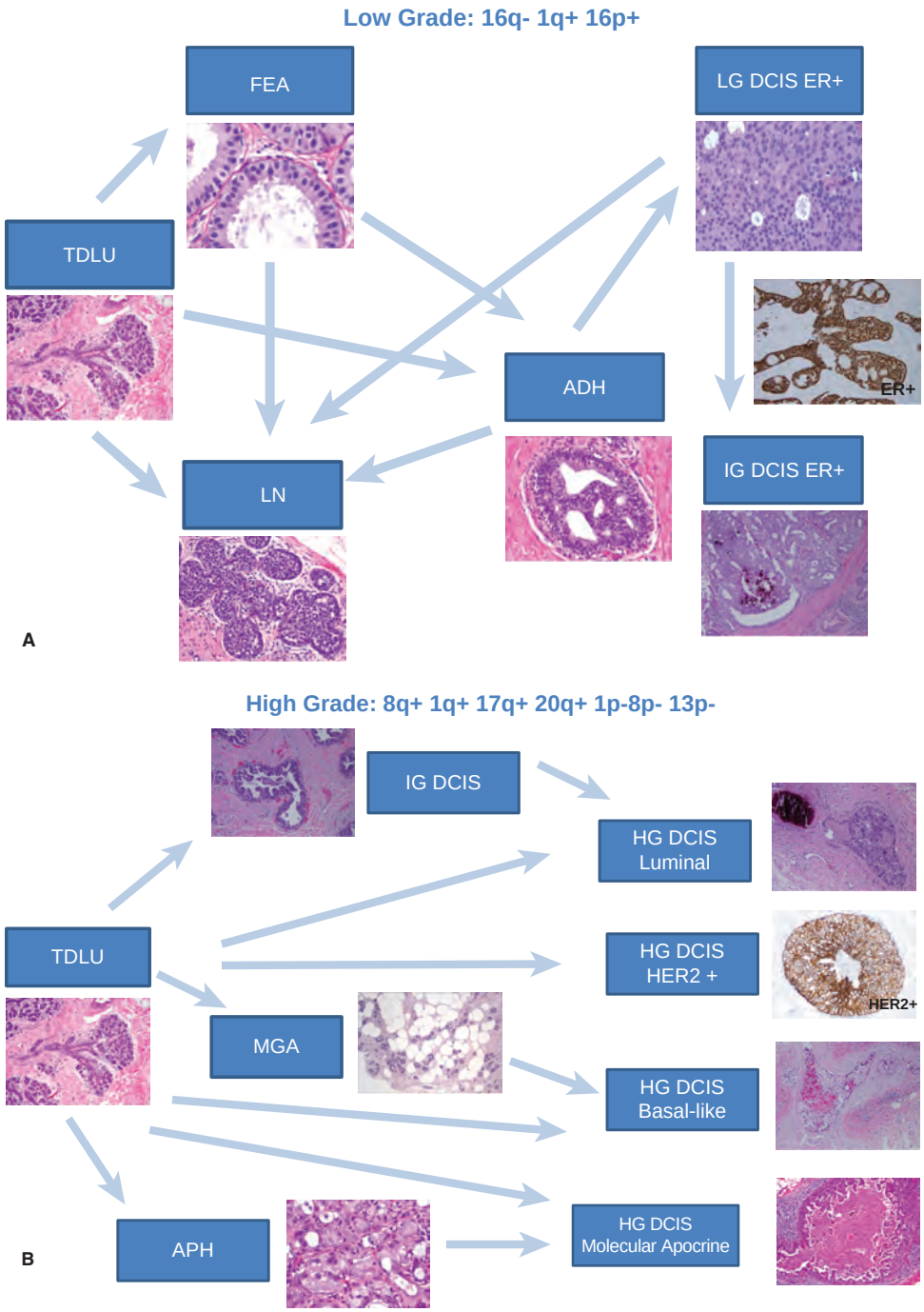


FIGURE 21-3 **(A)** "Low-grade breast neoplasia family." Similar genomic aberrations have been identified in FEA, ADH, low-grade DCIS, and lobular neoplasia (ALH/LCIS). FEA is the earliest morphologically recognizable precursor of this group of lesions. **(B)** High-grade (HG) DCIS. This heterogenous group of lesions lacks ER, PR and expresses HER2. A basal-type of DCIS is also present. The high-grade DCIS harbor numerous genomic chromosomal alterations. Connectors drawn with discontinuous lines (microglandular adenosis and atypical apocrine hyperplasia) represent hypothetical links yet to be demonstrated modified from diagram of Lopez-Garcia et al. (6).

distortion produces a pattern that can mimic invasive apocrine carcinoma. Immunostains for MEC markers are useful in the differential diagnosis with invasive carcinoma.

Intraductal apocrine lesions are typically androgen receptor (AR) positive and frequently lack ER and PR expression. HER2 expression has not been reported in benign apocrine lesions, but it has been described in up to 50% of *in situ* and invasive apocrine carcinomas (18).

Genetic studies of apocrine metaplasia have shown that at least a proportion carries genetic changes, suggesting that some lesions are clonal and may represent non-obligate morphologic precursors of carcinoma (19,20). Selim et al. (20) assessed LOH in 41 cases of benign apocrine lesions with different degrees of architectural complexity and found that 20% of cases showed allelic alterations in at least one chromosomal locus. Jones et al. (19) used CGH to compare 10 cases of apocrine micropapillary hyperplasia, 10 apocrine DCIS, and 4 invasive apocrine carcinomas, and found that the number of unbalanced genetic aberrations was directly related to the complexity and atypia of the lesion. In particular, the mean number of chromosomal alterations in apocrine hyperplasia was 4.1 compared to 10.2 in apocrine DCIS and 14.8 in invasive apocrine carcinoma. The most common alterations in apocrine hyperplasia included

gains of 2q, 13q, and 1p, and losses of 1p, 17q, 22q, 2p, 10q, and 16q (19). Apocrine *in situ* and invasive carcinomas most commonly showed gains of 1q, 2q, and 1p, and losses of 1p, 22q, 17q, 12q, and 16q (19).

The breast cancer risk associated with apocrine adenosis and atypical apocrine adenosis has not been well defined. In one study, none of 47 patients with atypical apocrine adenosis developed cancer at a mean follow-up of 35 months (21). A study of 37 patients with mean follow-up of almost 9 years documented a relative risk of 5.5 (17), but the authors acknowledged that some of their index cases may have represented apocrine DCIS involving sclerosing adenosis rather than atypical apocrine adenosis. A recent study (22) of 37 patients with atypical apocrine adenosis and average follow-up of 14 years identified 3 out of 37 women (8.1%) who developed breast carcinoma. In one patient DCIS was diagnosed in the contralateral breast after a 12 year follow-up. Two patients developed ipsilateral invasive carcinoma after 4 and 18 years. No apocrine atypia was present in the background breast parenchyma and the tumors showed no evidence of apocrine differentiation. Despite the limited number of study patients, the authors concluded that atypical apocrine adenosis does not appear to be an aggressive lesion and it should not be regarded as a direct precursor of breast carcinoma (22).

DUCTAL CARCINOMA *IN SITU*

The term *DCIS* is defined by the World Health Organization (WHO) as "a neoplastic proliferation of epithelial cells confined to the mammary ductal-lobular system and characterized by subtle to marked cytologic atypia and an inherent but not necessarily obligate tendency to progression to invasive breast cancer" (10). DCIS encompasses a heterogeneous group of lesions that differ significantly with regard to clinical presentation, morphologic features, biomarker profile, genetic abnormalities and biologic potential.

At present, DCIS accounts for about 20% to 25% of all newly diagnosed breast cancers, compared to less than 5% in the pre-screening mammography era. Overall, the incidence of DCIS rose from 1.87 cases per 100,000 women in 1973–1975 to 32.5 cases per 100,000 women in 1999–2004. Much of this increase is attributable to the widespread adoption of screening mammography and better detection of lower grade lesions. In general, the rate of noncomedo DCIS has increased across all age groups, whereas the rate of comedo DCIS has been constant or decreased.

In current clinical practice, 80% to 85% of cases with DCIS are detected because of associated mammographic calcifications (Ca^{2+}), which are usually rod shaped or linear branching in high-grade DCIS or granular and segmental in low-grade DCIS. Up to 20%–30% of DCIS may present as a soft tissue density with or without associated Ca^{2+} or as an area of architectural distortion. Rarely DCIS presents as a palpable mass, nipple discharge, Paget's disease of the nipple, or constitutes an incidental microscopic finding in breast tissue removed for another abnormality.

In most (98.8%) cases DCIS is unicentric and has segmental distribution, as elegantly demonstrated by Holland et al. (23). Multicentric DCIS, defined as foci of DCIS in two different quadrants separated by morphologically normal intervening breast parenchyma, is relatively uncommon (23). Discontinuous growth within ducts has been reported in 70% of low-grade DCIS, 55% of intermediate-grade DCIS, and 10% of high-grade DCIS (24), but the discontinuity could result from incomplete visualization of a complex branching three-dimensional structure in a two-dimensional plane. The designation of extensive ductal component applies whenever DCIS admixed with invasive carcinoma constitutes 25% or more of the tumor mass and/or extends away from it.

The diagnosis of DCIS with either high or intermediate nuclear grade is independent from the extent of the lesion, whereas size greater than 2 mm or involvement of at least two ducts is required for the diagnosis of DCIS with low nuclear grade. In core biopsy (CBX) material, it may be difficult to differentiate ADH (see Fig. 21-2D) and focal low-grade DCIS (see Fig. 21-2E) and a conservative approach is usually recommended. Ideally, the final interpretation of a small atypical borderline ductal lesion diagnosed at CBX would involve re-evaluation of the CBX material together with the surgical excision specimen, but this practice is not always possible. Fine needle aspiration (FNA) of DCIS shows large aggregates of neoplastic cells, admixed with single cells and rare small stromal fragments. In general, the FNA material obtained from DCIS contains fewer single cells and fewer stromal fragments than the FNA material obtained from an invasive carcinoma. These morphologic features, however, are variable and their interpretation is also operator dependent. Therefore, the positive predictive value and interobserver reproducibility of FNA in the diagnosis of DCIS versus invasive carcinoma are relatively low. Although combination of the cytology findings with clinical and radiologic features often allows to "best guess" whether the lesion represents DCIS or invasive carcinoma. CBX has become the preferred method of preoperative diagnosis, as it provides more definitive, consistent and reproducible information, as well as tissue suitable for ancillary studies.

DCIS is a non-obligate morphologic precursor of breast carcinoma, but its rate of progression varies greatly depending on the intrinsic biology of the lesion. Recurrence is also dependent on its complete removal and adjuvant treatment.

Gross Examination

At present, most cases of DCIS do not display overt macroscopic findings at gross examination. DCIS with high nuclear grade and extensive necrosis sometimes forms a mass lesion because of substantial periductal fibrosis. Specks of pasty material consisting of necrotic debris extruding from the ducts may be noted on the cut surface of a specimen containing high-grade DCIS with extensive necrosis. Mass-forming lesions regarded in the past as intracystic papillary DCIS are now re-classified as encapsulated papillary carcinoma, a recently recognized special variant of low-grade invasive carcinoma with extremely indolent behavior (10). Despite morphologic reclassification as an invasive process in the absence of an overt invasive carcinoma, the management of these tumors remains unchanged.

If a surgical excision was obtained to remove an area of DCIS with associated Ca^{2+} the specimen radiograph obtained to document removal of the calcified target is used by the pathologist to localize the area of interest in the corresponding gross specimen. At present, a preoperative diagnosis of DCIS obtained by CBX is available for most cases, and histologic evaluation of the CBX site needs to be documented in the report to ensure that the radiologic target was removed and examined histologically.

Because of the paucity of gross findings in most cases of DCIS, extensive histologic sampling of the resection specimen is required for optimal evaluation of the lesion, to assess the extent of DCIS, exclude the possibility of (micro)invasion, and accurately evaluate margin status. As recommended by the College of American Pathologists (CAP) (25), the surgical excision specimen is measured in all three dimensions, and

serially sliced in 0.3 to 0.4 cm thick sections perpendicular to the major axis. In some laboratories, radiographic images of the tissue slices are obtained to identify all Ca^{2+} and ensure that they are examined histologically. A surgical specimen obtained following CBX diagnosis of DCIS is usually entirely and sequentially submitted for histologic examination. Practically speaking, surgical excision specimens larger than 6 cm are often sampled selectively by submitting a wide area of tissue (radius of about 2.5 to 3 cm) centered around the biopsy site, any area of gross abnormalities, and representatively sections of the grossly unremarkable breast parenchyma away from the biopsy site. The remaining tissue is saved and can be submitted at a later time, if the pathologist deems it necessary.

At present, there is no universally accepted classification system for DCIS. The pathology report should include information about the morphologic features of DCIS that have been shown to correlate with clinical behavior and outcome. These parameters were first agreed upon by the panelists of a consensus conference on DCIS in 1997 and have been further detailed and expanded in the protocol for examination of breast specimens with DCIS released by the CAP in 2009 (25).

Size

The size of DCIS correlates with the likelihood of residual disease after re-excision, close or positive margins, local recurrence, and the possibility that undetected areas of invasion might exist. However, if wide margins are obtained, the extent of DCIS is not as important for predicting local recurrence. The following methods are used to assess the size of DCIS (Fig. 21-4A–E).

a) If DCIS is present in only one tissue block, its size is measured microscopically as the largest span between the two ducts involved by DCIS that are further away from one another. This situation is rare, as such small lesions are uncommon (see Fig. 21-4A).
b) If the surgical specimen is entirely and sequentially submitted, and DCIS is present in few consecutive tissue blocks, the size of DCIS is estimated by multiplying the number of blocks involved by DCIS by the thickness of the tissue in each block (approximately 0.4 cm) (see Fig. 21-4B).
c) If only representative blocks of the surgical specimen are submitted, account should be kept of the intervening sections not submitted for histologic examination. The extent of DCIS is estimated by adding the number of the blocks microscopically proven to contain DCIS and the number of the intervening blocks and multiplying the sum by the estimated thickness of each block (see Fig. 21-4C).
d) If DCIS involves opposing margins of a specimen, the span of DCIS is as great as the distance between the two margins (see Fig. 21-4D).
e) When high-grade DCIS forms a mass lesion, the size of the mass is measured grossly and confirmed microscopically (see Fig. 21-4E).

The largest estimate obtained using any of the above methods is the estimated extent of DCIS in the specimen. Gaps in ductal involvement suggestive of multifocality may occur, particularly in cases of low-grade DCIS.

In the current practice of breast-conserving surgery, DCIS may be incompletely excised by the first surgical procedure and is present in either multiple specimens from the same surgical procedure or in multiple specimens from subsequent procedures. In these cases, the span of DCIS present in different specimens cannot be added and the pathologic size is the largest span of DCIS in any of the specimens. Close correlation with imaging studies is recommended. The mean or median size of DCIS reported by few investigators ranges from 1.4 to 2.7 cm.

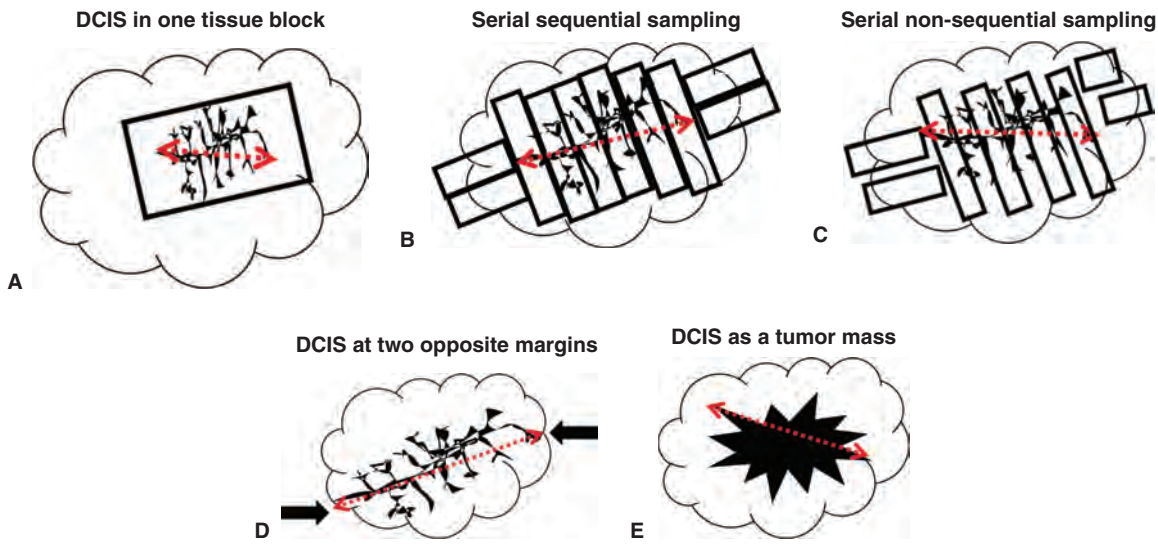


FIGURE 21-4 **(A)** If DCIS is present only in one tissue block, the size of DCIS is measured on the H&E slide as the largest distance between two ducts involved by DCIS. **(B)** If the specimen is entirely and sequentially submitted, the size of DCIS is estimated based on the number of the involved tissue blocks: i.e., 6 consecutive blocks × 0.4 cm = DCIS spans 2.4 cm. **(C)** If the specimen is not entirely submitted, the size of DCIS is estimated as in B) by adding the number of un-sampled intervening slices: i.e., (4 blocks + 3 intervening sections) × 0.4 cm = DCIS spans 2.8 cm. **(D)** If DCIS involves two opposite margins, the size of DCIS corresponds to the distance between the two margins. **(E)** If the DCIS forms a tumor mass, the size of DCIS is measured grossly modified from diagram of Lester et al. (25).

Nuclear Grade

DCIS is stratified primarily by nuclear grade. Low-grade nuclei are slightly enlarged (1.5×–2× the size of a red blood cell [RBC]) and uniform, have a regular nuclear membrane, fine and homogeneous chromatin and rare inconspicuous nucleoli. High-grade nuclei are large (size greater than 2.5× RBC), have marked variation in size and shape, coarse chromatin and prominent, sometimes multiple nucleoli. Mitoses are frequent. Intermediate-grade nuclei are less pleomorphic than high-grade nuclei, but lack the uniformity characteristic of low-grade nuclei. Nuclear grade within a given DCIS lesion tends to be relatively uniform in 84% of cases, but it is heterogeneous in the remaining 16% (26).

Architectural Patterns

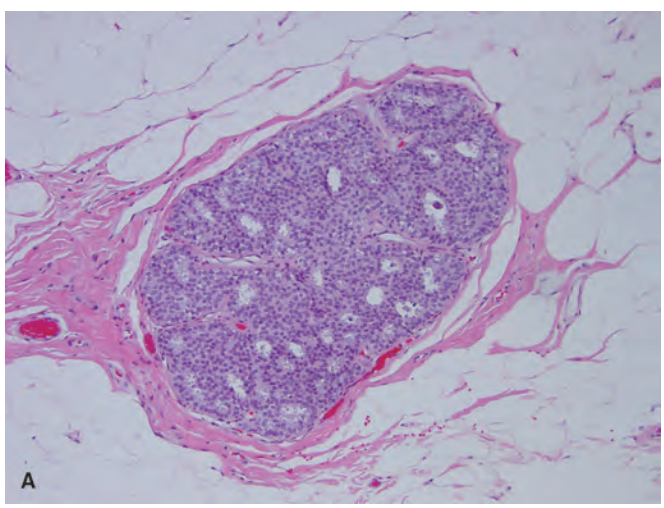
DCIS can show few different patterns (Fig. 21-5A–E) including cribriform, micropapillary, papillary, solid and clinging/flat. The comedo type is characterized by extensive central zonal necrosis. DCIS with mixed architectural patterns constitutes the majority of cases (62%), followed by solid DCIS (31%) (26). This classification has only minimal clinical or prognostic significance, although it shows some correlation with extent of disease. Bellamy et al. (27) found that involvement of more than one quadrant occurred in 71% of cases of micropapillary DCIS, irrespective of nuclear grade or necrosis, whereas comedo, solid and cribriform DCIS involved more than one quadrant only in 8%, 17%, and 25% of cases, respectively. When completeness of local excision was related to architectural pattern, solid DCIS (including solid DCIS with necrosis) was significantly more often completely excised (72%) than DCIS with any other architectural pattern (30%) (p <.01) (27).

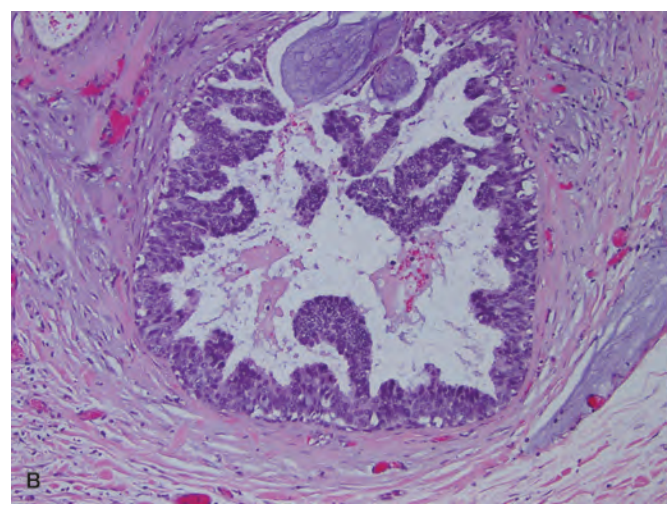
Necrosis

A number of studies have shown that the presence of necrosis in DCIS modifies the risk associated with nuclear grade. Necrosis is defined as the presence of ghost cells and karyorrhectic debris and can involve the central zone of a duct (comedo necrosis) or be punctate and non-zonal. Zonal necrosis usually occurs in DCIS with high nuclear grade and often contains coarse Ca^{2+}. *Comedo DCIS* is a descriptive term which refers to the gross finding of pasty material extruding from the ducts that may be in cases of DCIS with extensive necrosis, but it is not specific for a certain nuclear grade, architectural pattern, or extent of necrosis.

Margin Assessment

There is no standard method of margin evaluation for breast specimens with DCIS (or with invasive carcinoma). Furthermore, the definition of a positive margin (tumor at ink) is agreed upon, but there is no full agreement on what constitutes a "negative" margin. Margin status can be evaluated using different methods, but two are the most commonly used.





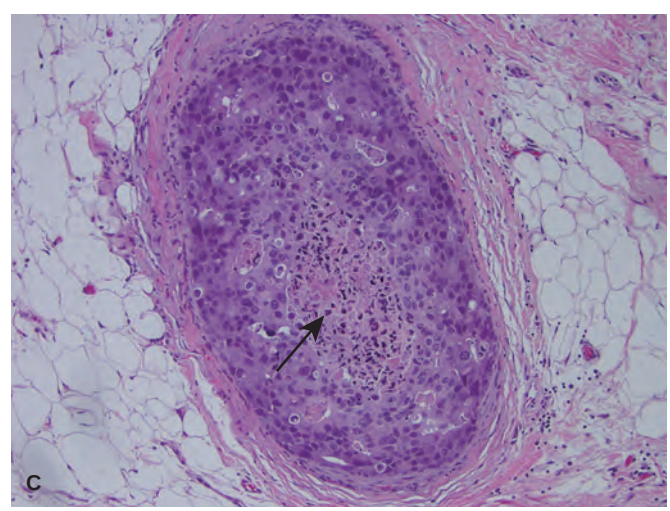


FIGURE 21-5 Nuclear grading and architectural patterns of DCIS: **(A)** low-grade, cribriform, **(B)** intermediate-grade, micropapillary, **(C)** high-grade, solid with central necrosis *(arrow)*,

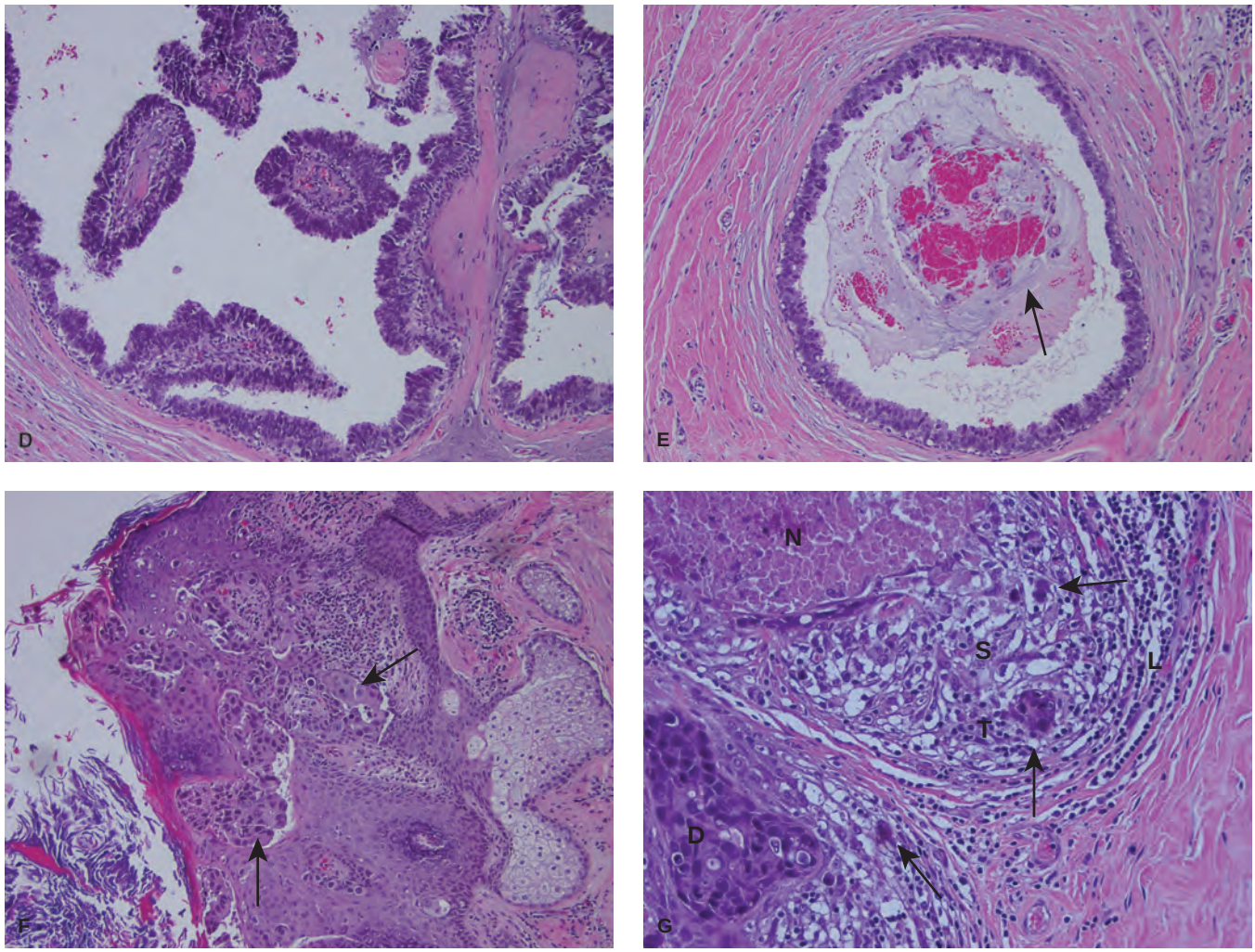


FIGURE 21-5 *(Continued)* **(D)** intermediate-grade, papillary, and **(E)** intermediate-grade, flat with mucin production *(arrow)*. **(F)** Paget's disease: scattered malignant glandular epithelial cells *(arrows)* are present in the epidermis. The cells have large nuclei with prominent nucleoli and pale, amphophilic cytoplasm. **(G)** Microinvasive ductal carcinoma: the foci of high-grade solid DCIS (D) are associated with Necrosis (N) and are surrounded by Stromal desmoplasia (S) and dense Lymphocytic infiltrate (L). Admixed within the lymphocyte-rich stroma are few Tumor cells (T, *arrows*), singly and in small nests.

a) *Radial (perpendicular) margin.* The specimen is oriented with at least two of the margins (usually superior and lateral margins) marked with metal clips or sutures. The six margins of the specimen are inked by the surgeon or by the prosector using different colors. The specimen is sectioned, and perpendicular sections of the inked margins are submitted for microscopic examination. This technique allows measuring the exact microscopic distance between DCIS and the closest inked margin present in the same tissue section.

b) *All margins of the lumpectomy cavity are separately submitted by the surgeon.* The surgeon resects the index lesion and then removes separate margins from the superior, inferior, lateral, medial, and posterior wall of the surgical cavity. An anterior margin specimen may or may not be submitted. The surgeon designates with a suture or clip the surface of each additional margin specimen that corresponds to the final surgical margin. This surface is inked by the prosector, and the specimen is sectioned with cuts perpendicular to the inked surface. The distance between DCIS and the closest linked margin is assessed. The main excision specimen containing the target lesion is usually not oriented and does not necessarily need to be inked. This method allows precise margin designation, accurate measurement of margin width, and avoids disruption of the tissue secondary to compression at the time of specimen radiography. A study has reported a reduced rate of re-excision for excisions that used this method (28).

Calcifications

Most cases of DCIS are diagnosed following biopsy of microcalcifications detected on screening mammograms. The radiologist usually qualifies the calcifications (Ca^{2+}) as "suspicious" or "pleomorphic" to indicate high level of concern for DCIS. At the time of the CBX the radiologist separates the core containing Ca^{2+} from those without. The cores with Ca^{2+} and the additional tissue cores without Ca^{2+} kept separate and placed in formalin-filled specimen container and submitted to pathology. The prosector submits the tissue in separate cassettes indicating whether the tissue contains Ca^{2+} or not. Core needle

biopsies performed for mammographic Ca^{2+} are also received with the specimen x-ray. When reviewing the hematoxylin and eosin (H&E) slides of a case, the pathologist examines the accompanying specimen x-ray to determine if the amount of Ca^{2+} present in the slides accounts for the amount, size and type of Ca^{2+} seen in the specimen x-ray. If insufficient Ca^{2+} are present in the H&E slides, the tissue blocks are x-rayed to verify which block(s) contain Ca^{2+} and how deep they are into the tissue block. Deeper sections are cut until the target Ca^{2+} are identified.

For proper correlation with the mammographic findings, the pathologist needs to detail whether Ca^{2+} are present in the surgical excision specimen and if they are associated with DCIS and/or present in benign breast parenchyma. The identification of residual Ca^{2+} in a post-excision mammogram is a strong predictor of residual DCIS and constitutes an indication for re-excision, even if the margin of the prior excision specimen was reported as negative.

Subtypes

Based on these above features, DCIS is subdivided into three large groups, generally referred to as high-grade, low-grade, and intermediate-grade DCIS.

High-Grade DCIS usually has high nuclear grade, solid or micropapillary architecture with central zonal (comedo) necrosis (see Fig. 21-5). The neoplastic cells show little to no polarization. Coarse pleomorphic Ca^{2+} are typically associated with necrotic debris. The periductal stroma often displays a cellular fibroblastic proliferation with collagen deposition (desmoplasia), chronic inflammation, and angiogenesis. The stromal response may be very prominent and result in a palpable breast abnormality. Paget's disease of the nipple is almost invariably associated with high-grade DCIS (see Fig. 21-5).

Low-Grade DCIS is a relatively monotonous proliferation of polarized cells with round and uniform nuclei. The neoplastic cells are orderly assembled into club-shaped micropapillae and/or cribriform spaces; a purely solid architecture is less common (see Fig. 21-5). The associated Ca^{2+} are often small and psammomatous. Albeit very uncommon, the presence of foci of punctate necrosis does not preclude the diagnosis of low-grade DCIS if the neoplastic cells show the characteristic cytologic features.

Intermediate-Grade DCIS typically has solid or cribriform architecture and most of the cells are polarized. The nuclei have features intermediate between low and high grade, and necrosis and mitotic activity can vary (see Fig. 21-5).

Unusual Morphologic Variants

A minority of DCIS lesions show unusual morphology. Variants of DCIS have signet ring, apocrine, spindled or even squamous morphology. There is no consensus or uniform approach to the grading of these unusual variants, although some believe that nuclear features and necrosis are most informative of the biology of the lesion. One of the most common variants is *DCIS with apocrine morphology* (see Fig. 21-3B). It usually has solid, micropapillary or cribriform architecture. The cells have abundant and somewhat granular eosinophilic cytoplasm and large nuclei with prominent nucleoli. Nuclear atypia is usually moderate to severe, but low-grade apocrine DCIS can also occur. Central necrosis is often present in high-grade apocrine DCIS, raising the differential diagnosis with high-grade non-apocrine DCIS. Calcifications may be seen in the involved ducts. A diagnosis of high-grade apocrine DCIS is usually straightforward because these lesions are characterized by marked cytologic atypia and frequently comedo necrosis. At the other end of the spectrum, it may be difficult to distinguish low-grade apocrine DCIS from apocrine metaplasia because they share similar features, such as round shape and single prominent nucleoli. An apocrine intraductal proliferative lesion composed of cells with only minimal cytoplasmic atypia should be categorized as DCIS only if it has fully developed architectural features of DCIS. Apocrine DCIS can extend into lobules and into areas of sclerosing adenosis, in a pattern that simulates invasive carcinoma. Immunostains for myoepithelial cells are valuable in resolving this differentiated diagnosis. Sometimes, it may be difficult to distinguish apocrine DCIS involving sclerosing adenosis from atypical apocrine adenosis, particularly when cytologic atypia is low or moderate.

Cystic hypersecretory DCIS is another uncommon, but extremely characteristic variant of DCIS. It is characterized macroscopically and microscopically by cysts filled with viscid and homogenous eosinophilic material that closely resembles thyroid colloid. Invasive carcinoma associated with cystic hypersecretory DCIS is usually high grade and has no specific morphology.

Post Treatment

Even if invasive carcinoma shows pathologic complete response in patients treated with neoadjuvant chemotherapy DCIS may persist. In such cases, DCIS usually shows chemotherapy effect, including bizarre cytomorphology and large coarse intraductal Ca^{2+}. The full spectrum of these alterations, probably dependent on different treatment agents, has not been fully characterized. Conversely, adjuvant radiotherapy greatly alters the normal ductal epithelium and some of the early changes induced by radiotherapy can mimic residual/recurrent DCIS. In particular, tissue biopsies obtained within the first few months since completion of radiotherapy need to be examined carefully, and the findings should be compared with those in the untreated DCIS, to avoid overdiagnosis.

Immunoprofile

Generally speaking, low-grade DCIS is characterized by diffuse and strong expression of ER-α in 90% to 100% of cells (see Fig. 21-3A). PR is also positive in most cells. The proliferation rate of low-grade DCIS tends to be low (around 5% to 6%) and does not differ significantly from that of FEA and ADH. HER2 is rarely expressed in low-grade DCIS, but may be detected in up to 10% of the cells. In contrast, high-grade DCIS is ER-positive in 30% to 90% of the cases, show variable positivity for PR, and has a higher proliferation rate (Ki-67 staining in up to 30% to 40% of the cells). HER2 protein expression and gene amplification is detected in about 70% of intermediate- and high-grade DCIS, and usually characterizes biologically aggressive DCIS (see Fig. 21-3B). The use of HER2 targeted therapy for DCIS is currently explored in clinical trials. Nuclear p53 protein and p53 gene mutations are seen in about half of high-grade DCIS cases (29). Intermediate DCIS lesions are more heterogenous with regard to the expression of the above biomarkers. AR is also expressed in some forms of DCIS. In one study (30), AR was detected in 89.3% of ER-positive DCIS, in 87.9% of PR-positive DCIS and in 80% of HER2-positive DCIS.

The benefit of tamoxifen treatment in patients with DCIS managed by surgical excision and radiotherapy correlates with ER-positivity (31). Status of ER in DCIS is assessed routinely using immunochemistry. In clinical practice, ER- or PR-positivity result is defined as nuclear staining in at least 1% of the cells.

All types of DCIS have strong and continuous linear membranous positivity for the adhesion molecule E-cadherin.

Following the identification of molecular subtypes of invasive breast carcinoma (i.e., Luminal A and B, HER2-rich, and basal subtypes) (32) and of surrogate molecular immunoprofiles based on reactivity for ER, PR, HER2, and basal markers CK5/6 and epidermal growth factor receptor (EGFR), investigators have documented similar molecular subtypes in DCIS. In particular, a basal subtype of DCIS (i.e., ER-, PR-, and HER-negative and CK5/6- and/or EGFR-positive) has been identified (33). Basal DCIS constitutes about 6% to 8% of all DCIS. It has intermediate to high-grade morphology (34) (see Fig. 21-3B), but the morphologic features of basal DCIS are not sufficiently characteristic to recognize it without the use of immunohistochemical markers. Cytoplasmic positivity for CK5/6 and/or EGFR in basal DCIS is focal and heterogeneous, and not too different from that observed in UDH, but nuclear atypia is high. Basal DCIS was identified in 32/392 (8.2%) women with DCIS. In one study (34) the nuclear grade was high in 20 (62.5%) cases, intermediate in 11 (34.4%) and low in one (3.1%) case. Twenty-six women underwent breast-conserving surgery and 10 received postoperative radiotherapy. Six women were treated by mastectomy. At median follow-up of 122 months (range 3–130), basal-like DCIS showed higher risk for local recurrence, invasive recurrence and systemic recurrence than non-basal DCIS, but the results were not statistically significant. These differences were not attributable to triple negative phenotype (34). At present, basal DCIS does not constitute a specific diagnostic entity and it is not commented upon in a pathology report.

Differential Diagnosis

The differential diagnoses of FEA versus clinging DCIS, UDH versus DCIS, and ADH versus DCIS are mentioned in prior paragraphs. Three other important differential diagnoses are discussed below.

DCIS versus LCIS

The distinction between solid DCIS versus LCIS has significant implications with regard to assessment of margin status and the extent of surgical excision and need for adjuvant radiotherapy. Some solid DCIS has morphologic features that overlap with those of LCIS, including classic LCIS (composed of small dyshesive cells with monotonous nuclei), LCIS with comedo necrosis (characterized by massive acinar expansion, central necrosis, Ca^{2+}, and low grade atypia), and pleomorphic LCIS (defined by nuclear pleomorphism, central necrosis, and Ca^{2+}). Cell dyshesion and intracytoplasmic vacuoles favor a diagnosis of LCIS (see Fig. 21-3A), whereas cohesive growth, lack of intracytoplasmic vacuoles, polarization of cells, and focal formation of microacini favor DCIS. In problematic cases the differential diagnosis is usually resolved with an immunohistochemical staining for E-cadherin, as LCIS is typically E-cadherin-negative, whereas the cells of DCIS have continuous linear membranous positivity for this marker.

DCIS versus Invasive Carcinoma

Some invasive carcinomas exhibit patterns that simulate DCIS (such as invasive cribriform carcinoma and adenoid cystic carcinoma). Conversely, DCIS involving lobules, sclerosing adenosis or a radial sclerosing lesion can closely resemble stromal invasion. Immunostains for myoepithelial markers are of great value in these situations. The presence of a peripheral MEC layer around nests of neoplastic cells supports a diagnosis of DCIS, whereas its absence supports a diagnosis of invasive carcinoma (35). The only exception to this rule is microglandular adenosis (MGA), a rare "benign" lesion composed of monostratified and cytologically bland glands devoid of myoepithelium, but surrounded by basement membrane. MGA has a haphazard infiltrative pattern and DCIS and invasive carcinoma often arise in association with it. MGA and MGA-associated carcinomas have triple-negative phenotype (see Fig. 21-3B) (36). Two studies have provided genetic evidence that MGA is a non-obligate morphologic precursor of MGA-associated invasive carcinoma (37,38).

Microinvasive Carcinoma (MIC)

MIC is defined as invasion spanning no more than 1 mm in greatest diameter (see Fig. 21-5G). MIC often occurs in a background of high-grade DCIS and is very unusual in the context of low-grade DCIS (or LCIS). Stains for MECs and keratin are helpful to demonstrate the presence of tumor cells in the stroma. ER (and PR) status of MIC is usually reported. Information on HER2 status of MIC is of debatable utility. If MIC is not present on the deeper sections used for these biomarker studies, the ER immunoprofile of the adjacent DCIS is usually reported.

Molecular Profile

Low- and high-grade DCIS are fundamentally different diseases and each is genetically related to its invasive counterpart (39).

Expression profiling analysis of matched *in situ* and invasive carcinoma has shown that lesions of similar histologic grade cluster together, indicating a close relationship within low-grade and high-grade DCIS and corresponding invasive carcinomas, but not across low- and high-grade lesions (39). Breast cancers also segregate into two groups based on the expression of ER and ER-regulated genes, confirming that ER-dependent pathways are fundamental in the development and progression of ER-positive carcinoma (32).

The current model of breast cancer (6), based on morphological, immunophenotypical, molecular features, identifies two main and fairly distinct groups of lesions.

The low-grade group, which encompasses the low-grade breast neoplasia family, includes FEA, ADH, DCIS, lobular neoplasia, and their invasive counterparts. This group of lesions is characterized by expression of ER and PR related genes, and lacks HER2 overexpression and expression of basal genes. It roughly corresponds to the Luminal A lesions. The cells have diploid/near-diploid karyotype and are characterized by recurrent chromosomal alterations, namely deletion of 16q (in over 80% of cases) and gains of 1q (in over 75% of cases) and 16p (in over 50% of cases) (40) (Fig. 21-3A).

The high-grade group is characterized by greater diversity and contains DCIS corresponding to the Luminal B, HER2-overexpressing and basal type carcinomas, and also includes apocrine carcinomas (6,41). The immunoprofile and patterns of genetic aberrations of high-grade DCIS are more heterogenous than in low-grade-DCIS. High-grade DCIS is characterized by aneuploidy, complex karyotypes and numerous unbalanced genomic changes mapping to several chromosomal arms, including recurrent losses at 8q, 9p, 11q, 13q, 17q, and 22q, and gains at 1q (in over 60% of cases), 8q (in over 75% of cases) and 17q (40). Studies have also described gains of 5p, 17q, 20q, and losses of 11q, 13q, and 14q. Recent molecular and genetic evidence suggests that progression from low-grade DCIS to high-grade DCIS may occur in some cases, but the pathways that lead to the development of low- and high-grade lesions are for the most part distinct and separate (6,42,43). Consistent with these data is the observation that only

TABLE 21-1

	Usual Ductal Hyperplasia (UDH)	*Flat Epithelial Atypia (FEA)*	*Atypical Ductal Hyperplasia (ADH)*	*Ductal Carcinoma In Situ (DCIS)*
Definition (as in WHO, 2012 (10))	• Solid or fenestrated proliferation of epithelial cells that often show streaming growth particularly in the center of involved spaces	• Neoplastic alteration of TDLUs characterized by replacement of native epithelial cells by one to several layers of a single epithelial cell type showing low-grade (monomorphic) cytologic atypia	• Proliferation of monomorphic, evenly placed epithelial cells involving TDLUs	• Neoplastic proliferation of epithelial cells confined to mammary ductal-lobular system and characterized by subtle to marked cytological atypia and an inherent but not necessarily obligate tendency for progression to invasive breast cancer
Clinical and Radiologic Features	• Incidental finding, no specific clinical or radiologic features	• Clinically asymptomatic • Often identified as (clustered) indeterminate mammographic calcifications	• Clinically asymptomatic • Usually identified mammographically as calcifications • Can be incidental finding	• Rare cases present clinically as mass, Paget's disease of the nipple or nipple discharge • Mammographic calcifications
Prognosis	• 1.5×–2× risk of breast cancer in either breast	• No established risk (risk probably higher than UDH, but lower than ADH)	• 4×–5× risk of breast cancer	• Can recur locally as DCIS or invasive carcinoma • Distant metastases are rare
Treatment	• Mammographic surveillance	• Diagnosis of FEA at core biopsy mandates surgical excision • No other treatment recommendations	• Diagnosis of ADH at core biopsy mandates surgical excision • Mammographic surveillance • Chemoprevention	• Surgical excision with negative margins + radiation therapy or mastectomy • Chemoprevention
Gross Findings	• Not specific	• Not specific	• Not specific	• Rarely evident as speckled ill-defined area or mass
Microscopic Findings	• Haphazard proliferation of three or more layers of epithelium with irregular slit-like lumina connected in 3-D	• One to several layers of ductal cells with cytologic atypia but no architectural complexity • Often coexists with ADH, low-grade DCIS, ALH/LCIS, and tubular carcinoma	• Uniform cell population with low-grade cytologic atypia and incomplete architectural features of low-grade DCIS • Focal (<2 mm or <2 ducts)	• Complex architecture (cribriform spaces, micropapillae, solid, papillary) • Nuclear atypia (low, intermediate or high) • Necrosis can be present • Mitoses • Discontinuous growth pattern within ducts in 70% low-grade DCIS, 55% intermediate-DCIS, and 10% high-grade DCIS • Variable size

Immunohistochemical Features	• Heterogeneous staining positive for CK5/6 and ER	• CK5/6-negative and ER-positive	• CK5/6-negative and ER-positive	• Usually CK5/6-negative (except basal DCIS) and ER-positive (90–100% low-grade DCIS; 30–90% high-grade DCIS) • HER2-positive in 70% of intermediate- and high-grade DCIS • Low-grade DCIS is rarely HER2-positive • Apocrine DCIS is AR-positive and ER-negative • Basal DCIS is ER-, PR-, HER2-negative, and CK5/6- and/or EGFR-positive
Differential Diagnosis	• ADH • DCIS	• Apocrine lesions • Cystic hypersecretory lesions • Flat/clinging intermediate-grade DCIS	• Low-grade DCIS • UDH	• LCIS (E-cadherin negative) • (Micro)invasive carcinoma (especially when DCIS involves a sclerosing lesion)
Molecular Findings	• Few and inconsistent chromosomal alterations that are different from those of invasive carcinoma	• Chromosomal alterations consistent with clonal population • Loss at 16q • Gains at 15q, 16p, 17q, and 19q	• Chromosomal alterations consistent with clonal population • Losses at 16q and 17p • Gain at 1q	• Chromosomal alterations consistent with clonal population • Low-grade DCIS: diploid/near diploid karyotype; deletion of 16q • High-grade DCIS: numerous, heterogenous, complex and unbalanced genomic alterations (see Fig. 21-3)

less than 30% of high-grade carcinomas show deletion of 16q, suggesting that only a small group of high-grade carcinomas are derived from low-grade DCIS, whereas the majority of high-grade DCIS either develops *de novo* or originates from a (still unidentified) putative precursor other than ADH/low-grade DCIS (6). Morphologic precursor lesions of most high-grade DCIS have not yet being identified, except for two, namely MGA for some basal-like DCIS (44) and apocrine atypia for apocrine DCIS (45) (see Fig. 21-3B).

Heselmeyer-Haddad et al. (46) used FISH probes for the oncogenes COX-2 (1q), MYC (8q), CCND1 (11q), HER2 (17q), and ZNF217 (20q), and the tumor suppressor genes DBC2 (8p), CDH1 (16q), and TP53 (17p) to determine nonrandom chromosomal gains and losses, to assess the degree of intratumor heterogeneity, and to reconstruct clonal relationships between synchronous DCIS and invasive ductal carcinoma by single cell analysis of 13 selected cases. They found that DCIS had a lower degree of chromosomal instability than the corresponding invasive ductal carcinoma. Gains of COX-2 and MYC, together with losses of DBC2, CDH1, and TP53 occurred most commonly during the progression of DCIS to invasive carcinoma (46), and in particular MYC gains and CDH1 losses were more frequent in invasive carcinomas.

Hernandez et al. (47) performed a comprehensive profiling of mutations of known cancer-related genes in matched DCIS and adjacent invasive ductal carcinomas. The authors confirmed that activating phosphatidylinositol-4,5-bisphosphate 3-kinase, catalytic subunit alpha (PIK3CA) mutations are frequent in DCIS (48), and more prevalent than in the adjacent invasive carcinoma. These results suggest that PIK3CA mutations play an important role in DCIS initiation rather than in its progression to invasive ductal carcinoma (48). Other studies have found no substantial genetic differences between matched DCIS and invasive carcinoma. A large constellation of genetic and/or epigenetic aberrations, some of which are mediated by the microenvironment (49), may be at play in the progression from DCIS to invasive disease.

Lee et al. (50) carried out comprehensive expression profiling of 53 DCIS and 51 invasive breast carcinomas, including separate samples of tumor epithelium and adjacent stroma prepared by laser-capture microdissection, and found increased expression of a total of 470 genes. Elevated expression of genes involved in the synthesis and organization of extracellular matrix was particularly prominent in invasive carcinoma compared to DCIS (50). The investigators analyzed *in vivo* the progression of DCIS to invasive carcinoma using three DCIS-like human breast epithelial cell lines DCIS.COM, SUM225, and h.DCIS.01, engineered to express specific genes into a "mammary intraductal DCIS (MIND)" xenograft model. In the xenografts the progression to invasive breast carcinoma was dramatically increased by suppression of four specific genes, namely Cystatin-A (CSTA), a protease inhibitor, DST, FAT1 and TMEM45A (50), involved in cell adhesion and signaling. On the contrary, the expression of these genes was elevated in cases of DCIS with no invasion. These results suggest that these genes are involved in suppressing the progression of DCIS to invasive carcinoma.

Summary

In summary, intraductal proliferative lesions are cytologically and architecturally diverse.

DCIS is a heterogeneous group of neoplastic intraductal lesions characterized by increased epithelial proliferation with different architectural patterns and cytological atypia ranging from mild to severe.

Molecular data suggest that DCIS is as heterogeneous as invasive carcinoma. Based on morphological, immunophenotypical and molecular features DCIS can be classified into two groups (see Fig. 21-3A and B). The low-grade breast neoplasia family includes FEA, ADH, low-grade DCIS, lobular neoplasia, and their invasive counterparts. These lesions are ER positive, HER2 negative and lack of expression basal markers. They are characterized by deletion of 16q. The high-grade DCIS lesions are more heterogenous. Most lack ER, some express HER2 and some are ER, PR, and HER2 negative but express basal markers. Numerous and complex unbalanced genomic alterations are found in high-grade DCIS.

Table 21-1 Highlights key features of the ductal lesions discussed in the chapter.

Margin status, nuclear grade, and necrosis are the most predictive parameters of clinical outcome, which is also significantly influenced by adjuvant radiation and hormonal treatment.

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CHAPTER 22

Lobular Carcinoma *In Situ*: Biology and Management

Tari A. King and Jorge S. Reis-Filho

CHAPTER CONTENTS

Lobular carcinoma *in situ* (LCIS) and atypical lobular hyperplasia (ALH) are relatively uncommon breast lesions, which are typically discovered in breast biopsies taken for other reasons. The first description of LCIS was reported by Ewing in 1919, who depicted this lesion as an "atypical proliferation of acinar cells" of the breast (1). The main characteristics of this lesion, however, were not thoroughly documented until 1941 in the seminal study by Foote and Stewart, in which the term *LCIS* was coined to refer to a spectrum of "noninfiltrative lesions of a definitely cancerous cytology" that would constitute precursors of invasive breast cancer, and be composed of a monomorphic population of dyshesive cells that expand the terminal duct–lobular units (2). A less-prominent *in situ* proliferation composed of cells cytologically identical to those of LCIS, and associated with a lower risk of breast cancer development, was subsequently identified and named ALH (3). In a review of 211 cases of LCIS not associated with other forms of breast cancer, Haagensen et al. (4) observed the difficulties in differentiating between LCIS and ALH, and suggested that the term *LCIS* not associated with invasive cancer would constitute a misnomer, given that the available evidence at that time supported the contention that these lesions would in fact constitute a "benign, non-infiltrating, special microscopic form of lobular proliferation of the mammary epithelium" (4). The term *lobular neoplasia (LN)* was subsequently put forward to refer to the entire spectrum of these *in situ* lesions, including ALH and LCIS (4). Although surgeons, oncologists, and pathologists are familiar with the concept of LCIS, the terminology and classification for these lesions, their biological significance (risk indicator vs. precursor for invasive cancer), and the best course of management following diagnosis remain controversial. This chapter will discuss the clinicopathological and molecular characteristics of LN, and the impact of recent developments on the management of these lesions.

Several of the concepts initially put forth by Foote and Stewart (2) on the biology of LCIS remain valid today. The term *LCIS* was chosen to emphasize the histologic similarities between the cells of LCIS and those of frankly invasive lobular carcinoma (ILC), and, importantly, was not meant to infer that the cell of origin resided in the lobules; in fact, it was acknowledged that LCIS would originate in the terminal duct–lobular unit and small ducts (2). In addition, LCIS was reported to be frequently multicentric and bilateral, and not readily identifiable on gross examination. Microscopically, the cells that constitute LCIS were thought to disseminate through the ductal system in a way akin to that of Paget's disease; however, LCIS was almost never seen in association with true Paget's disease of the nipple (2). Based on the frequent identification of LCIS in association with ILC and following the analogy of ductal carcinoma *in situ* (DCIS) and invasive ductal carcinoma (IDC), Foote and Stewart (2) hypothesized that the neoplastic cells of LCIS would still be contained within a basement membrane, and that this lesion would constitute a "hazard" (i.e., risk factor) of breast cancer development and a step along the pathway to the development of invasive cancer. Hence, based on the evidence available, simple mastectomy was suggested as the standard form of treatment (2).

Emerging data throughout the 1970s from Haagensen et al. (4) and others (5) demonstrating that the risk of breast cancer development following a diagnosis of LCIS was lower than expected for a direct precursor lesion (approximately 1% per year) and was conferred equally to both breasts generated controversy regarding the significance of these lesions and led to disparate recommendations for management, ranging from observation only to bilateral mastectomy. In current practice, a diagnosis of ALH or LCIS is typically perceived as a risk indicator rather than a precursor of subsequent carcinoma and, as such, radical treatment has fallen out of favor. Yet, observational evidence to suggest that the

risk of breast cancer development following a diagnosis of LN is higher in the ipsilateral than in the contralateral breast and compelling molecular data that demonstrate that ALH and LCIS are clonal neoplastic proliferations that commonly harbor the same genetic aberrations as those found in adjacent invasive cancers (6–10) have reinstated the notion that ALH and LCIS are both non-obligate precursors *and* risk indicators of invasive breast cancer. Questions regarding the biology and optimal management of these lesions have returned to the forefront of breast cancer research and practice.

EPIDEMIOLOGY AND CLINICAL FEATURES

LCIS is most frequently diagnosed in women aged 40 to 55 years (4,11). The true prevalence of LCIS in the general population, however, is difficult to estimate and likely exceeds the incidence, given that it does not present as a mass lesion nor does it have a specific radiographic appearance. Lesions diagnosed in the pre-mammography screening era were typically incidental microscopic findings in biopsies and excision specimens obtained for other reasons (2,4). The reported incidence of LCIS in otherwise benign breast biopsy specimens ranges from 0.5% to 3.8% (4,11), whereas population-based data reported to Surveillance, Epidemiology, and End Results (SEER) from 1978 to 1998 demonstrate an incidence of 3.19 per 100,000 women (12). It is noteworthy, however, that during this time period there was an observed four-fold increase in the number of LCIS cases reported among women over 40 years of age, with the highest incidence rate (11.47 per 100,000 person-years) in 1998 among women 50 to 59 years of age. While this trend may reflect the increasing use of mammography and image-guided biopsies during this time period (12,13), the impact of other factors, such as the use of postmenopausal hormone replacement and more accurate pathologic diagnosis of LN based on ancillary immunohistochemical markers (see below) remains a matter of speculation. LCIS is often multifocal, with more than 50% of patients diagnosed with LCIS showing multiple foci in the ipsilateral breast. Furthermore, bilateral lesions are reported in approximately one-third of patients (14,15). Such multifocality in a clinically non-detectable lesion is one of the reasons why planning subsequent management has proven problematic and contentious. More recent imaging series suggest that LCIS may be associated with microcalcifications (16), and LCIS has been reported to enhance on MRI (17); however, imaging criteria to differentiate LCIS from overt malignancy are lacking, and, as such, women with LCIS are frequently subject to multiple biopsies demonstrating otherwise benign findings.

The clinical characteristics of LCIS, including its multifocal and bilateral distribution, and evidence of familial clustering (18,19) have led to the hypothesis that these lesions could be underpinned by germline genetic abnormalities. Although a hereditary form of diffuse gastric cancer and breast lobular carcinoma caused by *CDH1* germline mutations (20) has been described, the potential genes involved and the pattern of inheritance of familial LCIS outside of this context remain unclear (see below).

The clinical characteristics of LCIS that support its role as a risk factor for the subsequent development of breast cancer include the cumulative long-term risk of breast cancer development that is generally conferred to both breasts, averaging 1% to 2% per year, and the observation that not all breast cancers developing after a diagnosis of LCIS are of lobular histology (reviewed in reference (21). The incidence of invasive breast cancer following a diagnosis of LCIS is steady over time (22), with a similar number of invasive lesions being reported within and after 5 years of follow-up (23). Others have also demonstrated the cumulative long-term risk, with one study reporting that over 50% of patients developed beast cancer between 15 and 30 years of follow-up (5). ALH is also associated with an increased risk of subsequent breast cancer; however, this is of a lower magnitude than that conferred by LCIS. Patients diagnosed with ALH have a four- to five-fold higher risk than the general population (i.e., women of comparable age who have had a breast biopsy performed with no atypical proliferative disease diagnosed), whereas a relative risk of 8 to 10 times is conferred by a diagnosis of LCIS (11,24,25). Hence, these observations suggest that the term *LN,* albeit helpful to describe this group of lesions collectively, may not suffice to guide the management of patients with lobular lesions, and specific classification of LN into ALH and LCIS may still be justified. It should be noted, however, that the distinctions between ALH and LCIS are subjective and, for some experts, the differences between these two categories of LN are more easily expressed in words than in actual practice (23).

The risk of breast cancer development following a diagnosis of ALH or LCIS is bilateral (14,22,26), which is consistent with the notion that these lesions are risk indicators; however, some have reported a higher rate of breast cancer in the ipsilateral breast (9,21,27), supporting a precursor role for LCIS. The histological type of breast cancer following a diagnosis of LN also differs among these reports. In studies that suggest the risk is conferred equally to both breasts, there are, similarly, an equal number of subsequent IDCs and ILCs reported to occur after a diagnosis of LCIS (22), which is consistent with the notion that LCIS would not constitute a true precursor lesion. On the other hand, in most studies that report a higher incidence of ipsilateral cancer development, the majority of the cancers are of lobular histology (8,21,23). This clinical observation, in parallel with SEER data demonstrating an increasing incidence of both LCIS and ILC from the late-1980s to the mid-1990s among women 50 years of age and older (12,28), have led to renewed interest the debate over the clinical significance of LCIS.

Taken together, the current epidemiological, observational, and clinical data support the contention that LN is not only a risk indicator, but also a non-obligate precursor of invasive breast cancer. This notion is lent further credence by the striking morphologic similarities between cells of ALH or LCIS and ILC, and molecular data demonstrating the clonality between LN and synchronous invasive breast cancer (see below); in particular, the presence of concordant gene copy number and allelic abnormalities (6,29), mitochondrial DNA mutations (7), and identical *CDH1* gene mutations in matched LCIS and ILC from the same patients (10).

HISTOLOGICAL FEATURES AND CLASSIFICATION

Despite the controversies surrounding the clinical implications of ALH and LCIS, their histologic features have been well characterized. The latest World Health Organization (WHO) classification of breast tumors defines LN as “a spectrum of atypical epithelial lesions originating in the terminal duct-lobular unit and characterized by a proliferation of generally small, non-cohesive cells, with or without pagetoid involvement of the terminal ducts” (30). At scanning magnification, these lesions are characterized by a variable enlargement of the acini, which are filled up and, at least in part, are expanded by a proliferation of monomorphic population of dyshesive

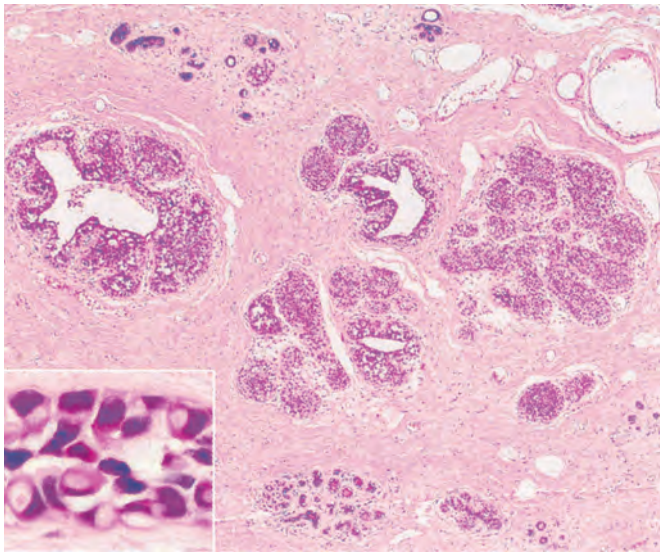

FIGURE 22-1 **Low-power (scanning electron microscopic) appearance of classic lobular carcinoma *in situ*, showing filling and distension of lobules.** Normal lobules are seen at the top and bottom center of the picture for comparison. Inset shows typical cytologic detail of the cells with prominent intracytoplasmic lumina and a magenta body.

small, round, or polygonal cells, with inconspicuous cytoplasm (Fig. 22-1). In fact, the main histological characteristic of LN is that its cells are loosely cohesive, regularly spaced, and fill and distend the acini, with an overall maintenance of the lobular architecture (Fig. 22-2). Intracytoplasmic vacuoles, sometimes containing a central eosinophilic dot (known as magenta body), are usually found (2,4,21,30). Despite the apparent monomorphism of the classic variant of LN, some variability in the cytomorphology between different cases, and frequently within the same case, is easily appreciated, and two cytologic subtypes have been recognized (Table 22-1). Type A cells are small, dyshesive cells with scant cytoplasm and nuclei approximately 1.5 times the size of that of a lymphocyte, whereas type B cells have more abundant, often clear cytoplasm nuclei that are approximately

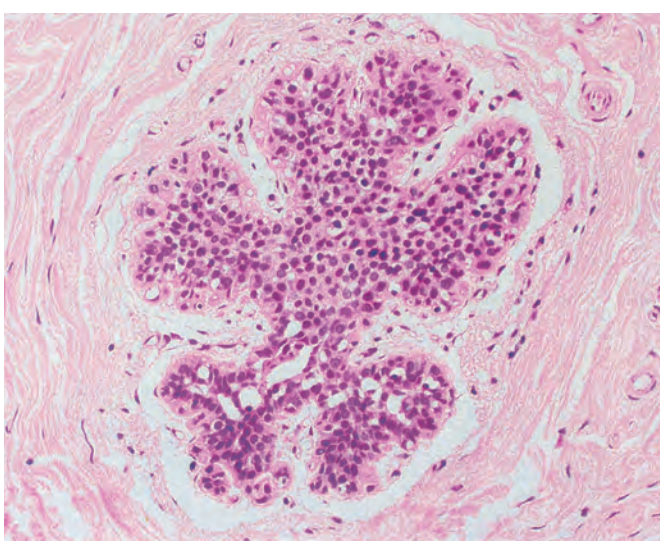

FIGURE 22-2 Typical appearance of a lobular unit distended by lobular carcinoma *in situ*.

two times bigger than a lymphocyte nucleus, mild-to-moderate nuclear atypia (nuclear pleomorphism 1 or 2), and indistinct or absent nucleoli (21,31). It should be noted, however, that this cytological classification scheme has not been shown to be of clinical utility and does not have a direct correlation with the risk of invasive breast cancer development. Other than an academic exercise, this classification system is only a reminder that some degree of cytologic variation can be observed in *bona fide* cases of classic LN. In the classic form of LN, mitoses and necrosis are uncommon. Pagetoid spread within the affected terminal duct–lobular unit, whereby the neoplastic cells extend along adjacent ducts between intact overlying epithelium and underlying basement membrane, is frequently observed (Fig. 22-3). The presence of glandular lumina is not seen in fully developed cases; it should be noted, however, that in lobules partially affected by LN, residual glandular structures can be found.

The sub-classification of LN into ALH and LCIS is quantitative rather than qualitative (30). While for a diagnosis of LCIS more than half the acini in an involved lobular unit must be filled and distended by the characteristic cells, leaving no central lumina, ALH is defined as a less well-developed and less-extensive lesion, where the characteristic cells only partly fill the acini, with only minimal or no distention of the lobule (Fig. 22-4), and glandular lumina can still be found (9,24,30,32). In an attempt to standardize the diagnosis of ALH and LCIS, it has been proposed that lobular distention should be defined as eight or more cells present in the cross-sectional diameter of an acinus, and that the number of acini involved in cases of ALH should account for less than half of the whole terminal duct–lobular unit (9,24,30,32). Although the use of this sub-classification would be justified on the basis of the lower risk conferred by ALH than by LCIS, the differentiation between ALH and LCIS based on the criteria described above is not only arbitrary, but also subjective, prone to interobserver and intraobserver variability, and dependent on the extent of sampling of a given lesion. Therefore, the use of the term *LN* to encompass the whole range of changes, and remove this variability, is preferable for diagnostic purposes, particularly in core needle biopsy specimens (21,33). In fact, in the context of diagnostic core biopsies, the term *LN,* with no attempt to distinguish ALH and LCIS, is recommended in the guidelines of breast cancer screening programs (e.g., the United Kingdom National Health Service Breast Screening Programme [NHS BSP]) (33).

Arguably, a more relevant distinction is between the classic form of LN and the pleomorphic variant of LCIS (PLCIS), which was first identified as a distinct entity by Eusebi et al. in 1992 (34). This variant is characterized by pleomorphic cells that are substantially bigger than those of classic LN (31,34), and by more abundant, pink, and often finely granular cytoplasm. Features of apocrine differentiation are frequently found (34,35). As compared to the nuclei of classic LN, PLCIS nuclei are bigger (four times the size of lymphocyte nucleus), more pleomorphic, and atypical nuclei, often containing conspicuous nucleoli (Fig. 22-5). PLCIS not uncommonly presents with central, comedo–type necrosis and microcalcifications; yet, necrosis is not required for the diagnosis. Recognition of the pleomorphic subtype is important because the combination of cellular features, necrosis, and calcification can lead to difficulty in differentiation from DCIS, and potentially overtreatment, although data regarding the natural history of PLCIS are very limited. Until additional data regarding the natural history of PLCIS are available, this distinction has important implications for treatment. Whereas some advocate for a more aggressive approach to PLCIS, with treatment recommendation akin to those for DCIS, it should be noted that this approach is supported

TABLE 22-1

Cytological and Histopathological Features of Classic and Pleomorphic Lobular Carcinomas

Type of Carcinoma	*Nuclear Size*[a]	*Nuclear Pleomorphism*[b]	*Nucleoli*	*Cytoplasm*	*Dyshesion*	*Central Necrosis*	*Calcifications*	*Apocrine Differentiation*
LCIS Type A	1.5×	1, rarely 2	Inconspicuous	Scant	Present, but inconspicuous	Absent	Occasional	Absent
LCIS Type B	2×	1 or 2	Inconspicuous to small	Moderate	Yes	Absent	Occasional	Absent
PLCIS	≥4	Usually 3	Present, often small	Moderate to abundant	Yes	Frequent	Frequent	Focal
Apocrine PLCIS	≥4	3	Present, prominent	Abundant	Yes	Frequent	Frequent	Defining feature

[a]Nuclear size in comparison with the size of a lymphocyte.
[b]Using the nuclear pleomorphism scheme for DCIS.
LCIS, lobular carcinoma *in situ*; PLCIS, pleomorphic LCIS.

only by molecular data demonstrating that PLCIS shares many similarities with pleomorphic ILC, not by long-term outcomes data.

Additional variants of LN have been reported, including apocrine, histiocytoid, rhabdoid, endocrine, amphicrine, and the apocrine PLCIS variant (21,30). The biological and clinical significance of these lesions also remains to be determined.

A further system for classification of LN has been proposed using the terminology *lobular intraepithelial neoplasia (LIN)*, with subdivision, based on morphologic criteria and clinical outcome, into three grades (LIN 1, LIN 2, LIN 3), with LIN 3 representing the PLCIS end of the spectrum (36,37). This system pre-supposes that the risk of invasive carcinoma development would be related to increasing grade of LIN. This classification system, albeit interesting and potentially sparing women from a diagnosis of "carcinoma" in the case of LCIS, is supported by limited evidence and has not been endorsed in the latest edition of the WHO classification (30).

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of LN includes artifacts, benign breast lesions, and other forms of breast cancer precursors. Prolonged periods of warm ischemia and poor tissue fixation, not uncommonly seen in mastectomy specimens, can result in an artifactual discohesion of cells within a lobular unit, which can mimic ALH and LCIS (21). Benign lesions that may superficially resemble LN include foci of lactational change, where the cells harbor intracytoplasmic lipid droplets, and clear-cell metaplasia (21). More troublesome is the histologic appearance of LN colonizing other benign breast lesions, including fibroadenoma, sclerosing adenosis, and radial scar, which, clinically and radiologically, can present as a mass. Particularly well-known but rather remarkably problematic examples of LN in sclerosing adenosis may resemble IDC to the unwary, due to the distorted appearance of the residual ductal and lobular structures lined by LN cells and immersed in a sclerotic stroma (21,30). In this context, immunohistochemical markers to demonstrate the presence

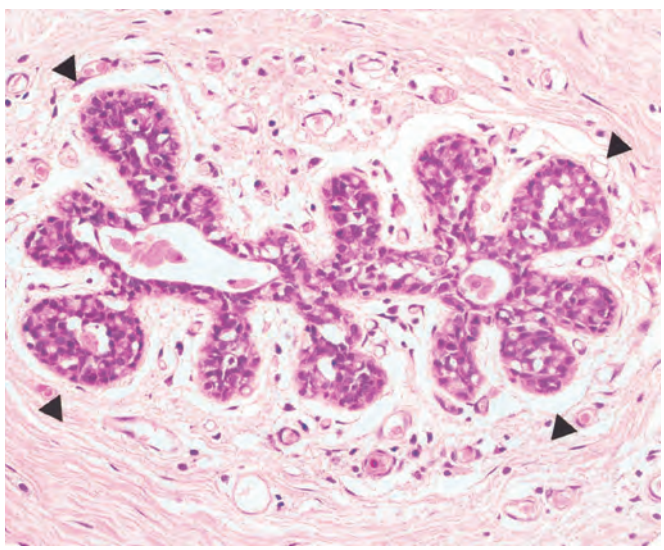

FIGURE 22-3 Pagetoid spread. Lobular carcinoma *in situ* cells (*arrowheads*) are seen growing beneath, and displacing inward, the luminal epithelium of a duct.

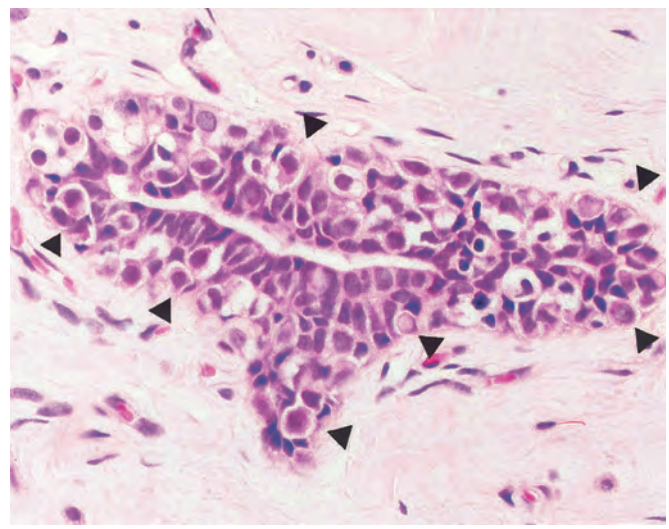

FIGURE 22-4 **Atypical lobular hyperplasia.** A lobular unit is focally and partially filled by characteristic cells with intracytoplasmic lumina (*arrowheads*).

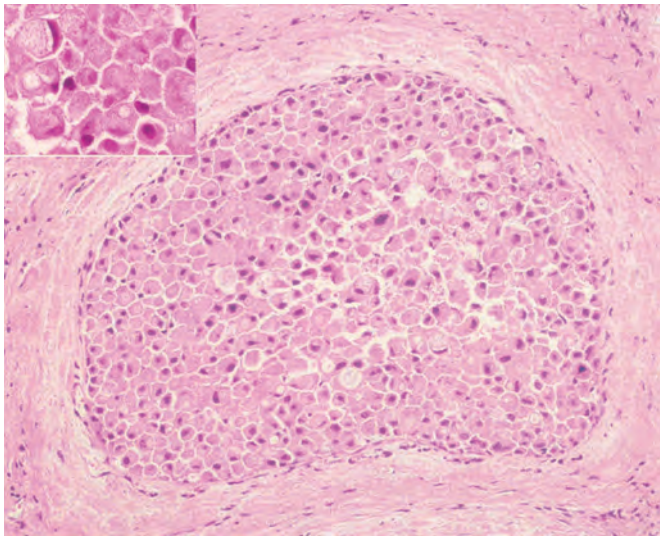

FIGURE 22-5 **Pleomorphic lobular carcinoma *in situ*.** The duct is filled with large, discohesive cells showing apocrine features, intracytoplasmic lumina, and occasional signet ring cells (detailed in insert).

of a myoepithelial cell layer, including nuclear (e.g., p63) and cytoplasmic (e.g., smooth muscle myosin heavy chain or calponin) myoepithelial markers, and markers to ascertain the LN nature of the neoplastic cells (e.g., E-cadherin, β-catenin, and/or p120 catenin) are useful in making the distinction.

Differentiating low-grade, solid DCIS from LN is challenging, even in surgical excisional samples. In cases of low-grade *in situ* proliferations with indeterminate features, the identification of some histologic features can be of help; the presence of a mosaic growth pattern with prominent intracytoplasmic vacuoles is suggestive of LN, whereas the presence of microacinar-like structures favors a diagnosis of solid low-grade DCIS. In this context, E–cadherin and p120 catenin are particularly helpful (see below) (38,39). It should be noted, however, that for some lesions, the distinction between LN and solid low-grade DCIS in limited core biopsy specimens may be impossible. In addition, mixed lesions composed of *bona fide* LN and low-grade DCIS have been reported. Another important differential diagnosis, particularly in core biopsies, is cancerization of the lobules by DCIS. In cases with equivocal histologic features, immunohistochemistry with anti–E–cadherin and p120 catenin antibodies is helpful, given that lack of membranous E–cadherin and p120 catenin cytoplasmic staining would be consistent with a diagnosis of LN rather than cancerization of the lobules by DCIS.

The differentiation of PLCIS from high-grade DCIS can be challenging, given that both are composed of pleomorphic cells with marked cytological atypia, both often display comedo-type necrosis, and both express similar patterns of ER, progesterone receptor (PR), and HER2 expression, including lack of or reduction in ER and PR expression, and overexpression of HER2 (35,40). Importantly, however, the neoplastic cells of PLCIS display the characteristic dyshesiveness, and these lesions consistently lack E-cadherin and β-catenin, and express cytoplasmic p120 catenin (see below).

MOLECULAR PATHOLOGY

The advent of laser capture microdissection and high-throughput genomic and transcriptomic methods have allowed for the study of pre-invasive lesions of the breast. In the last decade, molecular genetic studies have provided a wealth of increasingly more coherent data on the pathways of breast cancer evolution and how these findings correlate with morphological features (8,30). It is currently accepted that ER-positive and ER-negative breast cancers are fundamentally different diseases, with distinct patterns of gene expression changes (41) and repertoires of genetic aberrations (42).

ER-positive breast cancers are characterized by recurrent deletions of 16q, gains of 1q and 16p; additional genetic aberrations including *CCND1* and *FGFR1* amplification, gain of 8q, and losses of 11q, 13q, and 17q are observed in high-grade lesions. ER-negative breast cancers, on the other hand, are characterized by a more complex pattern of gene copy number aberrations, with multiple low-level gains and deletions affecting multiple chromosomal arms; deletions of 16q, however, are remarkably rare in these cancers (8,30). The repertoires of mutations in ER-positive and ER-negative disease are also different. For instance, while ER-positive cancers are characterized by recurrent *PIK3CA, PTEN, AKT1, GATA3, CDH1, MAP3K1, MAP2K4,* and *CDKN1B* mutations, ER-negative cancers often harbor *TP53* mutations (42).

Molecular studies of LN have been instrumental in highlighting the role of E-cadherin inactivation in the development of lobular lesions and in providing evidence to demonstrate that ALH and LCIS are in fact non-obligate precursors of invasive cancer rather than being simply risk indicators of subsequent breast cancer development.

Immunophenotype

All subtypes of LCIS are associated with strong expression of ER-alpha (ERα), ER-beta (ERβ), and PR in the majority of neoplastic cells (Table 22-2). Classic forms of LN usually display an immunohistochemical profile consistent with that of ER-positive breast cancer with a less-aggressive clinical behavior (i.e., luminal A), including lack of HER2 and *p53* expression, and exhibit low proliferation indices, as defined by Ki67. PLCIS, on the other hand, may express no or low levels of ER and PR expression, and frequently harbors HER2 gene amplification and positivity, and its Ki67 labeling indices are usually higher than those of classic LCIS. These features, however, are reported to be predominantly found in the apocrine subtype of PLCIS which also often express GCDFP-15 (gross cystic disease fluid protein-15), a marker of apocrine differentiation (21,30,35); however, the criteria to differentiate between PLCIS and apocrine PLCIS remain a matter of controversy.

Although the high molecular weight cytokeratins identified by the clone 34βE12 (i.e., cytokeratins 1, 5, 10, and 14) were reported to be consistently expressed in LN, and that this antibody would constitute a useful marker to differentiate between LN and low-grade solid DCIS, there is direct evidence to demonstrate that LN cells do not express cytokeratins 1, 5, 10, and 14, and that 34βE12 expression in LN may be an artifact of antigen retrieval. Hence, caution should be exercised when using the 34βE12 for a diagnosis of LN (21,30).

E-Cadherin and Related Proteins in Lobular Neoplasia

LN, including its pleomorphic variant, and ILC are characterized by a dysfunctional E-cadherin-catenin adhesion complex. E-cadherin is a transmembrane adhesion molecule found in adherens junctions and mediates homophilic-homotypic adhesion in epithelial cells; its intracytoplasmic domain is bound to p120 catenin and β-catenin. In breast epithelial cells, loss of E-cadherin results in cytoplasmic,

TABLE 22-2

Summary of Immunohistochemical Marker Status

	LN (ALH/ LCIS)	*ILC*	*Low-Grade DCIS*	*Low-Grade IDC*	*PLCIS*	*Pleomorphic ILC*	*High-Grade ER+ DCIS*	*High-Grade ER+ IDC*
ER	+	+	+	+	+/–	+/–	–/+	–/+
PR	+	+	+	+	+/–	+/–	–/+	–/+
HER2	–	–	–	–	–/+	–/+	+/–	+/–
E-cadherin	Negative[a]	Negative[a,b]	Membranous	Membranous	Negative[a]	Negative[a]	Membranous	Membranous[d]
β-catenin	Negative[c]	Negative[c]	Membranous	Membranous	Negative[c]	Negative[c]	Membranous	Membranous
p120 catenin	Cytoplasmic	Cytoplasmic	membranous	Membranous	Cytoplasmic	Cytoplasmic	Membranous	Membranous
GCDFP-15	–/+	–/+	–/+	–/+	+/–	+/–	–/+	–/+
p53	–/+	–/+	–/+	–/+	+/–	+/–	+/–	–/+
Ki-67	Low	Low	Low	Low	Intermediate/ High	Intermediate/ High	High	High

[a]Abnormal patterns can occasionally be seen in the form of discontinuous or fragmented staining or cytoplasmic "dots."
[b]Up to 15% of cases display E-cadherin membranous expression.
[c]Despite the lack of β-catenin membranous expression, nuclear expression is vanishingly rare in LN and PLCIS.
[d]Approximately 10% of cases may lack membranous E-cadherin expression (87).
ALH, atypical lobular hyperplasia; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; LCIS, lobular carcinoma *in situ*; DCIS, ductal carcinoma *in situ*; PLCIS, pleomorphic LCIS; ER, estrogen receptor; PgR, progesterone receptor; GCDFP-15, gross cystic disease fluid protein-15; LN, lobular neoplasia; –/+, often negative though sometimes positive; +/–, often positive though sometimes negative.

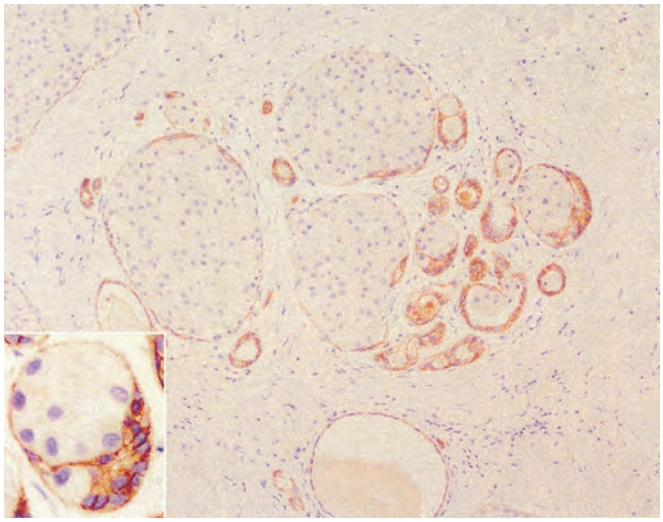

FIGURE 22-6 **E-cadherin immunohistochemical staining in lobular carcinoma *in situ*.** The outer rim of myoepithelial cells show strong membrane staining, whereas the lobular carcinoma *in situ* cells filling the lumen are uniformly negative.

and occasionally nuclear, accumulation of p120 catenin, and loss of β-catenin membranous expression, but without nuclear accumulation of β-catenin or activation of the canonical Wnt pathway (39,43).

Lack or marked down-regulation of E-cadherin expression (Fig. 22-6) is observed in over 95% of ALH, LCIS, PLCIS, ILCs, and metastatic deposits of ILCs, and is believed to be the cause of the characteristic dyshesiveness of LN and PLCIS cells (8,21,30,35,38,44). The study of other components of the E-cadherin-catenin complex in LN, PLCIS, and ILCs has revealed that these lesions are also characterized by lack of β-catenin membranous expression and cytoplasmic expression of p120 catenin. The use of E-cadherin as an ancillary marker to differentiate LCIS and DCIS, particularly in cases of solid *in situ* proliferations with indeterminate features, has been advocated. In this context, lesions with positive E-cadherin staining should be considered as DCIS, whereas those lacking E-cadherin expression should be classified as LCIS (8,21,38). In lesions where a mixed pattern of positively and negatively stained cells are observed, they should be classified as a mixed. The existence of mixed cases should not be surprising, given the molecular similarities between LN and low-grade DCIS (6,8) (see below).

The indiscriminate use of E-cadherin in diagnostic breast pathology has led to misunderstandings in regard to the actual diagnostic value of this marker, particularly when a detailed inspection of staining is not performed. LN not uncommonly displays "aberrant" expression of E-cadherin in the form of fragmented, focal, or beaded patterns (21,30,45). Furthermore, membranous expression of E-cadherin does not preclude the diagnosis of LN in a lesion with clear-cut histologic features of LN, given that approximately 10% to 16% of ILCs may be E-cadherin-positive (21,30,45). Although the actual prevalence of E-cadherin-positive classic LN is yet to be established, anecdotal cases of classic LN with strong and continuous E-cadherin expression have been reported (46), and in these cases, β-catenin and p120 catenin may provide additional evidence to differentiate between LN and DCIS.

An accurate differentiation between LN and DCIS is of paramount importance, in particular when these lesions are found at the surgical margins. Some validation for using E-cadherin in classification comes from clinical-pathological studies of patients having pure LCIS in core needle biopsy, where E-cadherin positive LCIS was associated with a higher risk for development of invasive carcinoma compared to E-cadherin negative LCIS.

Molecular Aspects of E-Cadherin Inactivation

One the most frequent genetic aberrations in ER-positive breast lesions, in particular, those of low histological grade, is 16q loss, which occurs in a high proportion of cases as an early event in the neoplastic development of LN and low-grade DCIS (6,8,10,21,30). While the target gene of 16q deletions in ductal lesions remains to be identified, in lobular lesions, the *CDH1* gene, which encodes E-cadherin, has been shown to be the target (8,10,21,30). The mechanisms resulting in *CDH1* gene silencing include a combination of genetic, epigenetic, and transcriptional mechanisms. In fact, loss of 16q is usually accompanied by *CDH1* inactivating mutations, *CDH1* homozygous deletions, and *CDH1* gene promoter methylation leading to biallelic silencing of the gene and loss of protein expression (8,21,30).

The study of *CDH1* gene mutations in ALH, LCIS, and synchronous ILC has provided direct evidence to suggest that some LN and ILCs are clonally related, given the presence of identical *CDH1* gene mutations in the LN and ILC components (8,10,21,30). Consistent with the lack of E-cadherin expression in ALH and LCIS, *CDH1* gene mutations have been documented in these lesions; however, some have suggested that these mutations would be less frequent in ALH (47). One potential explanation for the apparent lower frequency of *CDH1* mutations in ALH lies in the challenges posed by the extraction of DNA from samples with small numbers of ALH cells, which are intimately admixed with residual luminal and myoepithelial cells.

In addition to the genetic mechanisms reported to result in *CDH1* gene inactivation, there is evidence that E-cadherin expression can be transcriptionally regulated via a number of different transcription factors. Activation of the transforming growth factor β (TGF-β) pathway, and up-regulation of Snail, Slug, and *ZEB1* have been reported to result in down-regulation of E-cadherin in lobular lesions (30,45,48). In addition, transcriptomic and immunohistochemical analyses of members of the E-cadherin-catenin complex TWIST and SNAIL revealed that there is a stepwise decrease of the mRNA and proteins of the E-cadherin and catenin families from LCIS to ILC concurrent with up-regulation of TWIST and SNAIL (44).

The strong circumstantial evidence suggesting that *CDH1* gene inactivation is a driver of the lobular phenotype has been corroborated by direct evidence from a conditional mouse model, where *CDH1* gene mutations and *p53* knockout were targeted in an epithelium-specific manner (49). This study revealed that E-cadherin inactivation leads to the genesis of invasive tumors that display the cardinal features of human invasive lobular carcinomas, being composed of dyshesive cells, which infiltrate the mammary gland stroma as single cells and single cell-files, and metastasize to anatomical sites usually affected by ILC, including the gastrointestinal tract, serosal surfaces, and bone (49). It should be noted, however, that lesions consistent with LN were not documented in this animal model and that the pleomorphism exhibited by the cells from the tumors of this animal model, the presence of p53 inactivation, and lack of ER-expression would be consistent with the features of pleomorphic ILC rather than those of the classic variant (50).

Despite the familial predisposition reported for LN, the genes involved in this predisposition remain unclear.

CDH1 germline gene mutations account for approximately 30% of cases of hereditary diffuse gastric carcinoma, which have similar growth features to lobular carcinomas (20,30). Notwithstanding the clear pathogenetic role of somatic *CDH1* gene mutations in LN and ILC, germline mutations of *CDH1* have been shown to play a limited role in familial LN and ILC. In fact, although ILCs have been reported in the context of hereditary diffuse gastric cancer syndrome, patients with *CDH1* germline gene mutations presenting solely with LN and/or ILCs are vanishingly rare (30,51). Cancer predisposition genes, including *BRCA1, BRCA2, MLH1,* and *MSH2,* have been reported not to be significantly involved in the pathogenesis of familial lobular neoplasms (30). Intriguingly, an association between *CHEK2* U157T mutation and familial predisposition to lobular carcinomas has been reported (52).

Genomics of Lobular Neoplasia

Genome-wide genetic analyses of gene copy number aberrations and allelic changes, as defined by comparative genomic hybridization (CGH) and single nucleotide polymorphism (SNP) arrays of LN have revealed that these lesions are clonal and neoplastic, that their most frequent copy number changes include 16p, 16q, 17p, and 22q, and gain of material from 6q (6,8,29,30,35,53). In one study, pure ALH harbored a surprisingly high level of genetic instability compared to pure LCIS and lobular lesions from other studies (54). This was interpreted as a mechanism by which most pure ALH develop high-level genetic change and die off, rather than acquire select genetic changes allowing progression to LCIS and ILC; alternative explanations may stem from the limited amount of input DNA from ALH cells employed in the study. SNP array analyses have recently demonstrated that classic LCIS and a substantial proportion of adjacent synchronous lesions, including ER-positive DCIS, invasive lobular carcinoma, and ER-positive invasive ductal carcinoma, are often clonally related (6). This notion has been further corroborated by CGH studies of matched LCIS and ILC (29), and by the analysis of mitochondrial DNA heteroplasmy and mitochondrial gene mutations (7), which revealed clonal patterns in three out of five ILCs following a diagnosis of LCIS.

PLCIS and pleomorphic ILC are genetically related entities (35,37,55,56), highlighting the potential precursor role of PLCIS in the development pleomorphic ILC akin to the relationship between LCIS and ILC. *In situ* and invasive pleomorphic lobular lesions have similar genomic profiles to classic LN and ILC, including loss of 16q, and gain of 1q and 16p; however, they do have more complex genomes (35,37,55,56) and amplification of genomic loci involving oncogenes associated with an aggressive phenotype, such as *MYC* (8q24) and HER2 (17q12) (35,55,56). One study in which PLCIS was sub-classified into those with and without apocrine features suggested that only apocrine, but not conventional PLCIS, would have more gene copy number aberrations than classic LCIS (35); further studies employing an objective definition of this subtype of PLCIS are required to confirm these molecular observations and to determine the clinical significance of these lesions. Importantly, there is evidence, although limited, to suggest that PLCIS and matched invasive pleomorphic ILC are clonally related, based on the similarities of the gene copy number changes they harbor (55).

CLINICAL MANAGEMENT

In current practice, the management of LCIS continues to be a challenge. Although largely accepted as a risk factor for the subsequent development of breast cancer, the long-term cumulative risk and our inability to predict which women will develop breast cancer generates considerable uncertainty among providers, and management options in 2013 remain disparate, ranging from observation to bilateral risk-reducing surgery. Differences in individual patient responses to varying levels of risk also contribute to the wide variations seen in clinical practice (57).

Surgical Considerations

The advent of widespread breast cancer screening programs and image-guided core biopsy procedures has likely contributed to the increasing incidence of LCIS (12), and the presence of ALH and LCIS in core needle biopsy specimens of screen-detected lesions has changed the perception regarding the radiologic appearance of these lesions. Historically, LCIS was thought to lack a radiographic correlate; however, recent studies report calcifications in up to 67% of mammographically screen-detected classic LCIS lesions and in nearly all reported cases of screen-detected PLCIS (12,13,31,35,40). The current National Comprehensive Cancer Network (NCCN) guidelines recommend surgical excision following a core biopsy diagnosis of LCIS to rule out an adjacent malignancy (58). These guidelines, however, are largely based on limited data from retrospective series that report the upgrade rate at surgical excision for a core biopsy diagnosis of LCIS to range from 0% to 50% (57,59–63). Limitations of these series include the fact that many of them are small single-institution reports and that not all patients with LCIS underwent surgical excision, raising the possibility of an inherent selection bias for excision in certain cases, such as those with radiographic-pathologic discordance, and increasing the likelihood of finding an associated malignancy. Hussain and Cunnick illustrated these issues in a pooled analysis of studies published from 1999 to 2008. The authors identified 1,229 reported cases of LN on core biopsy, of which only 789 (64%) underwent surgical excision. Among these, 241 (31%) cases were further classified as LCIS. Following surgical excision, 32% of LCIS cases were upstaged to either DCIS or invasive cancer as compared to 19% and 29% of cases defined as either ALH (280 cases) and or unspecified LN (246 cases), respectively (16).

More recently, two single-institution series have demonstrated that, with careful exclusion of cases with other high-risk lesions on core biopsy (i.e., ADH, papilloma, radial scar) and with exclusion of cases with radiographic-pathologic discordance, the actual rate of upstaging to DCIS or invasive cancer is quite low (64,65). Rendi et al. reported an upgrade rate of 4% following surgical excision of 68 cases of LN on core biopsy, and similarly, Murray et al. (66) reported an upgrade rate of 3% following surgical excision of 72 cases of LN on core biopsy. In both of these series, the cancers identified were small, low-grade malignancies. Although both of these series are also retrospective and potentially subject to selection bias, they represent the most careful reviews of this clinical scenario to date and suggest that, in the context of multidisciplinary review, routine excision is not warranted for all cases of LCIS on core biopsy. Additional reports focusing on upgrade rates following a core biopsy diagnosis of pure ALH also support observation for select cases (67,68). In cases of ALH or LCIS that are not surgically excised, short-term mammographic follow-up is recommended.

Widespread use of core needle biopsies to evaluate screening abnormalities, in combination with advances in immunohistochemistry and molecular biology, have also resulted in a greater appreciation of the phenotypic and genotypic diversity within the spectrum of LN and to the diagnosis of so called *variants* of LCIS as described above. Although there is considerable speculation that PLCIS

TABLE 22-3

Upgrade Rates Following Surgical Excision for a Core Biopsy Diagnosis of PLCIS

		PLCIS		
Series		#	# *Excised*	% *CA*
Georgian-Smith and Lawton (59)	1999–2000	NA	5	40%
Pacelli et al. (63)	NA	5	5	60%
Mahoney et al. (62)	1999–2004	2	2	50%
Lavoue et al. (61)	2000–2005	10	10	30%
Carder et al. (88)	2002–2009	10[a]	10	30%
Chivukula et al. (89)	2002–2007	12	12	25%[b]
Sullivan et al.[c] (90)	2001–2009	LCIS-N = 11	11	45%
		LCIS-P = 17	17	29%

[a]2 of 10 cases possible "microinvasive carcinoma" on core biopsy.
[b]One-third of cancer cases presented as a "mass" on imaging.
[c]Includes 9 cases identified on E-cadherin staining of DCIS core biopsy cases.
PLCIS, pleomorphic LCIS; CA, carcinoma; NA, not applicable; LCIS, lobular carcinoma *in situ*; LCIS-N, LCIS with necrosis; LCIS-P, pleomorphic LCIS.

represents a more aggressive subtype, data regarding the natural history of this lesion are limited to two small retrospective reports describing recurrences of PLCIS after excision (31,69). Available data do, however, support routine excision when PLCIS is diagnosed on core biopsy with upgrade rates consistently exceeding 25% (Table 22-3). It should be noted that the small number of cases identified over the span of several years in all of these series suggest that the true incidence of PLCIS is likely quite low.

A diagnosis of classic LCIS or ALH made by surgical excision does not require further surgical intervention, and there is no indication to document margin status in a specimen that contains only LN (21). Similarly, the finding of classic LCIS or ALH in the surrounding breast parenchyma of a lumpectomy specimen containing DCIS or invasive carcinoma does not alter surgical management of the breast primary and does not increase the rate of local recurrence in patients undergoing breast conservation (58,70,71). In a review of 2,894 patients treated with breast-conserving therapy from 1980 to 2007, 290 (10%) of whom had LCIS in the lumpectomy specimen, there were no differences in the 5-year actuarial rates of local recurrence for patients with and without LCIS (2% for both groups). Among the 290 patients in the LCIS group, 84 were documented to have LCIS at the margin. The 5-year actuarial rate of local recurrence for patients with LCIS at the margin was 6% as compared to 1% for those with LCIS in the specimen but away from the margin (p = NS). On univariate analysis, the presence of LCIS in the specimen or at the margin did not predict for local recurrence, whereas patient age, menopausal status, use of adjuvant therapy, and the presence of an extensive intraductal component were significant predictors. On multivariate analysis, adjusting for differences between the LCIS and no-LCIS cohorts, the presence of LCIS in the specimen (HR, 1.66; 95% CI, 0.86–3.18) or at the margin (HR, 1.52; 95% CI, 0.48–4.83) was not significantly associated with local recurrence.

The importance of clear margins following excision of PLCIS is largely unknown as the available data are limited to one series reporting margin status and follow-up after excision with or without radiation in 26 cases of PLCIS (69). At a mean follow-up of 46 months (range 4 to108 months), one of six patients whose original excision showed PLCIS at the margin developed recurrent PLCIS. There were no other events reported. Until additional data are available, it is reasonable to pursue margin-negative excision for PLCIS, yet one should remember this is based on pragmatism rather than strong scientific evidence. Further, there are no data on the efficacy of radiation therapy following excision of PLCIS, and rather than assuming that its clinical behavior is known and recommending aggressive surgical treatment and/or radiation therapy, prospective efforts to document clinical outcomes and define the true magnitude of risk imparted by this lesion should be actively pursued.

Management of the High-Risk Patient

Once a concurrent malignancy has been excluded, women with LCIS should be counseled regarding their increased risk of breast cancer. Compared to the general population, women with LCIS have an eight-fold to 10-fold increased risk of breast cancer (11). In the series with the longest follow-up, the probability of developing carcinoma *in situ* or invasive cancer was 13% in the first 10 years after diagnosis, 26% after 20 years, and 35% by 35 years, or roughly 1% per year (72). When counseling women about their risk, it is important to stress that the risk remains steady over their lifetimes and that, therefore, the absolute risk of breast cancer for an individual is impacted by their age at LCIS diagnosis. Importantly, however, most women with LCIS will not develop invasive breast cancer.

Surveillance

The NCCN Breast Cancer Screening and Diagnosis Clinical Practice Guidelines for women with LCIS include annual mammography and clinical breast exam (CBE) every 6 to 12 months with consideration of annual MRI (73). Although enhanced breast cancer surveillance strategies that include screening with breast MRI are commonly recommended for women at high risk, the American Cancer Society (ACS) guidelines do not support routine use of MRI in this setting, stating that there is not enough evidence to recommend for or against MRI screening in women at increased risk from LCIS, making the NCCN guideline somewhat difficult to interpret (74). The ACS guidelines are based on the increased sensitivity of MRI

in women at high risk due to an inherited predisposition or strong family history of breast cancer; however, the biology of the breast cancers that develop in women with LCIS differs from those that develop in women at risk on the basis of BRCA mutations, and the optimal screening strategy for women with LCIS remains uncertain.

Until recently, data directly addressing the role of MRI in women with LCIS were limited to two retrospective radiology reports demonstrating that MRI finds mammographically occult cancers in approximately 4% of women with a prior history of LCIS (75,76) and a study from the Memorial Sloan-Kettering Cancer Center (MSKCC) Surveillance program by Port et al. In that study, 252 women with LCIS were included, 135 (54%) of whom were participating in MRI screening (77). The MSKCC experience has now been updated to include 776 patients with LCIS, 59% of whom have been participating in MRI screening, with longitudinal follow-up from 1996 to 2009 (78). This large, well-annotated dataset now includes 98 cancer diagnoses and continues to demonstrate no difference in the crude cancer detection rate among women having conventional screening or conventional screening plus MRI. Taking into account other breast cancer risk factors, length of follow-up, number of MRIs, and the time dependency of breast cancer development, using Landmark Analyses, King et al. further demonstrated that routine use of MRI screening does not result in increased rates of cancer detection in any of the first 3 years following LCIS diagnosis, nor does it result in earlier stage at diagnosis. Not surprisingly, women in the MRI-screened group were significantly more likely to undergo one or more benign biopsies during the surveillance period (36% vs. 13%, $p < .0001$), reflecting the low specificity of this imaging modality; a problem that translates to increased patient anxiety and increased health care costs.

Importantly, in this large, modern cohort of women with LCIS followed longitudinally, King et al. also noted that the subsequent invasive cancers that developed were equally divided between those of the ductal and lobular phenotype, and of the 26 lobular cancers that were diagnosed, 10 were diagnosed by MRI imaging, 10 by conventional imaging, and 6 by CBE, reiterating the importance of CBE in this high-risk population. Another pervasive misconception is the propensity of lobular cancers to be bilateral, leading to a strong consideration for contralateral prophylactic mastectomy among women diagnosed with unilateral invasive lobular cancer. Among the 6 LCIS patients in this cohort who developed bilateral breast cancer, none were bilateral lobular cancers. Data from SEER also clearly document that an initial diagnosis of lobular cancer does not increase the risk of a metachronous contralateral cancer compared to patients with ductal disease (79). Finally, this dataset demonstrates that women with classic LCIS, which displays an immunohistochemical profile consistent with that of ER-positive breast cancer, overwhelmingly develop ER-positive breast cancers, which are likely to be detected at small size during routine screening.

Until information on the natural history of PLCIS is available, minimal surveillance strategies for this lesion should include biannual CBE and annual mammography. The decision to incorporate MRI screening should be made on an individual basis following a full discussion of the potential risks and benefits of this approach.

Chemoprevention

Prospective randomized data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial (BCPT, P-1) demonstrated that among high-risk women, tamoxifen decreased the risk of developing invasive breast cancer by 49% (80). Similarly, the NSABP Study of Tamoxifen and Raloxifene (STAR, P-2) demonstrated that raloxifene was just as effective as tamoxifen in reducing the risk of breast cancer in high-risk postmenopausal women (81). Women with LCIS were well represented in both of these studies, comprising 6.2% of 13,338 participants in the P-1 trial and 9.2% of 19,747 participants in the STAR trial. In both subsets, chemoprevention reduced the risk of developing breast cancer by more than 50%. Collectively, these data led to a statement from the American Society of Clinical Oncology (ASCO) recommending 5 years of tamoxifen for high-risk premenopausal women to reduce the risk of ER-positive invasive breast cancer and raloxifene to reduce risk for postmenopausal women. Although there are no data to directly address the use of chemoprevention in PLCIS, the fact that the vast majority of these lesions are ER positive supports a potential role for chemoprevention in patients with this diagnosis.

More recently, the MAP.3 trial demonstrated that compared to placebo, exemestane reduced the risk of invasive breast cancer by 65% in postmenopausal women and appeared to be beneficial in women with a history of ADH, ALH, and/or LCIS (82), and in a large observational study of 2,459 women diagnosed with atypical breast lesions, including LCIS, Coopey et al. reported a significant decrease in breast cancer risk with chemoprevention for all types of atypia ($p < .001$), with estimates ranging from a risk reduction of 50% at 5 years to 65% at 10 years. Findings from the MSKCC surveillance program also validate the benefit of chemoprevention in women with LCIS in the clinical setting. Among 998 women, 163 (16%) of whom reported chemoprevention use of at least 6 months, there was a significant reduction in the incidence of breast cancer with chemoprevention, 14.5% versus 3.6% ($p < .0001$), at a median follow-up of 84 months (57).

Despite these findings, neither tamoxifen nor raloxifene has been widely embraced, and studies addressing patient and physician attitudes toward chemoprevention are limited. Port et al. found that among 43 high-risk patients offered tamoxifen, 41 declined due to perceived risks (83). Tchou el al. (84) reported a higher acceptance rate of 42% among 137 high-risk women offered tamoxifen, and specifically noted that older age and a history of atypical hyperplasia or LCIS were significant predictors of patient acceptance of tamoxifen at their institution. Collectively, these findings strongly support the need to improve our efforts to educate both high-risk patients and their health care providers about the benefits of chemoprevention in decreasing breast cancer risk.

Risk-Reducing Surgery

When LCIS was first described, it was treated as a malignancy necessitating mastectomy like all breast carcinomas at the time, and this remained the standard approach until studies demonstrated that the actual risk of breast cancer was lower than expected and that women with LCIS were equally likely to be diagnosed with ipsilateral or contralateral breast cancers; thus bilateral total mastectomy would be the only logical operation to truly reduce risk. In parallel with the trend toward more conservative therapy for the treatment of invasive breast cancer, aggressive surgical therapy for LCIS fell out of favor and, in the modern MSKCC experience, only a minority of women with LCIS (5%) pursue bilateral prophylactic mastectomy (57). Nevertheless, bilateral prophylactic mastectomy (BPM) may be a reasonable option for a subset of women with LCIS and other risk factors, such as a strong family history or extremely dense breasts.

Historically, BPM was reported to result in an approximately 90% risk reduction for the development of subsequent cancer (85). This figure was based on a retrospective analysis of 639 women with a family history of breast cancer undergoing bilateral prophylactic mastectomies between

1960 and 1993. While it is important to educate patients that prophylactic mastectomy *does not* completely eliminate cancer risk, many women in this series underwent subcutaneous mastectomy, an operation which has fallen out of favor due to the amount of breast tissue frequently left behind, and a more recent retrospective case-cohort study evaluating the efficacy of BPM in a community practice setting reported a 95% risk reduction (86). The current standard of care for prophylactic mastectomy is total mastectomy (with or without reconstruction) with the goal of removing the entire mammary gland as would be performed during therapeutic mastectomy. The desire for nipple preservation in this setting and others is becoming increasingly common, and while this may result in improved cosmesis and patient satisfaction, prospective data supporting this contention and/or the long-term oncologic safety of this approach are not yet available.

Patients considering surgery for risk reduction need to be fully aware of all the risks and benefits of this approach, and should be encouraged to consider the impact that prophylactic surgery may have on their quality of life with respect to body image and sexual functioning. If reconstruction is to be pursued, they should also have a reasonable expectation for the most likely cosmetic outcome. The decision to undergo BPM is highly individualized and should not be undertaken without ample time to consider all of the available options for risk management.

MANAGEMENT SUMMARY

- LCIS and ALH are uncommon pathologic findings, representing part of a spectrum of epithelial proliferations referred to as LN. They are typically incidental findings, identified in up to 4% of otherwise benign breast biopsies, yet, given that they have no distinctive clinical presentation or imaging features, the prevalence of LCIS likely exceeds its incidence.
- A diagnosis of LCIS confers a long-term cumulative risk of subsequent breast cancer that averages 1% to 2% per year and remains steady over time, resulting in relative risk of breast cancer that is eight-fold to 10-fold greater than the general population risk. ALH is associated with a relative risk of breast cancer four-fold to five-fold greater than the general population.
- Routine surgical excision following a core biopsy diagnosis of LN is supported by NCCN guidelines; however, emerging data support observation in cases in which there are no other indications for excision, and radiographic-pathologic concordance has been confirmed by multidisciplinary review. A core biopsy diagnosis of PLCIS should be followed by surgical excision due to the high rates of associated cancer in reported series.
- A diagnosis of LN made by surgical excision does not require further surgical intervention; there is no indication to document margin status in specimens that contain only LN. The presence of LN in a lumpectomy specimen or at the margin is not a contraindication to breast conservation and does not require re-excision.
- Given the available data, it is reasonable to attempt complete excision to a negative margin for cases of PLCIS. However, there are no data to support the efficacy of radiation therapy for this diagnosis.
- Patients with LN should be informed of their increased risk of breast cancer, and counseled regarding both medical and surgical risk-reducing options. Chemoprevention significantly decreases the risk of breast cancer in patients with LN by at least 50%, and bilateral prophylactic mastectomy reduces the risk of breast cancer by 90% to 95%.

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CHAPTER 23

Ductal Carcinoma *In Situ* and Microinvasive Carcinoma

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CHAPTER CONTENTS

INTRODUCTION

Ductal carcinoma *in situ* (DCIS), also known as intraductal carcinoma, is a noninvasive carcinoma. Historically, DCIS was an uncommon lesion that was routinely treated by mastectomy, and little attention was given to defining its natural history or exploring alternative local treatments. The widespread use of screening mammography has resulted in a significant increase in the rate of detection of DCIS (1) (Fig. 23-1). Although no prospective randomized trial has ever compared mastectomy with breast-conserving surgery for DCIS, the acceptance of breast-conserving therapy for the treatment of invasive carcinoma lead to its acceptance for the treatment of DCIS. Furthermore, four prospective randomized studies of radiation after breast-conserving surgery for DCIS have shown that breast cancer specific survival is excellent, with or without radiation (2–5). Therefore, there is a debate as to whether all DCIS should be regarded as early stage carcinoma and treated with either mastectomy or lumpectomy and irradiation, or whether excision alone can be used to treat some DCIS.

PRESENTATION

In 90% of cases, DCIS presents as an abnormal screening mammogram in an asymptomatic woman. Prior to widespread screening with mammography, DCIS presented with clinical symptoms and was an uncommon entity. In 1983, before screening was widely used, only 4,901 women were diagnosed with DCIS in the United States, accounting for 3.8% of all breast cancer (6). By 2013, approximately 64,640 new DCIS diagnoses will be made, representing approximately 20% to 25% of all new breast cancers (7). The SEER database has documented that the incidence of DCIS rose from 5.83 per 100,000 women in 1975 to 37.25 per 100,000 in 2009 (8). The increased incidence was observed in all age categories, with the greatest rise among women over 50 years of age (Fig. 23-1). The incidence of DCIS, like invasive breast cancer, is strongly related to age. DCIS is extremely uncommon before age 35 to 39; with incidences of less than 11 cases per 100,000. After that, the incidence rises steadily to a peak of 102 per 100,000 at ages 65 to 69. In contrast, invasive breast cancer incidence peaks at a later age (75–79 years) with incidence of 433.1 per 100,000 women (8,9).

The increase in DCIS diagnosis has not been uniform across histological types (Fig. 23-2). An earlier analysis of the SEER database from 1980 to 2001 demonstrated that comedo histology rose in incidence from 1980 through 1995 but then stabilized or decreased slightly thereafter, while non-comedo histology continued to rise thorough the end of the study period (10). The age-adjusted incidence of DCIS was the highest among Caucasian women, followed by African-American and Asian-Pacific Islander women (11).

Microcalcifications are the predominant finding on screening mammography leading to a diagnosis of DCIS. As an example, in a study of 217 women 50 to 69 years of age with DCIS detected by mammography while participating in the Breast Cancer Screening program in Norway from 1995 through 2007, calcifications were present for 93%. On pathology review, calcifications were associated with grade 1 DCIS in 15%, grade 2 in 11%, and grade 3 in 74% (12). Calcification morphology on mammography was most frequently described as “fine pleomorphic.” In comparison, in a large surgical series from France of 909 cases of DCIS diagnosed from 1980 to 1999, 76.2% were detected by mammography without clinical symptoms, 12% had a palpable mass, and 12% presented with nipple discharge (13). Of

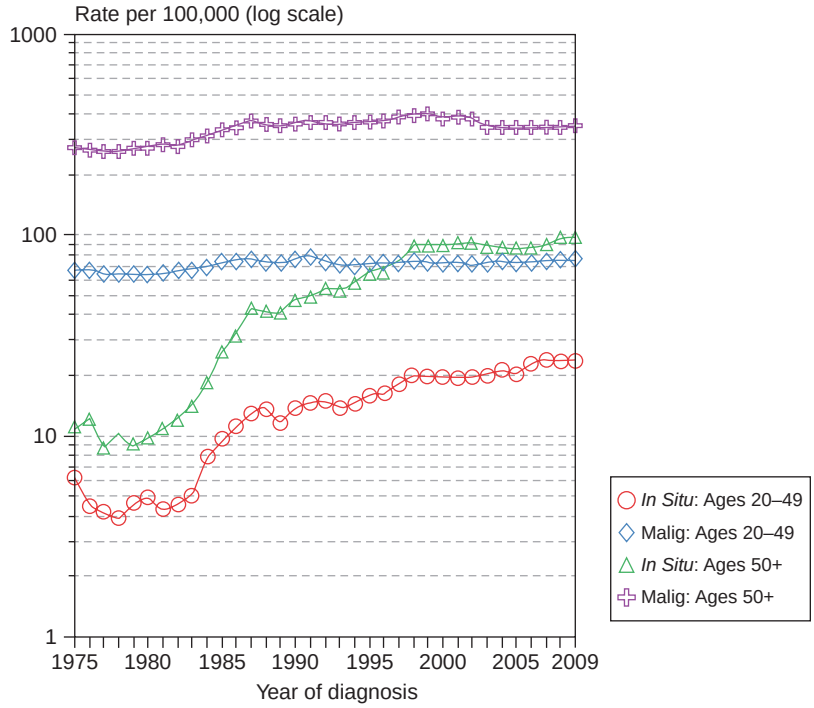

FIGURE 23-1 SEER Incidence rates 1975 to 2009 for *in situ* versus invasive breast cancer by age, all races. (From Howlader N, Noone AM, Krapcho M, et al., eds. SEER Cancer Statistics Review, 1975–2010, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2010/, based on November 2012 SEER data submission, posted to the SEER web site, April 2013.)

those with a palpable mass, 47.1% also had mammographic abnormalities. Microcalcification was the most common finding in 75.5%, with fine pleomorphic calcifications being the most frequently seen (40.4%), followed by amorphous or indistinct calcifications (35.9%). Fine pleomorphic and fine-linear branching calcifications were significantly associated with the presence of grade 3 DCIS and necrosis (13).

DCIS that is diagnosed with a palpable mass or nipple discharge is more likely to be extensive disease. Examination of 50 mastectomy specimens in a population of DCIS patients, of whom 58% were detected with mammography and 42% with clinical mass or nipple symptoms, revealed that presentation with a palpable mass, nipple discharge, or as Paget's disease was accompanied by a greater incidence of multicentricity and/or microinvasion than was DCIS detected by mammography (14). In addition, patients with comedo necrosis or micropapillary architecture were more likely to be multicentric than other histologic subtypes. More recent studies suggest that, in most cases, true multicentricity in DCIS is rare. Holland and Hendricks studied 119 mastectomy specimens containing DCIS by a subgross pathologic-mammographic technique (15). In all but one case, the tumor was confined to a single "segment" of the breast. Clear-cut multicentric distribution (defined in this study as foci of DCIS separated by 4 cm or more of uninvolved breast tissue) was seen in only one patient. Faverly et al., using stereomicroscopic three-dimensional analysis to define the growth pattern of DCIS in the mammary duct system, studied 60 mastectomy specimens containing DCIS (16). There was continuous growth pattern in the ducts for 50% and a discontinuous pattern in 50%, characterized by uninvolved breast tissue "gaps" between foci of DCIS. In most instances, these gaps were small (< 5 mm in 82% of cases). The likelihood of finding such gaps was related to the DCIS

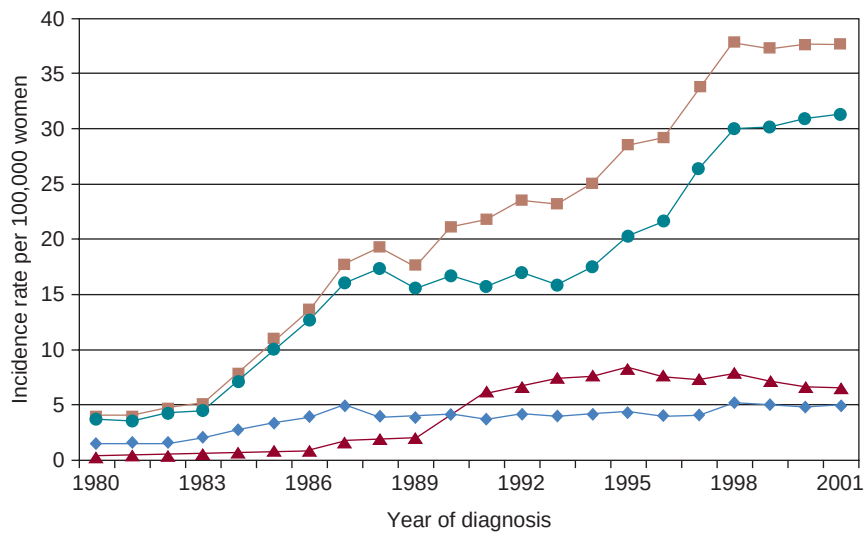

FIGURE 23-2 Incidence of *in situ* carcinoma (per 100,000 women) by different histological types among women ages ≥ 30 years, 1980 to 2001. (■ DCIS overall, ● non-comedo DCIS, ▲ comedo DCIS, ◆ LCIS. From Li CI, Daling JR, Malone KE, et al. Age-Specific Incidence Rates of *In situ* Breast Carcinomas by Histologic Type, 1980 to 2001. *Cancer Epidemiol Biomarkers Prev*. American Association for Cancer Research, 2005).

differentiation: 90% of poorly differentiated cases grew in a continuous manner without gaps, while 45% and only 30% of intermediate and well-differentiated lesions, respectively, were continuous. The findings in these two studies indicate that, in most cases, DCIS involves the breast in a segmental distribution, and truly multicentric disease is uncommon.

Mammography is the established method for detection and evaluation of extent of disease, but MRI is being increasingly studied for its clinical utility in DCIS diagnosis (17). Historically, MRI was considered a poor imaging tool to assess DCIS. The adoption of higher spatial resolution techniques and diagnostic criteria that are different than those used for invasive cancer has led to improved detection of DCIS by MRI. In the International Breast MRI Consortium study of patients with suspicious mammographic or clinical findings, the sensitivity of MRI for the detection of DCIS was 73%; significantly lower than the 91% observed for invasive cancer (18). The American College of Radiology Imaging Network (ACRIN) compared the diagnostic accuracy of mammography, clinical examination, US, and MRI prospectively in the preoperative assessment of 171 malignant foci, 38 of which were DCIS, in 121 breasts from 111 women. MR imaging identified 34 of 38 (89%) DCIS foci, which was significantly more than was detected with either US ($p < .001$) or mammography ($p < .01$) (19). These results were further supported by Kuhl et al. (20), who reported on 167 cases of DCIS that had, at some point during their workup, undergone both mammography and MRI. All imaging was re-read centrally and MRI studies were read blinded to the mammogram findings. MRI detected 92% of cases as compared to 56% by mammography ($p < .0001$). Of the 89 cases of high-grade DCIS, 48% were diagnosed by MRI but missed by mammography. Other studies have similarly demonstrated a 70% to 90% MRI sensitivity for DCIS detection (21). Additional investigation to clarify the clinical role of MRI for diagnosing DCIS and its prognostic implication are needed.

NATURAL HISTORY

There is significant evidence based on epidemiology, clinical observation, and growing numbers of genetic, molecular, and epigenetic studies that DCIS is a precursor lesion for invasive cancer. However, predicting which individual DCIS case will progress to invasive breast cancer if left untreated remains indefinable.

Epidemiologic studies that examine risk factors for DCIS show that they are remarkably similar to those for invasive breast cancer, including a family history of breast cancer, nulliparity, older age at first childbirth, and breast density (9). Clinical observation of DCIS progression to invasive cancer is limited as surgical resection is done once a diagnosis of DCIS is made. However, clinical follow-up from benign breast biopsies that received no additional intervention but on re-review many years later were diagnosed as DCIS offers some insight regarding clinical progression. Sanders et al. (22) identified 28 cases of small, low-grade, non-comedo DCIS during a review of 11,760 consecutive breast biopsies performed from 1950 through 1968. With a median follow-up of 28 years, 11 of 28 women (39%) developed ipsilateral invasive breast carcinoma, all in the same quadrant from which the original biopsy was taken. Seven (64%) of the 11 recurrences developed within 10 years, and 5 (45%) of the 11 (18% of all 28 cases) died of metastatic disease. Eusebi et al. reported on 80 cases of DCIS retrospectively diagnosed out of 9,446 breast biopsies done between 1964 and 1976, and with a median follow-up of 17.5 years. Pure "clinging carcinoma" (CC) was diagnosed in 41; 9 with pleomorphic nuclei (consistent with DCIS) and 32 with monomorphic nuclei which is currently considered flat epithelial atypia. Five (12%) developed an ipsilateral breast cancer: 2 of the 9 with pleomorphic nuclei developed ipsilateral invasive carcinoma, and 2 of the 32 with monomorphic nuclei developed DCIS. Of the 30 cases of CC associated with cribriform DCIS, LCIS, or both, 5 (17%) had an ipsilateral invasive recurrence. Two of 7 cases with cribriform DCIS developed an ipsilateral DCIS recurrence, and 2 of 2 cases with comedo DCIS developed an invasive recurrence (23). In a similar study, Rosen et al. (24), described 30 women with untreated DCIS; complete follow-up was available only for 15. Ipsilateral invasive breast cancers occurred in 7 of the 15 (53%) at a mean of 9.7 years after the diagnosis of DCIS. More recently, Collins et al. (25), found 13 cases of DCIS (0.7%) out of 1,877 breast biopsies performed from 1973 through 1991 on the Nurses' Health Study. Nuclear grading of the 13 cases revealed 6 to be intermediate, and 3 were high nuclear grade. A total of 10 cases recurred (77%); 6 (46%) developed invasive breast cancer at a mean of 9 years, and 4 (31%) developed DCIS at a mean of 3.75 years after the initial biopsy was performed.

The clear limitation of these studies is that the completeness of excision by the original biopsy is unknown; however, as a whole, they demonstrate that a significant portion of both low- and high-grade DCIS can progress to invasive breast cancer, supporting its role as a precursor.

Another source of indirect clinical evidence of DCIS as a precursor comes from autopsy studies. Alpers and Wellings (26) assessed a series of 185 randomly selected breasts from 101 women examined by a subgross sampling technique. One or more foci of DCIS were found in only 11 cases (6%). The lowest prevalence was noted in the oldest women: 3 of 56 (5%) in women younger than age 49; 7 of 70 women (10%) in women ages 50 through 69; and in 1 of 59 women (2%) older than 70 years were found. In a study with similar methodology, Bartow et al. (27), performed pathologic examination of the breast on 519 autopsied women 14 years of age or older without clinical evidence of breast cancer. Only one case of DCIS was identified in a 40 year old; five occult invasive carcinomas were found in women ages 45 to 87. These findings suggest that DCIS progresses to clinically evident breast cancer given its very low prevalence at autopsy, particularly in the oldest cohort of women.

There has been considerable research over the last several years in understanding the gene expression changes that occur in DCIS relative to what is known in invasive breast cancer. Over the past decade, the successful combination of highly specific tissue microdissection technologies with advanced high-throughput genomic, gene-expression, and proteomic technologies has enabled a better understanding of the pre-invasive stages of breast cancer progression (28). It is now acknowledged that significant genomic and gene expression parallels exist between the pre-invasive and invasive stages of breast cancer.

Several studies have examined genetic changes in DCIS, i.e., loss of heterozygosity (LOH), at genetic loci (typically considered to be approximate locations of inactivated tumor suppressor genes) known to exhibit high rates of loss in invasive breast cancer. These showed that the frequency of chromosomal losses, specifically regions 16q and 17p, in ADH is similar to that observed in DCIS and invasive carcinoma (28). O'Connell and colleagues examined 399 pre-malignant breast lesions, studying 15 genetic loci known to show high rates of LOH in invasive breast cancer (29). In breasts without invasive breast cancer, they found at least one locus of LOH in 42% of ADH, 70% of non-comedo DCIS, and 79% of comedo DCIS. Among specimens harvested from cancerous breasts, LOH was shared with the synchronous cancer in at least one locus in 45% of ADH, 77% of non-comedo

DCIS, and 80% of comedo DCIS lesions. This observation that the majority of both comedo and non-comedo DCIS share their LOH phenotypes with synchronous invasive breast cancer supports the concept that DCIS is a direct precursor of invasive breast cancer.

Ma and associates used laser capture microdissection and DNA microarrays to generate *in situ* gene expression profiles in 36 breast tissue specimens that exhibited one or more lesions of ADH, DCIS, and invasive carcinoma (30). No consistent gene expression alterations unique to ADH, DCIS or invasive carcinoma were found; instead, the greatest alterations in gene expression were seen by histological grades. Similar to what has been observed with invasive breast cancer, distinct gene-expression signatures are present in low- and high-grade DCIS lesions, and are consistent with genetic alterations and phenotypes seen in comparable grade invasive cancer. These data suggest that low-grade DCIS progresses to low-grade invasive and high-grade DCIS to high-grade invasive, with intermediate-grade DCIS representing intermediary behaviors.

There has been increasing focus on the DCIS microenvironment for identification of promoters of tumor progression. Recent gene-expression and epigenetic data strongly suggest that the stromal and myoepithelial microenvironment of pre-invasive breast cancer actively participates in the transition from pre-invasive to invasive disease (28). Allinen et al. (31) developed a purification procedure that allows the isolation of pure cell populations from normal breast tissue, DCIS, and invasive carcinoma. They demonstrated that genes coding for *CXCL14* and *CXCL12* chemokines were overexpressed in DCIS myoepithelial cells and myofibroblasts, respectively, compared to normal breast tissue. These chemokines can bind to receptors on adjacent epithelial cells and enhance their proliferation, migration, and invasion. Thus, chemokines may have a part in the transition from DCIS to invasive breast cancer by acting as paracrine factors. This illustrates how signaling from the DCIS stromal and myoepithelial microenvironment may play an important role in tumorigenesis.

These genetic and molecular studies give further evidence that ductal pre-invasive stages (ADH and DCIS) are non-obligate precursors to invasive disease with variable clinical behavior.

TREATMENT

The uncertainty regarding the natural history of DCIS has resulted in a wide range of local treatment practices, from excision alone to mastectomy. There is now a significant body of mature data from prospective, randomized trials in well-characterized populations of women with DCIS that provides information about the risks of local recurrence and death after treatment with lumpectomy alone, and lumpectomy and radiation therapy (RT). Clinical trials have also evaluated the benefit of endocrine therapy in patients with DCIS. There are no prospective studies evaluating mastectomy or comparing it to breast-conserving surgery.

Mastectomy

Theoretically, mastectomy should be 100% curative for pure DCIS. While no prospective studies of mastectomy for DCIS exist, large (at least 100 women) retrospective series, with at least 5 years of follow-up, report actual local recurrence rates in the 1% to 3% range (Table 23-1). A meta-analysis of 1,574 mastectomies reported a recurrence rate of 1.4% (95% confidence interval [CI], 0.7–2.1) at an average follow-up of 80 months (32). Recurrence after mastectomy is usually invasive carcinoma and may present as either local recurrence or distant metastases without evidence of local recurrence. Breast cancer-specific survival rates at 10 years after mastectomy for DCIS are ≥ 98% (33,34).

Skin-sparing mastectomy allows preservation of the native skin envelope, resulting in improved cosmesis with immediate reconstruction. At a mean follow-up of 82 months, local recurrence occurred in 3.1% of 223 consecutive patients undergoing skin-sparing mastectomy for DCIS (35). Others have reported local recurrence rates from 0% to 4% at 3.5 to 10 years of follow-up (35).

In an effort to further reduce the psychological and cosmetic impact of mastectomy, nipple-sparing mastectomy has been recently explored. To date, limited local recurrence data are available. In 158 patients undergoing mastectomy with intraoperative radiation of the nipple-areola complex for ductal intraepithelial neoplasia, Petit et al. reported a 5-year local recurrence rate of 5%, with a nipple-areolar complex recurrence rate of 2.9% (36). A prospective series of 33 women undergoing 54 nipple-sparing mastectomies from the University of Texas MD Anderson Cancer Center (MDACC) reported a 30% complication rate in the nipple-areola complex, 11% in the skin flaps, and the need to remove the nipple-areolar complex due to DCIS involvement in 12% (37). Cosmetic outcome was acceptable (as judged by plastic surgeons) in 73% of breasts and 56% of nipple-areolar complexes, with most (67%) being laterally displaced.

Treatment failure after mastectomy for DCIS may be due to unsampled or unrecognized invasive carcinoma that results in local recurrence or distant metastases, or it may be due to incomplete removal of breast tissue. Residual breast tissue may harbor DCIS; it also has the potential for development of a new carcinoma that would be manifested as a "local recurrence."

TABLE 23-1

Recurrences after Mastectomy for DCIS (recent series with >100 cases and >5 years follow-up)

Reference	*Years*	*N*	*Median F/U (years)*	*Local Recurrence*	*Regional or Distant First Recurrence*
Cutuli, 2001 (129)	1985–1992	145	6.3	3 (2%)	0
Carlson, 2007 (35)[a]	1991–2003	223	6.9	7 (3.1%)	4 (1.8%)
Tunon de Lara, 2011 (130)	1971–2001	342	9.8	7 (2.2%) (130)	3 (1.4%) (131)[b]
Kelley, 2011 (34)	1979–?	496	6.9	9 (2%)	2 (0.4%)
Owen, 2012 (33)	1990–1999	637	12	12 (1.7%)	9 (1.4%)

[a]All patients underwent skin-sparing mastectomy with immediate reconstruction
[b]Regional and distant first recurrence reported for 7.8 years follow-up (131)

TABLE 23-2

Radiotherapy Effect: Results of the Phase III Randomized Control Trials

Trial	No. of Patients Analyzed	Median Follow-Up (years)	% Ipsilateral Breast Cancer Recurrence				% Breast Cancer Specific Survival[a]	
			Lumpectomy		Lumpectomy + RT		Lumpectomy	Lumpectomy + RT
			ALL	Invasive	ALL	Invasive		
NSABP B-17 (2)[b]	813	17.25	35%	20%	20%	11%	96.9%[c]	95.3%[c]
EORTC 10853 (3)[d]	1010	10.5	26%	13%	15%	8%	96%[e]	96%[e]
UK/ANZ (4)[f]	1030	12.7	19%	9.1%	7.1%	3.3%	97.3%[g]	98.5%[g]
SweDCIS (5)[b]	1046	8.4[h]	27%	12%	12%	7.2%	97.1%[i]	96.6%[i]
RTOG 9804 (45)	585	7.2	6.7%	2.7%	0.9%	0.34%	-	-

[a]Includes freedom from distant metastases or mortality from breast cancer
[b]Events divided by N
[c]15-year freedom from breast cancer mortality
[d]10-year estimates
[e]10-year freedom from distant metastases. RT, radiation therapy
[f]10-year estimates for women randomized to RT or not; 54% received tamoxifen
[g]Freedom from breast cancer mortality divided by N, 52% received tamoxifen
[h]Mean
[i]Freedom from breast cancer mortality divided by N

Mastectomy is a highly effective treatment for DCIS, but it is a radical approach to a lesion that may not progress to invasive carcinoma during the patient's lifetime. It seems somewhat paradoxical that a woman with a palpable invasive carcinoma should be able to preserve her breast, whereas the "reward" for screening and early detection of DCIS is a mastectomy. The acceptance of breast-conserving therapy for the treatment of invasive carcinoma led to its use as a treatment for DCIS. However, no randomized trial has ever compared the treatment of DCIS by mastectomy with treatment by breast-conserving approaches, and no such trial is likely to occur. In some cases, the assumption has been made that because these two treatments result in equivalent survival for patients with invasive carcinoma, the same is true for patients with DCIS. This assumption is flawed because of the fundamental difference in the risk of metastatic disease for patients with invasive carcinoma and those with DCIS. In DCIS, unlike invasive cancer, the risk of metastases at diagnosis is negligible, while an invasive local recurrence carries with it the potential risk of breast cancer mortality. Therefore, the incidence of invasive recurrence and the results of salvage therapy should determine the suitability of breast-conserving approaches as a treatment for DCIS.

Breast-Conserving Surgery and Radiation Therapy

Five randomized control trials have evaluated the extent of benefit from breast radiotherapy in reducing cancer recurrence following complete excision for DCIS (Table 23-2). The first of these was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-17 clinical trial that, from 1985 through 1990, enrolled 818 women who had undergone lumpectomy for DCIS with microscopically clear margins and were randomized to observation post excision versus whole breast radiotherapy. The characteristics of the DCIS population accrued are seen in (Table 23-3). At 42 months median follow-up, a 59%

TABLE 23-3

Patient and Treatment Variables in the Phase III Randomized Control Trials Evaluating Radiotherapy Effect Post Lumpectomy for DCIS

Trial	Years Accrued	Age ≤ 50 years (%)	Mammo Detected (%)	Tamoxifen (%)	Size (Mean) mm	Negative Surgical Margin (%)	High Grade (%)	Comedo Necrosis (%)
NSABP B-17 (38,146)	1985–1990	33	80.5	0	12.5	100 (83[b])	48.4	47.8
EORTC 10583 (41,88)	1986–1996	6.5[a]	71	0	20	78	27	38.8
UK/ANZ (43,90)	1990–1998	9	91	54	—[c]	100 (85[d])	74.5	39.5
SweDCIS (5,42)	1987–1999	24	78.7	3	17.8	80	—	—
RTOG 9804 (45)	1999–2006	19.7	100	62	5[e]	100	0	—

[a]Age < 40 years; — data point not available in the citation
[b]17% of margins at central pathology review were uncertain
[c]mean size not available, 30% of cases <10 mm
[d]85% at central pathology review, 15% uncertain
[e]median size, 72.4% of cases <10 mm

average annual reduction in ipsilateral breast cancer events was demonstrated with the addition of radiotherapy after lumpectomy (38) that persisted at 8 (39)and 12 years median follow-up (40). The most recent analysis done after 17.25 years median follow-up demonstrates a sustained benefit of breast radiotherapy with a 52% relative reduction in the risk of invasive ipsilateral breast cancer recurrence (hazard ratio [HR], 0.48; 95% CI, 0.33–0.69; $p < .001$) and a 47% reduction in the risk of DCIS ipsilateral in-breast recurrence (HR, 0.53; 95% CI, 0.35–0.8; $p < .001$) compared to those randomized to lumpectomy alone. The same percentage of women developed contralateral breast cancer in the lumpectomy-alone group (10.3%) and in the group that received radiotherapy (10.2%). Likewise, overall and breast cancer mortality did not differ for the lumpectomy-alone versus the breast radiotherapy group (2).

The European Organization for Research and Treatment of Cancer (EORTC) conducted a similarly designed randomized clinical trial investigating the role of radiotherapy after lumpectomy for DCIS ≤ 5 cm in size (3,41). It enrolled 1,010 women between 1986 and 1996. Microscopically clear resection margins were not stipulated for eligibility in this trial. In comparison to NSABP B-17 (Table 23-3), this population had less screen-detected DCIS (71%) and fewer excisions with negative surgical margins (78%). The first results reported at a median of 4.25 years demonstrated a 43% relative reduction in cancer recurrence in the treated breast with the addition of radiotherapy; 16% for observation versus 9% with treatment ($p = .005$) (41). Ten-year outcomes from the EORTC 10853 trial demonstrated a sustained 47% relative reduction in ipsilateral local recurrence (3). An approximately equal reduction in DCIS and invasive cancer recurrences was seen. There was no difference at 10 years by treatment group in the rate of contralateral breast cancer, distant metastases, breast cancer deaths, and overall survival.

The Swedish Breast Cancer group, from 1987–1999, enrolled 1,067 women who had undergone lumpectomy for DCIS occupying a quadrant or less of the breast into the SweDCIS trial. Women were randomized to observation versus postoperative whole breast radiotherapy. Microscopically clear surgical margins were not required. In 97%, specimen radiography was done at the time of lumpectomy. The patient population was similar to that enrolled on the EORTC 10853 clinical trial (Table 23-3). At 5 years a 67% relative reduction in local recurrence in the treated breast was seen: 22% in the observation group versus 7% in the radiotherapy group ($p < .0001$) (42). At a mean of 8 years of follow-up, a sustained 60% reduction in local recurrence (corresponding RR of 0.40 (95% CI, 0.30–0.54) was seen with the addition of radiotherapy. There were similar reductions in risk for ipsilateral invasive and DCIS recurrences (Table 23-2) (5).

The United Kingdom, Australia, and New Zealand (UK/ANZ) DCIS Trial accrued 1,701 women with DCIS detected in the National Breast Screening Program who had undergone lumpectomy with cancer-free surgical margins between 1990 and 1998 (4,43). The trial used a 2×2 factorial design to assess radiotherapy, tamoxifen, or both in patients with completely excised DCIS. Patients could elect to either enter into the four-way randomization or one of two separate two-way randomizations. Among the various randomization schemes, 1,030 patients were randomized to radiotherapy or observation after lumpectomy. This population reflects its origins from the screening program, so most (91%) are 50 years or older, and given the trial design, 54% received tamoxifen (Table 23-3). At a median follow-up of 5.25 years, radiotherapy was associated with a 64% relative and 8.9% absolute reduction in risk for all ipsilateral events (13.7% in the control group and 4.8% in the irradiated group, $p < .0001$) (43). A durable effect of radiotherapy is seen at 12.7 years median follow-up with a 68% relative and 12.3% absolute reduction in ipsilateral cancer recurrences (from 19.4% in the control versus 7.1% with irradiation; HR, 0.32; 95% CI, 0.22–0.47; $p < .0001$) (Table 23-2) (4).

A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) provides a concise overview of radiotherapy effect following lumpectomy for DCIS (44). A total of 3,729 women were eligible for analysis from the NSABP B-17, EORTC 10953, SweDCIS, and UK/ANZ trials, with a median follow-up of 8.9 years. Radiotherapy approximately halved the rate of ipsilateral breast events (rate ratio 0.46; standard error [SE], 0.05; 2 $p < .00001$) with no evidence of heterogeneity between the trials in the proportional reduction. At 5 years after randomization, the absolute reduction in risk was 10.5% (SE 1.2%, 7.6% vs. 18.1%) and at 10 years after, it was 15.2% (SE 1.6%, 12.9% vs. 28.1%). Radiotherapy was effective in reducing ipsilateral breast events regardless of whether the woman was younger or older than 50 years at diagnosis, local excision or sector resection had been performed, and tamoxifen or not was given (tamoxifen only given on the UK/ANZ trial). Furthermore, radiotherapy was effective in reducing ipsilateral breast events regardless of the mode of detection, surgical margin status, focality, histologic or nuclear grade, or the presence of comedo necrosis or comedo/solid architecture. Radiotherapy resulted in a larger proportional reduction in the rate of ipsilateral breast recurrence for women older than 50 years of age than for younger women (rate ratios: age < 50 years 0.69, SE 0.12; ≥ 50 years 0.38, SE 0.06; $2p = 0.0004$ for the difference between these proportional reductions). The proportional reduction did not differ significantly according to any other factor. There was no significant difference in the meta-analysis for breast cancer or overall mortality between treatment arms. The 10-year cumulative risk of breast cancer mortality was 4.1% for the radiotherapy groups and 3.7% for observation post lumpectomy (44). Importantly, there was no significant difference in heart disease deaths in those irradiated versus observed.

Within the EBCTCG analysis a "low-risk" group was sought in which the absolute risk of ipsilateral breast events was so low that the addition of radiotherapy would provide little absolute gain. There were 297 such cases of DCIS identified that were low-grade, less than 20 mm in size, and had negative surgical margins. Among them, the 10-year risk of an ipsilateral event in those allocated to lumpectomy alone was substantial at 30.1%, and even with this relatively small number of women, the effect of radiotherapy was highly significant (rate ratio 0.48; SE 0.17; $2p = 0.002$), with a 10-year absolute gain of 18.0% (SE, 5.5%) (44).

Recently, the Radiation Therapy Oncology Group (RTOG) reported the results from its RTOG 9804 clinical trial for "Good Risk" DCIS post lumpectomy, randomizing patients to observation versus breast radiotherapy (45). The results from prior randomized trials likely reflect the inclusion of DCIS cases with higher risk features: high histologic and/or nuclear grade, involved surgical margins in some cases, larger tumor sizes, and limited tamoxifen use. RTOG 9804 sought to identify and determine radiotherapy benefit after lumpectomy for DCIS patients who were expected to have a low risk of ipsilateral breast recurrence. The study opened in 1999 and was targeted to accrue 1,790 women, but closed because of poor accrual in 2006 having randomized 636 patients. RTOG 9804 enrolled women with smaller lesions, all of which were low- or intermediate-grade DCIS. The study had a much higher rate of adjuvant tamoxifen use (62%) (Table 23-3). After a median follow-up of 7.2 years there have been 19 in-breast recurrences (42% invasive, 58% DCIS) in the observation arm (7-year rate, 6.7%) and 2 (50% invasive, 50% DCIS) in the radiotherapy group (7-year rate, 0.9%) for a hazard ratio of 0.11 (95% CI, 0.03–0.47; $p = .0003$)

TABLE 23-4

Outcome for DCIS Treated with Lumpectomy and Whole Breast Radiotherapy from Single- and Multi-Institution Experiences

Institution (author)	*Treatment Era*	*N*	*Median Follow-up (years)*	*% Ipsilateral Breast Recurrence*		*% Breast Cancer-Specific Survival*	
				5 yr	*10 yr*	*5 yr*	*10 yr*
Harvard (Halasz) (132)	2001-07	246	4.8	0	—	—	—
MDACC (Alvarado) (87)	1996-09	977	5.25	3.7	—	—	—
Fox Chase (Turaka) (133)	1978-07	440	6.8	3	7	—	—
Beaumont (Vargas) (134)	1981-99	313	7	6	9.5	99.3	98.8
Yale (Rodrigues) (135)	1973-98	230	8.2	5	13	—	—
Multi-institution (Solin) (52)	1973-95	1003	8.5	5	10	99	99
British Columbia (Wai) (54)	1985-99	482	9.3	5.5	7.5	100	100

—, data point not available

(45). The eligibility criteria for RTOG 9804 are similar to the low/intermediate-grade stratum of the Eastern Cooperative Oncology Group (ECOG) single arm registration-observation study for DCIS post lumpectomy discussed elsewhere (46). For the low/intermediate-grade stratum on ECOG 5194, the 7-year rate of ipsilateral breast recurrence is 10.5% (46). This discrepancy in 7-year rates of ipsilateral breast recurrence between the two trials may be influenced by the tamoxifen use that was double in the RTOG 9804 (62%) population compared to the ECOG 5194 low/intermediate-grade stratum (31%). Additional follow-up of RTOG 9804 is needed to ensure endurance of the results given its incomplete accrual and the longer time to failure that has been reported for lower-grade DCIS; however, it appears that, based on standard clinical-pathologic criteria, a cohort of DCIS could be identified with a low rate of in-breast recurrence at 7 years without radiotherapy (but with tamoxifen in most). However, even in this low-risk group, the addition of radiotherapy reduced the in-breast recurrence rate by a relative 89% and an absolute 5.8%.

In addition to the randomized control trials, there have been numerous institutional experiences with lumpectomy and RT for DCIS demonstrating similar in-breast cancer event rates, acceptable toxicity, good cosmetic results, and excellent breast cancer-specific survival (Table 23-4).

Radiation Therapy Methods

The radiotherapy delivered post lumpectomy was fairly consistent across the 5 randomized trials, and in all cases the entire breast was irradiated (Table 23-5). The most common radiotherapy regimen was to deliver 50 Gy to the whole breast over 25 treatments or fractions of 2 Gy daily over a treatment period of 5 weeks. Boost or additional dose to the lumpectomy cavity vicinity was not recommended. Given that radiotherapy after lumpectomy for DCIS does not give a survival benefit, there has been understandable concern regarding the known excess risk for cardiovascular mortality associated with breast radiotherapy in the past (47). Methods of breast radiotherapy post lumpectomy that avoid/minimize cardiac irradiation for left-sided DCIS cases are imperative. One of the important findings of the EBCTCG meta-analysis is that there was no statistically significant excess heart disease mortality for those given breast radiotherapy after lumpectomy (44). There were 26/1878 (1.38%) heart disease deaths for those allocated to post lumpectomy radiotherapy versus 29/1851 (1.57%) for lumpectomy alone with 8.9 years median follow-up.

Shortened whole breast irradiation (WBI) treatment courses that are achieved with hypofractionation, or the delivery of larger daily radiation doses of 2.67 Gy to a total of 40 or 42.67 Gy with 15 or 16 treatments over approximately 3 weeks time, are being increasingly used after excision for DCIS. New

TABLE 23-5

Breast Radiotherapy Delivered in Randomized Control Trials Evaluating Benefit after Lumpectomy for DCIS

Trial	*Whole Breast Total Dose (Gy)*	*Treatments (Fractions)*	*Dose per Fraction (Gy)*	*Boost (%)*
NSABP B-17 (38)	50	25	2	9
EORTC 10583 (41)	50	25	2	5
SweDCIS (5)	50	25	2	0
	48	20	2.4	
	54	27	2	
UK/ANZ (43)	50	25	2	0
RTOG 9804 (45)	50	25	2	0
	50.4	28	1.8	
	42.5	16	2.67	

York University reported a Phase I/II single arm prospective trial in 59 patients using hypofractionated WBI of 42 Gy in 15 fractions of 2.8 Gy for treatment of DCIS (48). At a median follow-up of 36 months, there were no grade 3 radiation toxicities early or late, 91% of women reported a good-excellent cosmetic outcome, and no in-breast recurrences were reported. The University of Toronto reported their retrospective analysis of 266 women with DCIS who received either standard fractionated (104 cases) or hypofractionated (162 cases) WBI post lumpectomy. With a median follow-up of 3.76 years, the actuarial risk of ipsilateral breast recurrence at 4 years was 7% with hypofractionated WBI and 6% with the conventional schedule (p = .9) (49). The American Society for Radiation Oncology (ASTRO) evidence-based guideline on Fractionation for Whole Breast Irradiation concluded that data were insufficient so far to recommend for or against hypofractionated WBI post lumpectomy for women with DCIS (50).

The potential benefit of adding a boost, or supplemental radiation dose focused on the lumpectomy cavity vicinity only following WBI, remains an area of controversy for radiation management of DCIS. Boost was not part of protocol therapy in any of the 5 randomized clinical trials (Table 23-5). In the treatment of invasive breast cancer with breast-conserving therapy, the EORTC 22881-10882 clinical trial demonstrated that the use of a boost dose to the lumpectomy cavity vicinity after WBI resulted in a 41% relative and 4% absolute reduction in local recurrence at 10 years (p = .0001) (51). Given these data for invasive disease, the practice of adding a boost has been adopted following WBI for DCIS. This is evident in the 1,003 pooled cases from 10 institutions treated with breast radiotherapy post lumpectomy between 1973 and 1995, where a boost was delivered in 72% (52). In that study, there was not a significant difference in local recurrence for those that received less than 60 Gy (9%) versus those who received more (11%) (p = .91) at a median of 8.9 years follow-up. The use of a boost for DCIS is supported by a retrospective pooled analysis by the Rare Cancer Network that studied 373 young women (age < 45 years) with DCIS across 18 institutions who all underwent lumpectomy and then were either observed or received WBI with or without a boost (53). After a median follow-up of 6 years, the 10-year local recurrence rate reported for no radiotherapy was 34%; 28% for WBI without boost; and 14% for WBI with boost (p < .0001). However, another retrospective analysis from the British Columbia Cancer Agency database found no benefit of boost in 995 cases of DCIS treated with breast-conserving therapy with a 9.3 year median follow-up. In this analysis, the rate of local recurrence at 10 years was 13% in 475 cases without radiotherapy, 6% in 378 cases with WBI without boost, and 9% in 144 cases of WBI with boost (p = .065) (54). A secondary unplanned analysis examining the benefit of the "boost" was done on the NSABP B-24 clinical trial that examined tamoxifen effect after lumpectomy and WBI for DCIS (55). In this sub-analysis of 1,569 women enrolled on NSABP B24 with a 14.1-year median follow-up, it was documented that the 692 women who received a boost after WBI (38%) were more likely to have had involved margins and the presence of comedo necrosis than the 877 who were not boosted. The use of a boost did not result in a reduction in the rate of ipsilateral breast recurrence: 14.3% without boost and 13.8% with boost (55). The use of boost in the EORTC 22881-10882 clinical trial was accompanied by a significant increase in severe fibrosis and worsening of the cosmetic outcome (51). In the setting of DCIS, it is important to weigh the local control benefit of using a boost against the potential for adverse toxicity and cosmetic outcomes. These unanswered questions regarding radiotherapy fractionation and boost for DCIS are being addressed in a phase III randomized trial (NCT00470236) by the Trans-Tasman Radiation Oncology Group (TROG), "Radiation Doses and Fractionation Schedules in Non-low Risk Ductal Carcinoma in Situ (DCIS) of the Breast." This trial opened in 2007 and is targeted to accrue 1,600 women.

Early reports of accelerated partial breast irradiation (APBI) that focuses a short course (5–10 treatments over 5–8 days) of post excision radiotherapy solely to the vicinity of the lumpectomy cavity for treatment of DCIS have been favorable. Twelve institutions participated in a phase II clinical study using the MammoSite® brachytherapy for APBI for DCIS post lumpectomy, enrolling 133 patients from 2003–2006 (56). With a mean follow-up period of 9.5 months, there were 2 DCIS failures in the ipsilateral breast. William Beaumont Hospital reported retrospectively on 99 cases of DCIS treated with post lumpectomy APBI (57), and with a mean follow-up of 3 years, there has been 1 ipsilateral breast recurrence for a reported 5-year rate of 1.4%. There are 194 cases of DCIS in the American Society of Breast Surgeons registry of 1,449 cases from 97 institutions of early-stage breast cancer treated with APBI using the MammoSite® brachytherapy device (58). The most recent update after a median follow-up of 4.5 years reported 6 patients (3.1%) who had an ipsilateral breast recurrence, for a 5-year actuarial local recurrence rate of 3.39%. Acknowledging that these early results in DCIS are promising, but that the overall experience so far is limited and without prospective data, the ASTRO consensus statement regarding the patient selection criteria and best practices for the use of APBI outside the context of a clinical trial categorized DCIS as a "Cautionary" group (59). The NSABP B-39/RTOG 0413 phase III clinical trial comparing ABPI versus standard WBI for early-stage breast cancer post excision accrued 4,216 women between 2005 and 2013, and 24.4%, or 1,028, are DCIS. The pending outcome from this trial will clarify which DCIS patients are best suited to APBI post lumpectomy.

Tamoxifen

Tamoxifen use for DCIS developed from its observed benefit in reducing ipsilateral recurrent and new contralateral breast events in the management of invasive breast cancer treated with breast-conserving therapy (60). While radiotherapy post lumpectomy for DCIS results in a relative 50% to 60% reduction in ipsilateral breast recurrence, the residual absolute recurrence rates of between 9% and 20% or higher in some cohorts at 10 to 15 years follow-up (Table 23-2) have left opportunity for improvement. Two clinical trials have tested the impact of tamoxifen after lumpectomy with or without WBI for further reducing breast cancer events for DCIS: NSABP B-24 (2,61) and UK/ANZ (4,43). The NSABP B-24 clinical trial tested the hypothesis that in patients with DCIS treatment with lumpectomy, postoperative WBI and tamoxifen would be more effective than lumpectomy with WBI alone in prevention of invasive and non-invasive cancers in the ipsilateral and contralateral breast (61). This double-blind, randomized controlled trial enrolled 1,804 patients between 1991 and 1994 who all received lumpectomy and ipsilateral breast radiotherapy and then were randomly assigned to receive either placebo (n = 902) or tamoxifen (n = 902). Tamoxifen dose was 10 mg twice daily. Thirty-one percent of patients who started therapy discontinued treatment before 5 years. The patient population in this study included 33.5% who were less than 50 years of age, 83% whose DCIS was detected by mammography, 84% that had a lesion size less than 1 cm, and 25% who had positive or unknown surgical margins. At a median follow-up of 6.2 years, there were 37% fewer breast

cancer events in the tamoxifen group than the placebo group (p = .0009). A lower rate of ipsilateral-breast recurrences in the tamoxifen group was apparent only for invasive tumors (44% reduction). The rate of ipsilateral DCIS recurrences was not significantly lower in the tamoxifen group (p = ·43), but the reduction in contralateral breast DCIS was 13 versus 3, a 78% reduction (p = .02). Long-term outcomes of NSABP B-24 reporting at a median follow-up of 13.6 years (2) demonstrate a sustained 32% reduction in the risk of invasive ipsilateral recurrence in the tamoxifen compared with the placebo group (HR, 0.68; 95% CI, 0.49–0.95; p = .025). Regarding ipsilateral DCIS recurrences, the addition of tamoxifen resulted in a non-statistically significant risk reduction of 16% compared with placebo (HR, 0.84; 95% CI, 0.60–1.19; p = .33). There was a 32% reduction in contralateral breast cancer for patients who received tamoxifen versus placebo (HR, 0.68; 95% CI, 0.48–0.95; p = .023).

A combined analysis of outcomes from NSABP B-24 and B-17 that looks across trials demonstrates that radiotherapy and tamoxifen together resulted in a 70% relative risk reduction of invasive ipsilateral breast recurrence compared to lumpectomy alone (2). RT decreased the cumulative incidence of invasive ipsilateral recurrence at 15 years from 19.4% in the lumpectomy-only to 8.9% in the B-17 Lumpectomy-RT group, and to 10% in the B-24 lumpectomy-RT + placebo group. The cumulative incidence of ipsilateral invasive cancer recurrence was lower in the lumpectomy-WBI-tamoxifen group: 8.5% at 15 years.

In NSABP B-24, the addition of tamoxifen did not result in a statistically significant reduction in breast cancer mortality risk (HR, 0.86; 95% CI, 0.66–1.11) compared with lumpectomy and radiotherapy alone. However, across the B-24 and B-17 trials, women who developed an invasive ipsilateral breast recurrence, relative to those who did not, had a greater risk of all-cause death (HR, 1.75; 95% CI, 1.24–2.45), and the effect was larger (HR, 7.06; 95% CI, 4.14–12.03) if only breast cancer–related deaths were considered (2). In contrast, there was no statistically significant increase in overall mortality risk (HR, 0.81; 95% CI, 0.51–1.27) or breast cancer mortality risk (HR, 1.49; 95% CI, 0.71–3.15) for those who had DCIS recurrence. Of note, women who developed an invasive contralateral breast cancer had an increase in mortality risk (HR, 2.62; 95% CI, 1.82–3.77) similar to those who developed an ipsilateral invasive breast cancer recurrence.

The estrogen receptor (ER) status was unknown for the DCIS cases enrolled in NSABP B-24. Retrospectively, ER and/or progesterone receptor (PR) status has been attained in 732 cases, either from tissue blocks (449 patients) or from the laboratories (283 patients) used by enrolling institutions (62). The ER and PR were positive in 76% and 66% of patients, respectively. Patients with ER positive DCIS who received adjuvant tamoxifen versus placebo showed significant reductions in any breast cancer event (HR, 0.58; p = .0015), any invasive breast cancer (HR, 0.53; p = .005), and any contralateral breast cancer (HR, 0.50; p = .02). No significant benefit of tamoxifen in addition to lumpectomy and radiotherapy was seen with ER negative DCIS.

The benefit of tamoxifen after lumpectomy alone or with breast radiotherapy was also evaluated in the UK/ANZ trial in which 1,576 patients were randomly allocated to receive tamoxifen dosed at 20 mg per day (n = 794) or not given tamoxifen (n = 782). Of these, 912 were randomized in a 2×2 design to radiotherapy and tamoxifen, while 664 chose no radiotherapy and were only randomized to tamoxifen. Eleven percent stopped taking the drug before 5 years. Sixty-seven percent did not receive breast radiotherapy after lumpectomy (n = 1,053), and 33% underwent WBI post lumpectomy (n = 523). At a median follow-up of 4.4 years, tamoxifen did not significantly reduce the overall event rate nor the ipsilateral breast recurrence rate (13% with tamoxifen versus 15% without, p = .42) (43). In contrast, by median follow-up of 12.7 years, the use of tamoxifen did reduce the overall breast cancer event rate (ipsilateral + contralateral) (18.1% with tamoxifen vs. 24.6% without, p = .002) and the ipsilateral breast cancer event rate (15.7% with tamoxifen and 19.6% without, p = .04) (4). There was a significantly reduced rate of recurrent ipsilateral DCIS (8.6% with tamoxifen vs. 12.1% without, respectively, p = .03), but not ipsilateral invasive disease (6.8% with and 6.9% without tamoxifen, p = .79). Women who were randomly assigned to tamoxifen but were not treated with radiotherapy (n = 1,053) also had a significant overall reduction in new breast events (13.2% with tamoxifen and 17% without, p = .04). However, this benefit was confined to a reduction in DCIS events (7.4% with tamoxifen vs. 10.4% without, p = .04); no difference in invasive recurrences was seen (5.5% with tamoxifen versus 6% without, p = .6). There was no apparent benefit from receipt of tamoxifen among those who had lumpectomy *with* radiotherapy (n = 532; ipsilateral event rate with tamoxifen 2.4% vs. 2.6% without, p = .8) (4). There was a significant reduction in all contralateral events in those randomly assigned to tamoxifen (1.9% vs. 4.2%, p = .005).

The apparent discordance in the results from NSABP B-24 and UK/ANZ, especially in regard to tamoxifen benefit in the irradiated patients, may reflect the differences in patient populations enrolled in these respective trials. Thirty percent of patients enrolled in NSABP B-24 were less than 50 years of age compared to only 9% in the UK/ANZ trial. This disparity in younger women who have a higher likelihood of in-breast recurrence and proportionally smaller benefit from radiotherapy compared to women older than 50 (44) may explain the greater tamoxifen impact in irradiated patients in the NSABP B-24 trial.

Aromatase Inhibitors and Trastuzumab

The success of tamoxifen in lowering all rates of recurrence encourages the search for more effective and/or less toxic agents to reduce recurrent and new breast cancer events following lumpectomy for DCIS. Aromatase inhibitors have been documented to prevent invasive breast cancer in postmenopausal women (63) and reduce new contralateral breast cancer to a greater extent than tamoxifen after treatment of endocrine-sensitive invasive breast cancer (64). The outcomes from two randomized clinical trials that have completed accrual and that test the relative benefit of anastrozole in comparison to tamoxifen for reducing breast cancer events after lumpectomy for DCIS are awaited. Between 2003 and 2007, NSABP B-35 randomized 3,000 postmenopausal women diagnosed with DCIS treated with lumpectomy and breast radiotherapy in double-blind fashion to 5 years of tamoxifen 20 mg daily (and an anastrozole appearing placebo) versus anastrozole 1mg daily (and a tamoxifen appearing placebo). The International Breast Cancer Intervention Study II (IBIS II) similarly randomized 2,980 women over age 40 who had undergone lumpectomy for DCIS to either 5 years of tamoxifen or anastrozole between 2003 and 2011.

Trastuzumab has been demonstrated to be effective and safe in the treatment of HER2 overexpressing invasive breast cancer. HER2 overexpression in DCIS can range from 30% to 50% (65) and has been associated with higher rates of subsequent ipsilateral breast cancer recurrence (66). NSABP B-43 is actively accruing women with HER2 overexpressing DCIS treated with lumpectomy to be randomized to standard WBI versus 2 doses of trastuzumab every 3 weeks during

radiotherapy to determine whether trastuzumab given concurrently with radiotherapy is beneficial in preventing subsequent breast cancer events. The targeted accrual is 2,000, and as of the close of 2012, over 1,000 patients have been randomized.

Breast-Conserving Surgery Alone

The four published prospective, randomized trials (2–5) have demonstrated that the addition of RT to excision significantly decreases ipsilateral breast tumor recurrence (IBTR) but does not improve overall or disease-specific survival. It is possible that with larger populations and follow-up that some difference would emerge, but with randomization of approximately 4,000 women and median follow-up of 8 to 17 years, no hint of such a trend exists. Because radiation has not improved survival, and because there are rare but potentially serious risks associated with radiation, including secondary malignancies and cardiac disease (47,67), there has been persistent interest in treating some subsets of women with DCIS by excision alone. In fact, most academic radiation oncologists surveyed would not recommend radiation to all women with DCIS (68). Numerous risk factors for local recurrence have been identified, leading to the belief that at least some subset of DCIS may have a recurrence risk low enough to not justify radiation. A number of retrospective studies, usually including a highly select group of patients with small mammographically detected tumors of low histologic grade, have suggested that DCIS can be treated with excision alone with a high rate of local control. A number of these studies are shown in Table 23-6.

There have been two prospective studies of wide excision alone for DCIS (Table 23-7). The Dana-Farber/Harvard Cancer Center conducted a single-arm, prospective trial of wide excision alone from 1995 to 2002 (80,136). Entry criteria included DCIS of predominant grade 1 or 2 with a mammographic extent of no greater than 2.5 cm and final margin width of at least 1 cm. Tamoxifen was not permitted. The accrual goal was 200 patients; in July 2002 the study closed to further accrual at 158 patients because the number of local recurrences (n = 13) met the stopping rules. The median patient age was 51 years, and 94% had mammographically detected DCIS. Re-excision was performed in 133 (84%) of which no residual disease was identified in 92%. The median follow-up was 3.6 years (range, 0 to 6.9 years). Thirteen patients had local recurrence as the first site of failure between 0.6 and 5.2 years, resulting in a rate of ipsilateral local recurrence of 2.4% per patient-year (95% CI, 1.3%–4.1%), corresponding to a 5-year rate of 12%. Ten recurrences were in the same quadrant as the initial DCIS and three were elsewhere in the ipsilateral breast. Four (31%) recurred with invasive disease, all under 1 cm in size, and none with nodal metastases. No patient developed distant metastasis. A recent update with median follow-up of 11 years reported an annual local recurrence rate of 1.9% per patient-year and a 10-year local recurrence rate of 15.6% (136).

Another prospective, single-arm study examining the role of excision alone in the treatment of DCIS was reported by the Eastern Cooperative Oncology Group and North Central Cancer Treatment Group (46) (Table 23-7). Eligibility criteria for this study included DCIS at least 3 mm in size, excised with a margin width of 3 mm or more as determined by sequential sectioning and complete embedding. The study was open to patients with low- or intermediate-grade DCIS 2.5 cm or less in size, and high-grade DCIS (defined as nuclear grade 3 with necrosis) up to 1 cm in size. A postexcision mammogram was required for all participants. At a median follow-up of 6.7 years, the 7-year IBTR rate was 18% (95% CI, 10.2%–25.9%) for patients with high-grade DCIS, while IBTR occurred in 10.5% (95% CI, 7.5%–13.6%) of those with low- or intermediate-grade DCIS. In the high-grade group, 35% of IBTR were invasive; in the low/intermediate-grade stratum, 53% were invasive. The 7-year rate of contralateral breast cancer in the high- and low-grade groups was 7.4% and 4.8%, respectively. Comparison of 5- and 7-year results suggests a plateauing of recurrences in the high-grade but not in the low-grade stratum. This observation is further supported by a recent update for a subset of the population (91). Previous studies of patients treated with

TABLE 23-6

Results of Treatment of Ductal Carcinoma *In Situ* with Excision Alone, Retrospective Series

Study (Reference)	*Treatment Years*	*N*	*Follow-up (mos)*	*Recurrences N*	*Recurrence Crude %*	*Actuarial Recurrence Rate (Years of Calculation)*	*Invasive Recurrences (%)*
Arnesson, 1997 (69)	1981–1994	169	80[a]	25	15	22% (10)	36
Ottesen, 2000 (70)	1982–1989	168	120[a]	54	32	—	46
Cutuli, 2002 (71)	1985–1995	190	84[b]	59	31	44% (10)	53
Lagios, 2002 (72)	1972–1987	79	135[b]	17	22	22% (15)	59
Schwartz, 2002 (73)	1978–2000	256	67[a]	71	28	41% (10)	37
Lee, 2006 (147)	1972–2005	496	54[a]	86	17	31% (12)	34
Schouten van der Velden, 2007 (75)	1989–2003	237	59[a]	61	26	25% (5)	~47[c]
Rudloff, 2010 (76)	1991–2006	811	67[a]	121	15	22% (10)	~40[c]
Silverstein, 2010 (77)	1979–2009	604	75[a]	103	17	—	36
Holmes, 2011 (78)	1983–2002	141	125[a]	60	43	—	18
Fong, 2011 (79)	1994–2005	342	59[a]	55	16	15% (5) 18% (8)	~41[c]

[a]Median
[b]Mean
[c]The proportion of recurrences that were invasive was provided for multiple treatment groups, not just excision alone.

TABLE 23-7

Prospective Observational Studies of Wide Excision Alone for Ductal Carcinoma *In Situ*

			Eligibility Requirements			*Patient characteristics*				*Ipsilateral breast recurrence*			
	Year	*N*	*Grade of DCIS*	*Margin Width*	*Size*	*Percentage With ≥1 cm Margins*	*Median Size (cm) (Range)*	*Median Age (Years) (Range)*	*Median Follow-up (Years)*	*5-Year Rate*	*7-Year Rate*	*8-Year Rate*	*10-Year Rate*
Harvard/Dana Farber													
Wong (80)	2006	158	Predominantly low/intermediate-grade	≥1 cm or negative re-excision	≤2.5 cm	100%	0.9 (0.1–2.5)	51 (35–81)	3.6	12%			
Wong (136)	2013	143							11.0	9.8%		13.3%	15.6%
ECOG													
Hughes(46)	2009	565	Low/intermediate-grade	≥0.3 cm	≤2.5 cm	48%	0.6 (0.1–2.5)	60 (28–88)	6.2	6.1%	10.5%		
Solin (91)	2011	291							8.8				14.6%
Hughes(46)	2009	105	High-grade	≥0.3 cm	≤1 cm	53%	0.5 (0.2–1)	59 (33–87)	6.7	15.3%	18.0%		
Solin (91)	2013	54							8.8				19.0%

excision and RT have shown that while early IBTR is more common in high-grade DCIS, after 10 years of follow-up, IBTR rates do not differ on the basis of grade (81).

The RTOG 98-04 included low-risk patients similar to those in the ECOG low-intermediate grade stratum, although the proportion taking tamoxifen in the RTOG study (62%) was double that in the ECOG study (31%). Patients were randomized to RT or observation. The reported 7-year IBTR rate is 6.7% with excision alone as compared to 0.9% with radiation (45).

The prospective data from these studies suggest that while careful selection can identify patients who can be treated with excision alone and achieve IBTR rates similar to those that received radiation in the randomized trials, there remains a substantial local recurrence rate despite margins of 1 cm or more. These results support the findings of the randomized trials that no subset of patients has been identified for which radiation does not reduce IBTR rate.

RISK FACTORS FOR LOCAL RECURRENCE

A number of studies have addressed prognostic factors for local recurrence in patients treated for DCIS by either excision alone or excision and RT.

Margin Status

Margin status is seen in almost all studies to be associated with local recurrence, although the categorization schemes used to report margin status are variable. Whether outcomes are analyzed with close and positive margin status combined, or with strictly positive margins (tumor on ink), almost all studies show significantly higher rates of local recurrence in patients with close or positive margins as compared to those with margins reported as negative (Tables 23-8 and 23-9).

The question of optimal margin width remains controversial. Because of the variability in specimen processing and grouping of margin widths, comparisons between studies are difficult. Silverstein reported a strong association between margin status and local recurrence in retrospective reviews of patients treated with excision alone and with RT. In a report of 469 patients, with a mean follow-up of 81 months, the 8-year incidence of local recurrence after excision alone was 58%, 20%, and 3% for margins less than 1 mm, 1 to 9 mm, and at least 10 mm, respectively, as compared to 30%, 12%, and 4%, respectively, for women treated with excision and RT (82). These data led the authors to conclude that RT is not justified if the margin width is large. In a more recent report, 12-year rates of local recurrence for women with margins at least 10 mm were 14% for excision alone and 2.5% for excision and RT (74), consistent with the idea that radiation does reduce the rate of local recurrence in all subsets. In the prospective ECOG study of excision alone, comparison of those with at least 10 mm margins to those with between 3 and 10 mm margins showed no difference in 5-year local recurrence rates in either high- or low/intermediate-grade strata (46).

One reason for the inconsistent association between margin status and local recurrence may be the variability in methods of assessing margin status and the sampling error inherent in the examination of a three-dimensional irregular specimen to determine completeness of excision. Supporting the concept that margin determination has significant sampling error are series that have found an

TABLE 23-8

Relative Risk of Local Recurrence after Breast-Conserving Surgery for DCIS, According to Margin Status

			Hazard Ratios by Margin Status			
Study (Reference)	*N*	*Median Follow-up (Years)*	*Negative*	*Uncertain/ Close/Positive*	*Positive (Tumor at Ink)*	*p*
Boland et al. (101)[b,c]	237	3.9	1[f]	9.8	—	<.001
Pinder et al.(UK/ANZ) (90)[b,c]	1,224	4.4	1[f]	1.64	—	.03
MacDonald et al. (137)[b]	445	4.8	1[i]	—	14.3	<.001
Rudloff et al. (76)[a,c]	294	5.6	1[h]	1.73	—	.002
Vargas et al. (134)[a,c]	367	6.1	1[h]	3.65	—	.007
Cutuli et al. (No radiation) (71)[a]	190	7.0	1[j]	1.64	—	<.05
Cutuli et al. (Radiation) (71)[a,d]	515	7.0	1[j]	1.39	—	.016
Wai et al (138)[a]	460	9.4	1[j]	4.1	—	<.001
Bijker et al. (EORTC) (3)[a,e]	1,010	10.0	1[g]	1.84	—	.0005
Rudloff et al. (85)[a,c]	1,681	11.0	1[i]	2.63[k]	—	.06
Wapnir et al. (NSABP B-24) (2)[d]	900	13.6	1[l]	—	2.61 (invasive) 1.65 (DCIS)	<.001 .05

[a]Multivariate analysis
[b]Univariate analysis
[c]Some patients received RT and/or tamoxifen
[d]All patients received RT
[e]Some patients received RT
[f]Negative margin defined as ≥1 mm
[g]Negative margin defined as >1 mm
[h]Negative margin defined as >2 mm
[i]Negative margin defined as ≥10 mm
[j]Negative margin definition not stated
[k]Close margin defined as ≥2 ducts with DCIS <10 mm from ink
[l]Negative margin defined as ink not on DCIS

TABLE 23-9

Annual Local Recurrence Rate in Relation to Margins and Treatment

		Excision Alone				*Excision and Radiation Therapy*			
Study	*Median Follow-up (Years)*	*Negative*	*Close*	*Close/ Positive (<1 or ≤1 mm)*	*Positive (Tumor on Ink)*	*Negative*	*Close*	*Close/ Positive (<1 or ≤1 mm)*	*Positive (Tumor on Ink)*
MacDonald et al. at 5 years (137)[a]	4.8	1.4%[c]	5.4%[f]	—	10.4%	—	—	—	—
Neuschatz (139)[a]	5.0	2.2%[d]	—	4.9%	—	0%[d]	—	5.2%	—
Fisher et al. (NSABP B-24) (40)	6.9	—	—	—	—	1.5%	—	—	3.1%
Cutuli et al. (71)[a]	7.0	3.7%[e]	—	—	8.0%[e]	1.4%[e]	—	—	3.6%[e]
Solin et al. at 10 years (84)[a]	9.4	—	—	—	—	0.9%[g]	0.7%	—	2.4%
Wai et al. at 10 years (138)[a]	9.4	0.9%[e]	1.7%[e]	—	3.1%[e]	—	—	—	—
Bijker et al. (EORTC) (3)[b]	10.5	2.4%[d]	—	4.3%	—	1.5%[d]	—	2.5%	—
Rudloff et al. at 10 years (85)[a]	11.0	2.1%[c]	2.7%[f]	4.2%	—	1.3%[c]	1.2%[f]	1.1%	—
Wapnir et al. (NSABP B-24) at 15 years (2)	13.6	—	—	—	—	0.5% (invasive IBTR)	—	—	1.2% (invasive IBTR)

[a]The estimate is the actuarial rate at X years divided by X
[b]The estimate is the crude rate at median X years divided by X
[c]Negative margin defined as ≥10 mm margin
[d]Negative margin defined as >1 mm margin
[e]Definition not stated
[f]Close margin defined as 1–9 mm margin
[g]Negative margin variably defined as >1, >2, or >3 mm margin

association between volume of breast tissue excised (83,84) or volume of disease near the margin (84,85) and local recurrence rates. In a series of 294 women with 11 years of follow-up, Rudloff et al. showed an association between greater volume of disease near the margin and greater reduction in risk of local recurrence with radiation (85).

A meta-analysis of 22 studies of the impact of margin width on local failure of DCIS included 4,660 patients treated with excision and RT (86). The relative risk of IBTR for those with negative margins was 0.36 (95% CI, 0.27–0.47; $p < .0001$) compared to those with positive margins. For those with negative versus close margins (defined by each study, ranging from <1 to >5 mm), the relative risk of IBTR was 0.59 (95% CI, 0.42–0.83; $p < .001$). Furthermore, the relative risk of IBTR for a 2 mm or greater margin was 0.53 (95% CI, 0.26–0.96; $p < .05$) compared to a lesser margin. When compared to margin widths of at least 5 mm, those with margin width of 1 mm had a relative risk of 2.89 (95% CI, 1.2–8.1; $p < .05$), and those with margin width of 2 mm had a relative risk of 1.51 (95% CI, 0.51–5.0; $p > .05$) (86). The 2 mm vs. 5 mm margin width comparison may be underpowered due to limited number of patients in these groups.

Taken together, these studies demonstrate that margin status is associated with risk of IBTR. The rate of local recurrence is lower with negative margins compared with close, positive, or uncertain margins. To date, there is no convincing evidence that a margin width larger than 2 mm lowers recurrence rates for women receiving RT. However, the optimal margin width for those receiving and not receiving RT remains uncertain.

Age

Young age has consistently been associated with higher rates of ipsilateral breast cancer recurrence following lumpectomy for DCIS with or without radiotherapy in the randomized control trials as well as single institution and multi-institution experiences (3–5,39,52,71,87) (Table 23-10). In the SweDCIS trial and UK/ANZ trials, young age was not associated with worse local recurrence after lumpectomy alone; however, older women in these trials had a proportionally greater benefit from the addition of breast radiotherapy compared to younger women (4,5). This is further reflected in the EBCTCG meta-analysis where radiotherapy resulted in a larger proportional reduction in the rate of ipsilateral breast recurrence for women older than 50 years of age than for younger women (44). When the meta-analysis was subdivided into five groups according to age (<40, 40–49, 50–59, 60–69, ≥70), the trend in the proportional reduction in ipsilateral breast recurrence with increasing age was significant ($p = .02$). The difference between the proportional reductions in younger and older women did not appear to be accounted for by differences in histological grade or comedo necrosis, or by differences in nuclear grade or architecture. Other investigators have proposed that worse local control rates in younger women with DCIS are explained by the greater prevalence of poor prognostic features. Younger women are more likely to present with clinical symptoms and have higher nuclear grade lesions, each of which has been associated with increased risk of ipsilateral breast recurrence (3,87).

TABLE 23-10

Frequency[a] of Local Recurrence in Younger versus Older Women with DCIS Who Have Been Treated with Lumpectomy With or Without Breast Radiotherapy

Clinical Trial or Study	*Timepoint*	*Treatment*	*Age ≤ 50*	*Age > 50*
NSABP B-17 (39)	5 year	L	17	8.1
		L + RT	12.3	5.9
SweDCIS (5)	8 year	L	26	27
		L + RT	20	9.4
UK/ANZ (4)	15 year	L	23	22.5
		L + RT	27	9
Multi institution USA (52)	10 year	L + RT	16.5	6.5
			Age ≤ 40	*Age > 40*
EORTC 10853 (3)	10 year	L	54	26
		L + RT	23	16
MDACC (87)	5 year	L	22.9	5.6
		L + RT	6.4	2.3
Multi institution France[b] (71)	7 year	L	43	24
		L + RT	23.5	9.5

[a]Event divided by N in treatment group; L, lumpectomy; L+RT, lumpectomy and breast radiotherapy
[b]Complete excision cases

Method of Detection

DCIS that is detected by clinical symptoms instead of mammographic screening carries a higher risk of ipsilateral breast recurrence following lumpectomy with or without breast radiotherapy (2,85,87–89). In a SEER-based cohort study of 1,026 women with DCIS in the San Francisco Bay Area, ipsilateral invasive cancer recurrence was more likely in women whose initial DCIS lesions were detected by palpation than in women whose initial DCIS lesions were detected by mammography (OR, 4.9; 95% CI, 1.7–14.2) (89). The 10-year risk of breast cancer mortality in this study was greatest for women who were age 40 years at diagnosis with DCIS detected by palpation (2.5%; 95% CI, 2.4%–2.5%) or with a high nuclear grade (2.5%, 95% CI, 2.1%–3.0%) (89). The poorer prognosis associated with clinical detection may be confounded by young age. Women age 40 to 50 are less likely to receive regular mammogram screening than their older counterparts. Investigators from MDACC found in their large, single institutional series of 2,037 patients with DCIS, 56.1% of those under 40 presented with clinical rather than radiologic signs of breast cancer, compared with 14% over age 40 ($p = .001$) (87). However, another series found clinical detection to be associated with a higher local recurrence risk even on multivariable analysis that controlled for age (HR, 2.3; 95% CI, 1.2–4.5) (85).

Pathologic Features

The presence of comedo necrosis, high nuclear grade, and larger lesion size are frequently but not consistently associated with increased rates of in-breast recurrence following lumpectomy with or without breast radiotherapy. This may be related to the acknowledged inter-pathologist variability in the description/grading of DCIS, the existence of different DCIS pathology grading systems, and treatment bias inherent in retrospective datasets examining this issue. Therefore, data from prospective trials with central pathology reviewed represent a good opportunity to examine the influence of pathology features.

In the EORTC 10853 clinical trial, the 10-year risk of a subsequent breast event was associated both with poor or intermediate-grade histology and comedo-solid architecture (3). DCIS with poor or intermediate differentiation had a 26% or 27% rate of a subsequent breast cancer event versus 14% for well differentiated lesions ($p < .001$). Similarly, the recurrence rate was 27% for a solid/comedo histology, 26% for cribriform and 9% for clinging/micropapillary ($p = .001$) (3).

A central review of pathology slides was performed on 623 patients, or 77% of the entire NSABP B-17 cohort: 303 treated by lumpectomy only, and 320 by lumpectomy and WBI at a median follow-up of 8 years (146). Nine pathologic features were examined for association with in-breast recurrence: comedo necrosis, histologic type, margins, lymphoid infiltrate, nuclear grade, focality, cancerization, stroma, and tumor size. When all nine pathologic features were examined jointly for prognostic significance, only comedo necrosis remained as a significant predictor for in-breast cancer recurrence.

A total of 72% of 1,694 cases entered into the UK/ANZ DCIS trial had full pathological review, and many pathology features were assessed for their association with ipsilateral recurrence (90). All reviewed cases were graded according to several recognized classifications of DCIS, including cyto-nuclear features (National Pathology Coordinating Group, 2005), traditional/historical nomenclature, Van Nuys grade, Nottingham grade, differentiation (Holland), main architecture, and necrosis. At a median follow-up of 4.4 years, all of the grading systems applied showed a significant increase in ipsilateral breast recurrence rates with higher grade, comedo type necrosis, and predominant growth pattern/architecture of the disease. Specifically, patients with a solid morphology as the main architectural pattern of DCIS had a 15.2% recurrence rate compared with 14.3% of those with micropapillary DCIS, and only 7.3% of those with predominantly cribriform DCIS.

These findings are corroborated by the SEER/San Francisco Bay Area study of lumpectomy only for DCIS, in which the 5-year risk of ipsilateral invasive cancer recurrence was greater with high nuclear-grade lesions (11.8%; 95% CI, 9.9%–14.1%) than for those with low nuclear-grade lesions (4.8%; 95% CI, 3.7%–6.8%) (89). In contrast, in a review of 287 cases of DCIS from 10 institutions with a 10.3-year median follow-up, investigators reported that comedo

histology and nuclear grade 3 combined did not predict higher rates of in-breast recurrence, but instead predicted a shorter interval to recurrence. The median interval to local recurrence was 3.1 years (mean, 4.4; range, 1.6 to 13) for patients with the combination of comedo plus nuclear grade 3 features; the median interval to local recurrence was 6.5 years (mean, 7.0; range, 1.9 to 16.8) for patients without this combination (81).

The similarity in local recurrence between high-grade and low/intermediate-grade DCIS was also found with later follow-up in the ECOG study, where 10-year IBTR rates were 19.0% and 14.6%, respectively (91). Taken together, these data suggest that high nuclear grade lesions have a higher rate of local recurrence initially, but with longer follow-up, the low-grade lesions eventually "catch up" to the rate of IBTR seen in the high-grade group, suggesting that the recurrences of low-grade DCIS are ultimately of similar frequency but are slower to manifest themselves.

Size of the DCIS lesion has been associated with a greater risk of in-breast recurrence in some series (87,89,90) but not in others (146). In a study from MDACC, the 5-year recurrence risk of 5.6% was seen for lesions ≥ 1.5 cm versus 2.2% for those under 1.5 cm in size, a difference that persisted on multivariate analysis (p = .013) (87).

Biomarkers

For women undergoing lumpectomy for DCIS, the ability to consistently stratify patients, using known clinical and histologic features to differentiate those whose risk of recurrence in the breast warrants adjuvant therapies, has remained elusive. The development of biomarkers may help better discriminate which patients' prognoses following lumpectomy warrant adjuvant radiotherapy and/or tamoxifen, and help prevent both under- and overtreatment that exists currently.

The utility of biomarkers in DCIS management has already been shown in the case of ER and PR receptors. In the NSABP B-24, only those DCIS cases with hormone receptor-positivity derived the benefit of reduced breast cancer events from tamoxifen use (62). A small study from the University of Toronto performed immunohistochemistry (IHC) staining for nine markers: ER, PR, Ki-67, p53, p21, cyclinD1, HER2/neu, calgranulin, and psoriasin on the specimens of 213 patients with DCIS treated with either lumpectomy alone (n = 141) or with breast radiotherapy (n = 72) (66). The rate of recurrence at 10 years (median follow-up, 7.7–8.7 years) was 36% for patients treated with lumpectomy alone and 18% for women who received adjuvant breast radiotherapy. HER2/neu overexpression was the only molecular marker associated with an increased risk of any local recurrence on univariate analysis (HR, 2.11; 95% CI, 1.21–3.68; p = .01). Ki-67 did not predict for local recurrence on univariate analysis; however, after adjustment for age and use of RT, individuals with HER2 positive/Ki-67 positive DCIS had a higher likelihood of developing local recurrence at 10 years: 39% (20/51) versus 18.5% (30/162) for cases without this profile (p = .0024) (66). Similarly, in the SEER/San Francisco Bay Area cohort of 1,162 DCIS cases treated with lumpectomy alone, IHC for ER, PR, Ki-67 antigen, p53, p16, epidermal growth factor receptor-2 (ERBB2, HER2/neu oncoprotein), and cyclooxygenase-2 (COX-2) was done. In a multivariable model, DCIS lesions that were p16 positive, COX-2 positive, Ki-67 positive or those detected by palpation were significantly more likely to develop subsequent ipsilateral invasive cancer recurrence (92).

Gene expression has been correlated with DCIS prognosis post lumpectomy and represents an important area of future investigation. ECOG investigators presented a "DCIS Score" subset of the 21 Gene Oncotype DX Recurrence Score for hormone receptor-invasive cancer. The DCIS Score, consisting of 12 genes, was able to stratify cases by risk of ipsilateral invasive recurrence on a subset of 327 cases or 49% of those enrolled in the ECOG 5194 single-arm observation post lumpectomy trial (91). Similarly, loss of retinoblastoma (RB) and phosphate and tensin homolog (PTEN) suppressor genes was strongly associated with ipsilateral invasive breast cancer recurrence in 236 patients with DCIS treated with lumpectomy alone (93).

There are numerous areas of promising investigation toward biomarker development for DCIS; however, so far, hormone receptor status is the only one validated for clinical practice.

Treatment Era

Variability in the outcome of DCIS can be seen by era of treatment, with improvement noted for those patients treated more recently. An analysis of a SEER database of 7,072 women at least 40 years of age with DCIS who were treated from 1978 to 1989 and had an 8.25-year median follow-up, revealed that among those diagnosed from 1978–1983, 1.5% died of breast cancer within 5 years and 3.4% within 10 years. In comparison, women diagnosed from 1984–1989 were less likely to die of breast cancer: 0.7% and 1.9% within 5 and 10 years, respectively (94). Results were similar for women 40 to 49 years of age, and those 50 years of age and older. Using a Cox proportional hazard model adjusted for age and race, the relative risk of death from breast cancer for women diagnosed with DCIS in the latter treatment era was 0.6 (95% CI, 0.4 to .0.8) compared with that for women diagnosed between 1978–1983. Women diagnosed from 1984 to 1989, but not those diagnosed earlier, were also less likely than women in the general population to die of all causes (10-year standardized mortality ratio, 0.8; 95% CI, 0.7–0.8).

The Cancer Research Network consortium of 14 health maintenance organizations demonstrated the effect of treatment era on ipsilateral breast recurrence in 2,995 women with DCIS treated between 1990 and 2001 (95). In this population, the treatment was lumpectomy alone in 42.5%, lumpectomy with breast radiotherapy in 42.4%, lumpectomy with tamoxifen in 4.4%, and lumpectomy with radiotherapy and tamoxifen in 11%. The 5-year risk of any breast cancer event (ipsilateral, contralateral, or regional/distant disease) decreased from 18.5% (95% CI, 13.6–23.5) for patients diagnosed in 1990–1991, to 11.0% (95% CI, 8.4–13.6) for patients diagnosed in 1998–1999. Among patients treated with lumpectomy alone (no radiotherapy or tamoxifen), the five-year risk of any second breast cancer was 20.8% (95% CI, 14.7–26.9) in 1990–1991, and 15.2% (95% CI, 10.0–20.4) in 1998–1999; and for the lumpectomy and radiotherapy cohort, it was 15.4% (95% CI, 6.1–24.7) and 11.2% (95% CI, 7.4–15.0), respectively, for the earlier and later time periods. Trends in the pathology features by treatment era were also seen. The proportion of patients with high nuclear-grade tumors decreased; in calendar years 1990–1991, 1995–1996, and 2000–2001, it was 46%, 28%, and 32%, respectively (p = .03). The proportion with involved surgical margins decreased over the years 1990–1991, 1995–1996, and 2000–2001 were 15%, 10%, and 0%, respectively (p = .03) (95). In a series from Memorial Sloan-Kettering Cancer Center, a multivariate analysis of 1,681 women treated from 1991 to 2006 with breast-conserving surgery, with or without radiation, showed that the time period of surgery was highly correlated with risk of IBTR, with the later years being associated with a 43% reduction in IBTR risk after controlling for 9 clinical, pathologic, and treatment factors (76). The observed improvements in outcomes over time are likely due to improvements in detection with mammographic screening, pathologic evaluation including discernment of margins for completeness of excision, and treatment.

ESTIMATING RISK OF LOCAL RECURRENCE

There are numerous factors associated with risk of local recurrence for a woman with DCIS undergoing breast conservation. The risk associated with a factor is generally expressed as a risk ratio, rather than as an absolute risk, making it difficult to estimate the absolute risk of local recurrence for an individual. Furthermore, because there are many factors that are associated with IBTR, it is difficult to combine several to arrive at an overall risk estimate for local recurrence for an individual patient. Therefore, there has been interest in combining them to allow such estimation. An individualized risk estimate can assist patients and clinicians in decision making regarding the various treatment options available.

Silverstein et al. (96) combined four factors into the Van Nuys Prognostic Index (VNPI). The risk factors included were high nuclear grade, narrow margins, necrosis, and larger size of lesion, based on the work of Lagios. Lagios had reported on 79 patients with mostly small (< 2.5 cm), mammographically detected DCIS treated by excision alone (72). Specimens were sequentially embedded in their entirety, with extent determined by three-dimensional reconstruction. The mean tumor size was 6.8 mm. After a mean follow-up of 135 months, the 15-year actuarial local recurrence rate was 22%. Silverstein developed the VNPI using retrospective data from 254 patients and was validated using Lagios's series of 79 patients (72). The populations were then combined for the published report, which showed no benefit for radiation in the low-risk subgroup, where the 8-year actuarial local failure rate was 3%, regardless of treatment with radiation (96).

A potential source of bias in the VNPI is that it was applied to the same population of patients in whom it was derived. Furthermore, these patients were treated over a long period of time, from 1972 to 1995, and those treated before 1989 generally received radiation, while those treated after 1989 generally did not receive radiation (86). As discussed above, IBTR rates are generally higher in earlier years as compared to later treatment eras, raising the possibility that other factors played a role in the low rate of recurrence seen in patients without radiation (97,98). In addition, the applicability of the classification system depends on the reproducibility of the individual components. Because the tissue processing performed by Silverstein et al. is not routinely used, comparable DCIS size and margin width measurements are not generally available.

Application of the VNPI to independent populations has validated its ability to separate patients into risk groups, but has not confirmed the finding that among the lowest risk group, the incidence of IBTR is extremely low (2% in Silverstein's report) (96,99).

The VNPI has subsequently been modified to include patient age (100). In a retrospective analysis of 538 patients treated with breast-conserving therapy, those with the lowest VNPI scores were not found to benefit from breast irradiation (100).

Silverstein et al. (82) has also suggested that any DCIS lesion, regardless of size or grade, that could be excised with a margin of 1 cm in all directions did not require RT or tamoxifen. This approach eliminates the problems of consistent size measurement and histologic grade that are inherent in the VNPI. In a retrospective review of 469 patients, Silverstein et al. (82) found no statistically significant decrease in 8-year local failure with the use of RT in patients whose tumors were excised to a margin width of 10 mm or greater (4% with RT, 3% without RT, $p = .92$).

Updated results of widely excised DCIS (>1 cm margins) are available from Macdonald et al. (74). Among 212 patients treated with excision alone, the 12-year probability of any breast recurrence was 14%, and the 12-year probability of an invasive recurrence was 3.4%. Among the 60 patients treated with excision and RT, there was only one recurrence (12-year local recurrence = 2.5%), and it was an invasive recurrence.

Boland et al. (101) applied the original VNPI (96) to a population of 237 patients who had undergone breast conservation with a median follow-up of 47 months. Sixteen percent received RT. They found that the VNPI stratified patients into low, intermediate, and high risk for IBTR ($p < .001$), but that the practical application of the VNPI was limited by the fact that most patients (78%) were categorized as intermediate risk. MacAusland et al. (102) retrospectively analyzed 222 patients treated with excision alone using the original VNPI classification (96), the age modified VNPI (100), and margin width of 1 cm or greater (82). With a median follow-up of 4.6 years, the crude rate of IBTR was 8.6%. At 5 years, IBTR rates were not statistically different for the low-, intermediate-, or high-risk groups using any of the three Van Nuys models. However, Di Saverio et al. (103) retrospectively applied the age-modified VNPI to 259 patients with a mean follow-up of 130 months, treated from 1976 to 2006. Most did not receive RT. Among the 186 patients who underwent surgery alone, the 10-year risk of local recurrence was lower for those with low VNPI (6%) as compared to those with intermediate or high VNPI (17%; $p < .05$).

In summary, the VNPI provides a method of risk stratification for women with DCIS treated with breast-conserving surgery. However, others have not been able to validate its ability to identify a subgroup at extremely low risk of IBTR who do not benefit from RT.

In an attempt to better provide individualized risk estimates for women with DCIS, Rudloff et al. (76) combined 10 clinical, pathologic, and treatment factors from 1,681 patients into a nomogram that estimates risk of IBTR at 5 and 10 years after breast-conserving surgery. Median follow-up was 5.6 years, with 294 women followed for at least 10 years. Internal validation with bootstrap resampling was performed (C-index, 0.704; bootstrap validated, 0.688). The model separated the population into octiles of 10-year local recurrence risk ranging from ~5% to ~35%. The model is available as an online tool, where the user can enter the values of all variables, and the result is given as a probability of local recurrence at 5 or 10 years. (http://nomograms.mskcc.org/Breast/DuctalCarcinomaInSituRecurrencePage.aspx)

Yi et al. applied this nomogram to an independent population of 734 women with median follow-up of 7.1 years, with 206 women followed for at least 10 years (104). They also divided their smaller population into octiles of risk and found that the observed 10-year local recurrence rates were well-approximated by the nomogram risk estimates. Discrimination, as assessed by the C-index, was 0.654. Using a case-control analysis, Collins et al. reported that application of the nomogram to their large population-based cohort of DCIS resulted in highly accurate prediction of 5-year risk (105). Recently, Sweldens et al. applied the DCIS nomogram to a Belgian population of 467 women with a median follow-up of 7.2 years. Nearly all received radiation. Calibration was accurate, and the C-index was 0.67 for cases with complete data (106). Together, these studies show that the DCIS nomogram can risk stratify for local recurrence of DCIS in diverse patient populations.

Many investigators have sought molecular markers that would allow risk stratification for DCIS, both for local recurrence and for prediction of progression to invasion. Recently, Solin et al. reported the development of a multi-gene assay that estimates 10-year risk of local recurrence after excision alone (91). This assay was applied to 327 patients with DCIS treated with excision alone from the ECOG E5194 study (46), and it was able to stratify women into three 10-year local

recurrence risk groups: low (12%; 95% CI, 8–18%), intermediate (25%; 95% CI, 14–41%) and high risk (27%; 95% CI, 15–46%). Unfortunately, this assay was unable to identify a group of women with very low (< 9%) risk of IBTR, even within this especially favorable population, and the risk of IBTR was virtually identical between the intermediate- and high-risk groups. Furthermore, there is no evidence to date that this assay is predictive of benefit from RT; i.e., that it is able to identify those who would or would not benefit from use of RT.

These methods of risk estimation hold promise in assisting patients in the decision making regarding various treatment options for DCIS. Prediction of invasive recurrence and development of a molecular marker predictive of benefit from radiation remain future goals of the research community.

TREATMENT SELECTION IN DUCTAL CARCINOMA *IN SITU*

The available information on DCIS suggests that many are candidates for treatment with excision and irradiation, and a smaller group may be appropriately treated with excision alone. Mastectomy is indicated for extensive DCIS not amenable to a conservative approach. The initial step in treatment selection is to determine, on the basis of the history and physical examination, imaging, and pathologic findings, whether the patient is a candidate for a breast-conserving approach. If so, the risks and benefits, and what is entailed in breast-conserving surgery with or without radiation as well as mastectomy (including reconstruction), should be described in detail. The risk of local recurrence, particularly an invasive recurrence, is a major focus of this discussion because regardless of the type of local therapy selected, the risk of breast cancer–specific mortality is extremely low. Guidelines for the selection of local therapy in DCIS have been developed by a joint committee of the American College of Surgeons, American College of Radiology, and the College of American Pathologists (107).

Absolute indications for mastectomy include multicentric DCIS or diffuse, malignant-appearing microcalcifications covering an area too large to encompass with a cosmetic resection. The persistence of tumor at resection margins after a reasonable number of surgical attempts is also an indication for mastectomy. Although DCIS lesions are generally not clinically detectable, they may be quite extensive.

Most patients who require mastectomy can be identified before surgery with a careful imaging evaluation to determine the extent of the lesion. Holland et al. (108) have reported that the extent of poorly differentiated DCIS assessed by microscopy correlated well with the extent of the lesion evaluated radiologically, but the mammographic appearance of well-differentiated DCIS substantially underestimated the microscopic extent. However, the routine use of magnification views as part of the mammographic evaluation allowed the detection of additional calcifications that reduced the discrepancy between the pathologically and mammographically determined extent of well-differentiated DCIS.

While magnetic resonance imaging (MRI) has been increasingly used in the patient with DCIS, its benefit has yet to be defined. While some studies have found that MRI is more sensitive in the detection of DCIS than is mammography (19,20), improved outcomes have not been demonstrated, and increases in additional biopsies and mastectomy rates have been found in retrospective studies (109–111).

A retrospective study evaluated preoperative MRI in 352 women whose DCIS was diagnosed by core needle biopsy from 2008 to 2010 (109). All cases had preoperative mammogram, and 217 underwent MRI. Women who underwent MRI were younger, and more likely to be pre/perimenopausal, have dense breasts, present with a clinical abnormality, have microinvasion or suspicion for microinvasion on core biopsy, and undergo sentinel lymph node biopsy. The rate of additional biopsy was significantly higher in the MRI group; 38.3% underwent a second biopsy, and 18% underwent three or more additional biopsies, compared with 6.7% and 2.2%, respectively ($p < .0001$), in the mammography group. Overall, mastectomy was more common in the MRI group (37%) as compared to the mammography group (28%) ($p = .06$). No multivariate analysis was reported, and interpretation of retrospective studies such as this are limited by the inherent differences in the MRI and no-MRI groups. Other retrospective studies that suffer from the same potential confounding have also reported higher mastectomy rates for DCIS when preoperative MRI was used (110,111). In contrast to these studies, Allen et al. retrospectively examined 98 patients with DCIS, 63 of whom underwent MRI after diagnosis with core needle biopsy (112). Patients in the MRI group had mastectomy rates similar to the patients in the no-MRI group (20.3% vs. 25.7%; $p = .62$).

Two prospective randomized studies of the addition of MRI to preoperative screening failed to show a decrease in re-excision rates in women with DCIS and invasive carcinoma (113,114). In the COMICE trial, the re-excision rate of 19% was identical with or without MRI (113). In the MONET trial, the re-excision rate in the preoperative MRI arm was 34%, paradoxically higher than that in the control arm (114). Of the 23 additional surgeries required in the MRI group, most (n = 14) were in patients with DCIS. This suggests that especially among women with DCIS, MRI underestimated extent of disease.

Most importantly, there is no evidence of decreased recurrence rates in patients undergoing breast-conserving therapy and perioperative MRI. In a retrospective study of the utility of MRI, 136 women with DCIS were treated with breast-conserving surgery and RT, and the incidence of local recurrence was compared (115). In the subset of 31 women with DCIS who had an MRI, the 8-year incidence of local recurrence was 6%, identical to that of the 105 women with DCIS who did not undergo MRI. Pilewskie et al. (116) examined the association of MRI with local recurrence in a population of 2,255 women with DCIS treated with breast-conserving surgery with or without RT. On multivariate analysis controlling for 8 clinical and pathologic characteristics, the use of MRI did not affect the rate of IBTR at 8 years ($p = .48$), even in the subset that did not receive RT ($p = .32$). Therefore, at present, MRI cannot be considered part of the routine preoperative evaluation of the woman with DCIS.

Radiologic localization should be used to guide the surgical excision; if the calcifications are extensive, bracketing is useful to aid in complete excision. Specimen mammography is essential to confirm the excision of calcifications. Postexcision mammogram is useful to document the removal of all suspicious calcifications. Even when the margins of excision are negative, postexcision mammography can demonstrate residual calcifications indicative of the need for further resection. In most patients, a postexcision mammogram can be obtained within 2 to 4 weeks after surgery.

For the woman who appears to have mammographically localized DCIS and is a candidate for breast conservation, a decision regarding the magnitude of benefit that will be obtained from RT cannot be made until the lesion has been excised and a pathology report is available. To facilitate decision making, a detailed pathologic evaluation is necessary. The evaluation should include inking of the specimen and measurement of both specimen and tumor size (if there is a gross lesion) before sectioning. Because accurate measurement of microscopic DCIS is often difficult, reporting the

number of blocks in which DCIS is present and the number of blocks examined, as well as its largest single extent in any one slide, is often useful. The correlation of microcalcifications with DCIS (i.e., whether calcifications are present in the DCIS or in adjacent breast tissue) as well as the margin status should be noted. If margins are involved, the extent of involvement should be stated; when margins are negative, proximity of the lesion to the margin should be noted. The nomogram discussed previously is available online to easily calculate individualized risk estimates to assist in decision making (76).

The authors approach patients before surgery with the assumption that breast irradiation will be a part of their treatment if they choose breast-conserving therapy. Contraindications to RT, as for invasive cancer, include prior therapeutic irradiation to the ipsilateral breast, diagnosis early in pregnancy, and active scleroderma or systemic lupus erythematous. Large areas of DCIS that cannot be excised to clearly negative margins with an acceptable cosmetic outcome should prompt a discussion of mastectomy. An adequate excision is of particular concern in patients younger than 40 years of age with high-grade, ER negative DCIS because of their higher baseline risk of recurrence. In patients who are candidates for breast irradiation, the final decision about the risks and benefits of RT and tamoxifen in an individual case is made when the final pathology report is available. Although it is clear that there are some patients who receive a small absolute benefit from either irradiation or tamoxifen, the final decision regarding the use of RT and tamoxifen is heavily influenced by the patient's perception of what level of benefit is meaningful to her. The ability to treat local recurrence with further breast preservation using re-excision and RT is one of the potential benefits of initial treatment with excision alone. However, local recurrence is psychologically traumatic, and only 44% of patients who had recurrence after initial treatment by excision alone in the NSABP B-17 trial chose breast-conserving surgery again (39). Furthermore, approximately 50% of recurrences are invasive and carry a risk of distant metastasis (2). To date, no clinical or molecular characteristics have been identified that reliably predict a minimal benefit from RT.

The use of sentinel node biopsy is reserved for patients undergoing mastectomy. If a pre-surgical diagnosis of DCIS is made by percutaneous core needle biopsy, invasive carcinoma is found in approximately 20% of cases at the time of surgical excision (117). Invasion is more frequent in large areas of DCIS, and the performance of a mastectomy precludes subsequent sentinel node biopsy. In patients undergoing breast conservation, sentinel node biopsy can be selectively applied to the subset of women found to have invasive carcinoma after surgical excision.

In summary, the term DCIS encompasses a heterogeneous group of lesions of varying malignant potential. In the future, advances in research may allow researchers to reliably identify those lesions that have the propensity to recur locally as invasive cancer and those that will display the metastatic phenotype. Until this goal is reached, therapy must be directed toward minimizing the risk of local recurrence while maintaining quality of life. The appropriate therapeutic strategy will vary based on both patient and disease characteristics, as well as patient preferences.

MICROINVASIVE BREAST CANCER

The widespread adoption of breast cancer screening with mammogram has increased the detection rate of microinvasive breast cancer as well as DCIS. Microinvasive breast carcinoma is defined as invasive carcinoma of the breast with no single invasive focus (multiple foci may be present) measuring more than 1 mm (118). It is almost always encountered in the setting of ductal carcinoma *in situ* (DCIS); and much less commonly with LCIS. A frequently encountered problem in examination of histological specimens is identifying a small focus or foci of invasive carcinoma, or microinvasion (119). Microinvasion can be overdiagnosed because of misinterpretation of the pattern of DCIS or the presence of artifacts. Examples of pathology entities that can make interpreting microinvasion challenging include: DCIS involving lobules (lobular cancerization) or benign complex sclerosing lesions, such as a radial scar; associated chronic inflammatory reaction that obscures involved ducts and acini; branching of ducts; fibrosis from prior needle biopsy distorting ducts; crush artifacts; and cautery effects (119). Similarly, microinvasion can be underdiagnosed as a result of tissue sampling.

The presence of myoepithelial cells around nests of carcinoma cells defines the process as being *in situ*. IHC for myoepithelial cells has been used to help determine whether a process represents *in situ* carcinoma or stromal invasion. A variety of markers have been used to detect myoepithelial cells; the most commonly used antibodies are smooth-muscle myosin heavy chain (SMM-HC) and calponin. Optimal specificity and sensitivity for detection of myoepithelial cells can be achieved when the SMM-HC marker is used in conjunction with the more sensitive but less specific marker, calponin (120). Serial sectioning of the specimen supported by IHC staining for the presence of myoepithelial cells provides the best method for diagnosis of microinvasion.

Different definitions of microinvasion have existed in the past contributing to inconsistent reporting of its incidence. The diagnostic dilemma that arises from an inconsistent definition of microinvasion is illustrated in the study by

TABLE 23-11

Incidence of Sentinel Lymph Node Involvement in Patients with Microinvasion

			Number (Percentage) of Patients			
First Author	*Year*	*N*	*Any Involvement*	*Macro-metastasis (>2 mm)*	*Micro-metastasis (>0.2 mm, <2 mm)*	*Isolated Tumor Cells (<0.2 mm)*
Veronesi (140)	2007	129	16 (12%)	3 (2%)	5 (4%)	8 (6%)
Gray (141)	2007	77	6 (8%)	2 (3%)	2 (3%)	2 (3%)
Pimiento (142)	2011	87	9 (10%)	4 (5%)	2 (2%)	3 (3%)
Ko (143)	2012	293	22 (8%)	4 (1%)	12 (4%)	6 (2%)
Lyons (144)	2012	112	14 (13%)	3 (3%)	5 (4%)	6 (5%)
Margalit (126)	2012	68	7 (10%)	0	3 (4.4%)	4 (6%)

TABLE 23-12

Treatment Outcomes of Microinvasive Breast Cancer

First author	*Year*	*N*	*Median Follow-up (Years)*	*Breast Conservation (%)*	*Local Recurrence n (%)*[a]	*Distant metastasis n (%)*[a]	*Survival (%)*
Lyons (144)	2012	112	6.0	54%	5 (4.5%)	0	100%
Margalit (126)	2012	83	6.4	63%	6 (7.2%)	2(2.4%)	100%
Parikh (127)	2012	72	8.9	100%	6 (8.3%)	2 (2.7%)	95.7%
Kwon (128)	2010	120	5.0	53%	3 (2.5%)	1 (1.8%)	—
Sanchez-Munoz (145)	2010	49	5.0	74%	2 (4.0%)	1 (2%)	98%
Vieira (125)	2010	21	3.0	67%	0	0	100%
Colleoni (124)	2004	24	3.6	58%	0	0	100%

[a]Event n divided by population n

Padmore et al. of 59 cases of microinvasion diagnosed from 1982 to 1992 at Fox Chase Cancer Center that underwent secondary pathology review. On re-review, the microinvasion was reclassified as pure DCIS in 16 cases, equivocal microinvasion in 7, microinvasive in 11, and T1a-c (i.e., invasive cancer > 1 mm in size) in 25. The fifth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, published in 1997, is the first one that recognized a specific T category for microinvasive breast cancer, defined as "the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension" and formally classified it as pT1mic. With this definition, the estimated overall incidence is less than 1% (119,121,122). Microinvasion has been noted to be more frequently associated with DCIS that is more than 2.1 to 2.5 cm in size (122,123), or high grade (123–125), and with the presence of comedo necrosis (123,126). The likelihood of hormone receptor positivity and HER2 overexpression is mostly unknown for microinvasive breast cancer, as the information is often incomplete in the studies reporting and/or there was insufficient material for analysis (126,127,144). However, a higher frequency of HER2 overexpression in microinvasive breast cancer has been reported in one study (128).

As illustrated in Table 23-11, the rate of sentinel node involvement can be as high as 13% for cases with microinvasion on core biopsy. However, the rate of macrometastases is low in this population: 0% to 5%. Micrometastases and isolated tumor cells (ITC) are found with similar frequency. When microinvasion is present with DCIS on core biopsy, there is a general agreement that due to the significant rate of sentinel node findings and the absence of final histologic analysis from complete surgical resection, that sentinel lymph node biopsy is a recommended procedure.

The favorable prognosis of microinvasive breast cancer as defined by the AJCC is seen in Table 23-12. In these studies, at 3 to 9 years median follow-up after treatment, there were 0% to 8.3% local recurrences, 0% to 2.7% distant metastases, and 95.7% to 100% overall survival. For patients treated with breast-conservation therapy, cumulative incidences of local recurrence at 5 and 10 years of 4.2% and 8.3%, respectively, have been reported (126,127). Margalit et al. from the Harvard Oncology program reported that close/positive DCIS margins (compared to negative margins) with both breast-conserving therapy and mastectomy were significantly associated with an increased risk of local recurrence (hazard ratio [HR], 8.8; 95% CI, 1.6–48.8; $p = .003$) (126). Yale University investigators retrospectively compared the outcome in 373 DCIS to 72 microinvasive cases treated during the same time period and found similar 10-year local recurrence rates: 6.8% with DCIS and 8.3% with microinvasion experienced a local relapse, for a 10-year local recurrence-free survival rate of 89.0% and 90.7%, respectively (127). Overall, this supports the belief that the prognosis for microinvasive breast cancer is intermediate—better than that of small invasive breast cancer and approaching what is seen with DCIS.

MANAGEMENT SUMMARY

- DCIS is a heterogeneous disease with varying potential for progression to invasive cancer.
- Pathologic or molecular factors that reliably predict for an individual woman's risk of progression to invasive cancer after excision of DCIS have not been identified.
- Appropriate treatment options for DCIS are primarily determined by the extent of disease in the breast relative to the size of the breast.
- A detailed mammographic evaluation of the extent of DCIS is essential for treatment planning. The role of MRI is uncertain.
- Total mastectomy results in excellent local control with local failures of approximately 1% to 2% and breast cancer-specific survival of ≥ 98% for patients with DCIS.
- Patients with localized DCIS are candidates for treatment with excision.
- RT reduces the rate of local recurrence by approximately 50%. Subsets of DCIS patients for whom RT does not reduce the local recurrence rate have not been reproducibly identified.
- Excision and RT in suitable candidates results in 10-year local failure rates of 7% to 13% when treated in the more modern screening era with careful mammographic and pathologic evaluation.

- In highly selected patients with favorable or lower-risk features, excision alone for DCIS results in local recurrence rates of 10% to 15% at 7 to 8 years, which may be an acceptable outcome to a patient depending on her individual and clinical circumstances.
- Breast cancer-specific survival after excision with or without RT is ≥ 96%, numerically similar to what is reported from mastectomy series.
- Negative margins are associated with a lower risk of local recurrence than positive margins (ink on DCIS). "Close" margins have been variably defined, but are associated with higher risk of local recurrence than "negative" margins on meta-analysis. For women undergoing RT, evidence is lacking to show a lower local recurrence rate is associated with margin widths larger than 2 mm. However, a specific margin width that optimizes local control for those who do or do not receive RT has not been identified.
- Local recurrence rates after excision with or without RT have decreased over time, probably due to improvements in imaging and pathologic analysis.
- Patients should be included in the treatment decision making to learn what magnitude of risk reduction is meaningful to them; particularly for DCIS with clinical and pathologic features associated with a small absolute benefit from adjuvant radiotherapy or tamoxifen postexcision.
- Biomarkers, in addition to hormone receptors, for both prognosis and prediction of adjuvant treatment response are under investigation, but none are yet ready for routine clinical use.
- Tamoxifen benefits ER positive DCIS. The combination of tamoxifen and RT maximizes local control in ER positive DCIS post lumpectomy and reduces the number of new contralateral breast cancers.
- Sentinel lymph node biopsy is not routinely indicated in DCIS. In women undergoing mastectomy for extensive DCIS, a sentinel lymph node biopsy obviates the need for axillary dissection if invasion is found and is recommended.
- Nodal metastases are present in 4% to 7% of patients with microinvasive carcinoma, and sentinel lymph node biopsy is indicated when the results will influence subsequent treatment.
- A detailed discussion of the pros and cons of the various treatment options is needed to allow each woman with DCIS to make an informed treatment choice.

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SECTION VI

Pathology and Biological Markers of Invasive Breast Cancer

CHAPTER 24

Genomic Events in Breast Cancer Progression

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Cynthia X. Ma, and Matthew J. Ellis

CHAPTER CONTENTS

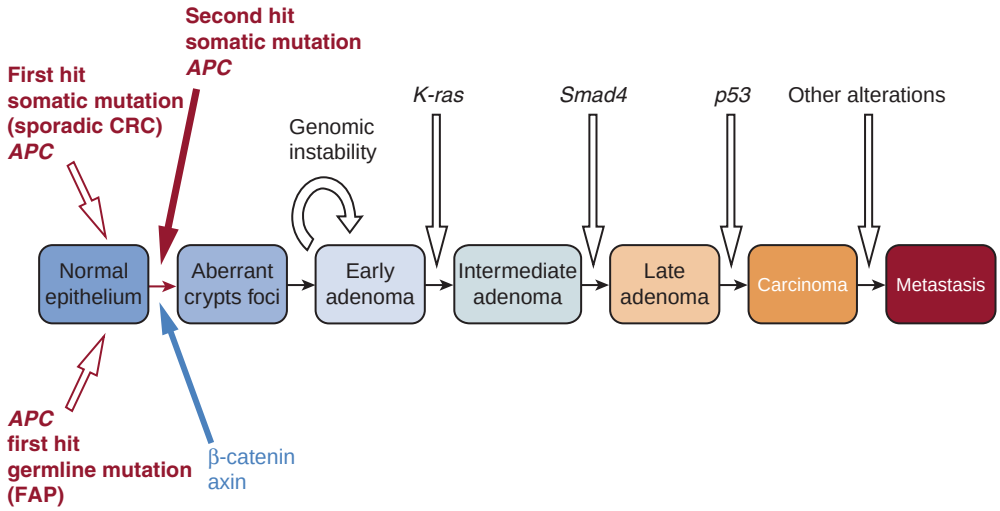
INTRODUCTION

Breast cancers are thought usually to develop from regions of cellular atypia into clinically evident preinvasive or invasive lesions with subsequent evolution of lethal features such as metastatic spead and therapeutic resistance. Biological and statistical models that guide our thinking about breast cancer genomic progression events that underlie this process include linear, stepwise models, such as those proposed by Vogelstein and coworkers for colon cancer (Fig. 24-1A) and branched, Darwinian evolutionary models, such as that proposed by Nowell, where there is no fixed order of events or steps (Fig. 24-1B) (1,2). The recent application of next-generation sequencing technology has uncovered immense genomic complexity but has mostly focused on a single time point—the breast cancer genome at diagnosis. Longitudinal studies of individual cancer genomes over time will ultimately be required to completely characterize the genomics of breast cancer progression and are now possible as massively parallel sequencing platforms become more accessible. In this chapter, we will describe the theoretical basis for breast cancer evolution, from the earliest stages to advanced disease. We will review what is known about the dynamic structural changes in the genome that underlie the disease.

NEXT-GENERATION DNA SEQUENCING

The revolution in DNA sequencing technology, with the development of next-generation sequencing instruments, has provided a wealth of new data on the genomic evolution of cancer, and it is worthwhile beginning our discussion with an overview of this technology as many of the discussions in this chapter rely on data derived from these "massively parallel sequencing" (MPS) approaches. The development and commercialization of next-generation DNA sequencing instruments began around 2006 and has made DNA sequencing thousands of times faster and considerably cheaper. With this technological advance, projects to sequence large numbers of cancer genomes became feasible. Here, we will mostly focus on an MPS process called "sequencing-by-synthesis," as most data sets have used Illumina-based technology. The steps in this process involve generating a DNA library from the sample of interest (Fig. 24-2A) and attaching individual DNA molecules to a glass slide called a flow cell. The individual sequences are then amplified into "clusters" to increase signal intensity (Fig. 24-2B). A sequencing reaction is then performed whereby a different colored fluorophor is activated when each of the four different nucleotides are added to the DNA polymer (Fig. 24-2C) (3,4). These sequential light reactions are captured by a sensitive light detector and the sequences entered into programs that align the sequences to the reference human genome. The process is remarkably efficient, and sequencing throughput is advancing rapidly. Currently more than 100 billion base pairs (Gigabases, Gb) can be generated per instrument run. Other methodologies and companies for next-generation DNA sequencing include the SOLiD system developed by Applied Biosystems, and single-molecule DNA sequencers, which are still under development (3).

A key advantage of the MPS approach is that the analysis begins with an individual DNA molecule. This is fundamentally different than the original Sanger DNA sequencing method, developed over 35 years ago, which averages sequences across millions of DNA molecules and, as a



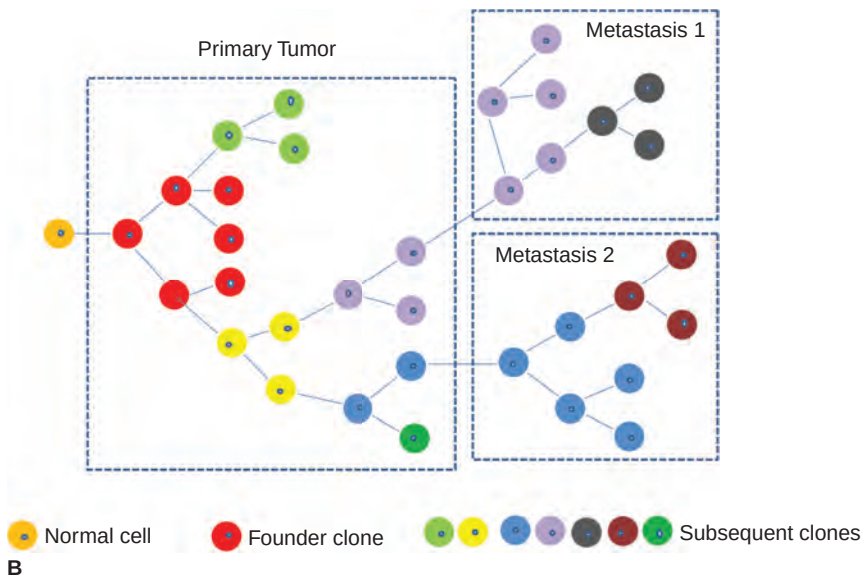


FIGURE 24-1 **(A)** The development of cancer through sequential steps. This model proposes that colon cancers develop from aberrant foci (atypia) and adenomas in a stepwise process. (From Pinto D, Clevers H. Wnt, stem cells and cancer in the intestine. *Biol Cell* 2005;97:185–196.) **(B)** Evolutionary models of cancer with the development of subclones.

result, has limited ability to distinguish variations in DNA sequences. Because MPS provides data on the frequency of a DNA mutation within a population, tumor clonality or heterogenity can be inferred from the variant allele frequency, and this provides new means for studying the clonal progression of cancer. Rare alleles can be detected down to a frequency of between 0.1% and 1% depending on the depth of the sequencing instrument and the fidelity of the enzymes used to generate the original clusters on the flow cell.

Much of the sequencing funded by the National Cancer Institute has focused on the initial diagnostic sample from invasive cancers through The Cancer Genome Atlas Project, with the goal to catalogue all the somatic mutations and structual abnoramlities in breast cancer (5). The application of this approach in the study of breast cancer is still in its infancy. Our current understanding of the genomic alterations that promote preinvasive to invasive breast cancer is still largely based on comparative genomic hybridization (CGH) techniques, loss of heterozygosity (LOH) analysis, gene expression profiling, and selective gene sequencing studies that have been applied to synchronous preinvasive and invasive breast cancers.

GENOMIC MODELS OF BREAST CANCER PROGRESSION

To understand breast cancer progression, a description of the anatomy of the breast and the histology of preinvasive versus invasive breast cancer is required; the reader is guided to Chapters 1, 9, 21, and 25 which deal with these issues in depth. In brief, several models have been proposed to describe the development of breast cancer that focus on the relationship between preinvasive and invasive breast cancers. The most

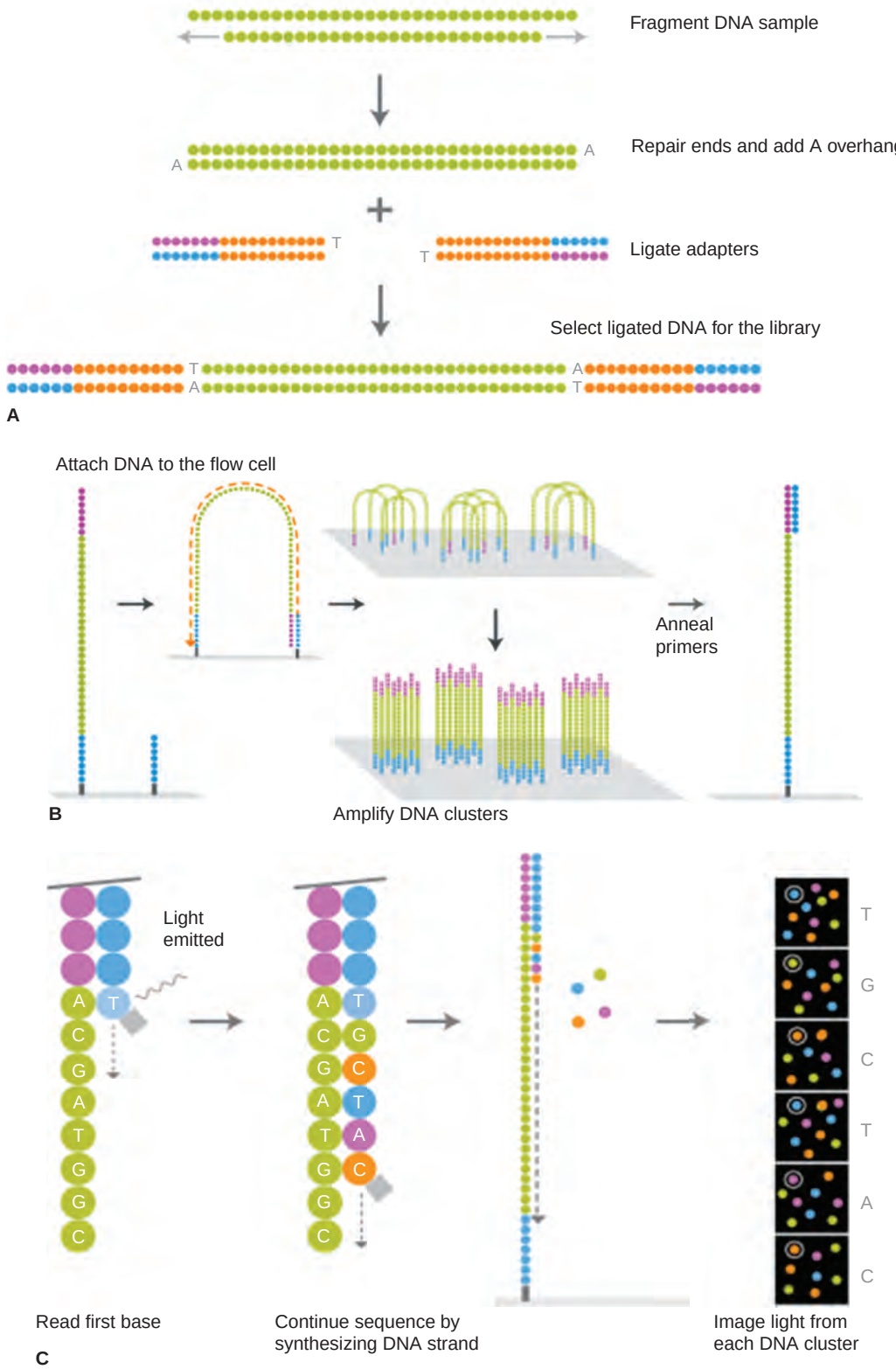


FIGURE 24-2 Next-generation DNA sequencing on the Illumina sequencing instruments. **(A)** DNA Sample preparation to create the library for sequencing. **(B)** Attaching the DNA to the surface of the flow cell and generating clusters of identical DNA molecules for sequencing. **(C)** Sequencing by synthesis. Each round attaches a DNA nucleotide to the DNA molecule and releases light, which is detected by a very sensitive camera. (From Ansourge WJ. Next-generation DNA sequencing techniques. *New Biotechnol* 2009;25(4):195–203.)

widely accepted "linear" multistep model suggests a transition from normal epithelium to invasive breast cancer via non-atypical and atypical hyperplasia and *in situ* carcinoma through accumulation of genetic mutations (6). In this classic Wellings model, premalignant breast lesions arise from terminal ductal lobular units (TDLUs) and give rise to flat epithelial ayplasia (FEA), atypical ductal hyperplasia (ADH), and ductal carcinoma in situ (DCIS), which subsequently progresses, over a long period of time, to invasive ductal carcinoma (IDC), whereas atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) progress to invasive lobular cancer (ILC) (Fig. 24-3) (7). This theory was originally based on the histologic observation of the gradual histologic continuity, but it also has been supported by analyses of genetic alterations that compared preinvasive and invasive breast cancers, especially when they occur in the same breast (8–11). Subsequent findings introduced the concept of usual ductal hyperplasia (UDH), in which cells pile up to fill the terminal duct (TD) and acini compared to the single or minimally pseudostratified layer of cells in FEA that distends the TDLU, as the direct precursor to ADH (12,13). However, UDH as the precursor for ADH has not been supported by recent immunohistochemical and molecular evidence. The LOH pattern observed in UDH is notably different from that associated with ADH and DCIS (8,14–18). This linear model of breast cancer progression provided the rationale for detection methods such as mammography in the hope of diagnosing and treating breast cancer at earlier and preinvasive stages before lethal features of the disease have developed (19). However, the occurrence of a preinvasive lesion is probably not an obligatory event in the development of invasive breast cancer. Although many premalignant lesions progress through the lifespan of some

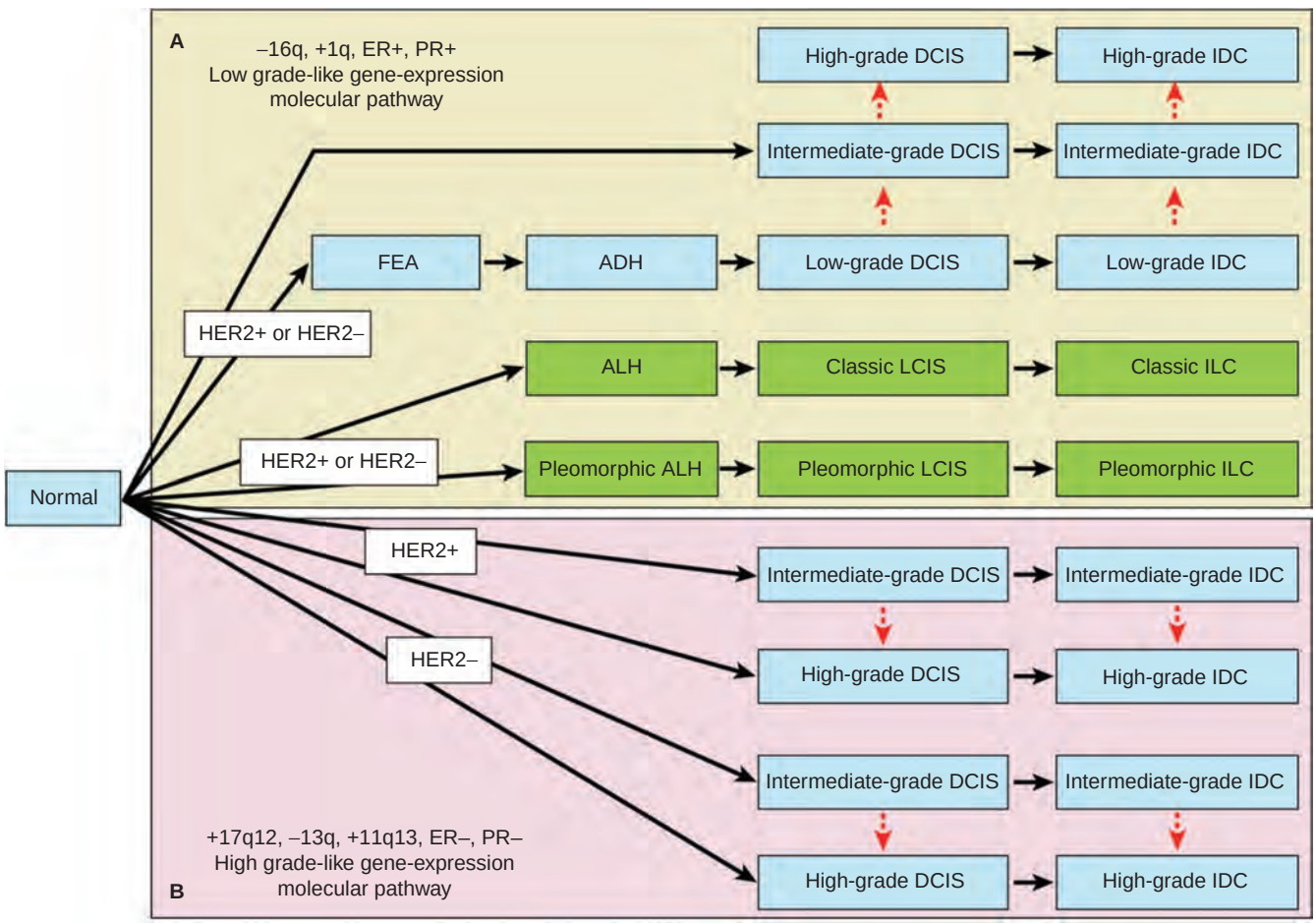


FIGURE 24-3 Multistep human breast cancer progression model. The low grade–like gene-expression molecular pathway is characterized by chromosome 16q loss, predominant ER and PR expression, and a low-grade gene expression profile populated with genes associated with ER positivity. **(A)** This low-grade pathway is observed in preinvasive lesions of both ductal and lobular subtype. **(B)** The high grade–like gene-expression molecular pathway is characterized by loss of chromosome 13q; gain of 11q13 and/or amplification of 17q12; infrequent expression of ER and PR; and a high-grade gene expression signature populated with genes associated with cell cycle, centrosomal function, and DNA repair. Pleomorphic atypical ductal hyperplasia (ALH), pleomorphic lobular carcinoma in situ (LCIS), and pleomorphic invasive lobular carcinoma (ILC) phenotypically resemble high-grade tumors, and immunohistochemical (ER positivity) and genetic data (16q loss and 1q gain) support an evolutionary association with the low grade–like gene expression molecular pathway. (From Sgroi DC. Preinvasive breast cancer. *Annu Rev Pathol* 2010;5:193–221.)

patients, others might stay stable throughout their lives; it remains unclear which lesions have the capacity to progress to invasive cancer. The "nonlinear" or "branched" model builds upon the "linear" model in that it agrees that DCIS is the precurser for IDC, but hypothesizes that different grades of DCIS progress to corresponding grades of IDC. In contrast, the "parallel" model hypothesizes that DCIS and IDC are parallel and independent developments from a common progenitor cell through different grades (20). This is supported by the investigation of gene copy number changes in synchronous DCIS and IDC lesions, which demonstrated changes that are specific to DCIS or IDC (21).

GENOMIC ALTERATIONS SUPPORTING PREINVASIVE LESIONS AS PRECURSORS OF INVASIVE BREAST CANCER

The molecular differences among the preinvasive and invasive breast cancers are largely unknown but have been an area of great research interest with the hope to identify the key events that drive the development and progression of invasive breast cancer. The pathological heterogeneity and the microscopic size of the preinvasive lesions have posed a practical challenge in isolating sufficient material that is devoid of contaminating tissues. The availability of laser capture microdissection (LCM) and genome-wide analysis tools provide a new opportunity to discover genetic events specifically activated or inactivated in the course of breast cancer development.

LOH and CGH Studies

Multiple studies indicate that genetic alterations that confer the potential for invasive growth already exist in the earliest phenotypically recognized preinvasive stages. Initial studies of the genetic evolution of breast cancer progression used relatively insensitive loss of heterozygosity (LOH)/comparative genomic hybridization (CGH) techniques (8,10,22,23). For example, O'Connell et al. studied 399 microdissected preinvasive lesions (211 UDH, 51 ADH, 81 noncomedo DCIS, and 56 comedo DCIS) for LOH at 15 polymorphic genetic loci known to exhibit high rates of loss in invasive breast cancer (IBC) and assessed the sharing of LOH between synchronous preinvasive and invasive cancers. For breast samples without DCIS and IBC, 37% of UDH and 42% of ADH lesions showed LOH in at least one locus, although loss at any given locus was uncommon (range, 0%–15%), suggesting that the development of hyperplasias can involve many different genes. In breast samples without IBC, LOH was common in DCIS, with 70% of noncomedo lesions and 79% of comedo lesions showing at least one loss with up to 37% of samples harboring LOH on chromosomes 16q, 17p, and 17q. When DCIS lesions from breasts with or without IBC were compared, substantially more LOH was observed in the breast with IBC at a few loci (on chromosomes 2p, 11p, and 17q), suggesting that genetic alterations in these regions may be important in the progression of DCIS to invasive disease. Among specimens harvested from breasts with IBC, 37% of concurrent UDH, 45% of ADH, 77% of noncomedo DCIS, and 80% of comedo DCIS lesions shared LOH with synchronous cancers at one locus or more. Similarly, in another CGH study performed on a panel of breast tumors that included 10 DCIS, 18 IBC, and two lymph node metastasis, there was an overall trend toward an increase in the number of genetic gains and losses in the IBC (24). In a study of 41 cases of sporadic breast cancer that focused on LOH of chromosome 11q13, LOH on chromosome 11q13 was present in 24 of 36 (67%) of the informative invasive breast cancer cases. The identical allelic loss was shared in the microdissected DCIS and the corresponding invasive breast cancer in 71% (15 of 21) of the available cases (23). Moelans et al. analyzed 21 genes including transcription factors and thyrosine kinases in DCIS and adjacent IDC (25) and found that there were no copy number differences between them. These studies provided molecular genetic support for the notion that invasive breast cancer arises from preinvasive lesions and that DCIS is genetically as advanced as IDC and the driving genetic events already occurred at the preinvasive stage. This conclusion is thus somewhat paradoxical because DCIS is a benign disorder and invasive disease is not. We therefore still do not have a clear idea of the genomic determinants of the DCIS to invasive transition, which is a clear impetus for more detailed studies using MPS.

Expression Profiling

The molecular similarity between preinvasive lesions and invasive breast cancer has also been observed at the level of gene expression. Using LCM, T-7 based RNA amplification and DNA microarrays analysis, Ma et al. compared the gene expression profile of normal TDLU epithelium and synchronous ADH, DCIS, or IDC in a study of 36 breast cancer specimens (26). Compared to patient-matched normal epithelial cells, significant alterations in global gene expression occurred at ADH, which persisted in the later stages of DCIS and IDC. There were extensive similarities at the transcriptome level among the paired ADH, DCIS, and IDC without any consistent gene expression unique to each of the three identities. These observations were consistent with an earlier study of global gene expression profiles using serial analysis of gene expression (SAGE), although performed on a limited cohort of normal mammary epithelial cells, DCIS, IDC, and metastatic disease (27).

Similar to IBC, DCIS exhibits significant histologic and biological diversity between different cases. Under microarray gene expression analysis, intrinsic subtypes originally described for IBC have also been observed in DCIS (28–30). In a recent immunohistochemistry (IHC) analysis of a tissue microarray composed with 188 cases of pure DCIS (31), a frequency of 38.3% for Luminal A (ER+/PR+/HER2–), 6.9% Luminal B (ER+ and PR– and/or HER 2+), 14.9% HER2 (ER–/PR–/HER2+), 7.5% TN (ER–/PR–/HER2–) and 4.2% basal-like (ER–/PR–/HER2–/CK5/6 and/or EGFR+) was observed according to IHC criteria of intrinsic subtypes (32). These studies indicated that the molecular heterogeneity of IBC is reflected at the stage of DCIS, and DCIS may be classified in a manner similar to invasive breast cancer.

GENETIC ALTERATIONS INDICATING DISTINCT GENOMIC PATHWAYS ASSOCIATED WITH LOW- AND HIGH-GRADE BREAST CANCERS

In gene expression profiling studies of synchronous DCIS and IDC lesions, the greatest alterations were among the different histological grades of DCIS and IDC (26). Notably, the grade I and grade III tumors demonstrated reciprocal gene expression patterns, whereas grade II tumors exhibited a hybrid pattern of grade I and grade III signatures. ADH samples demonstrated a grade I gene expression signature and clustered with the low-grade DCIS and IDC. Similarly, several comparative genomic hybridization studies revealed that the low-grade and high-grade DCIS have distinct gains and losses of genetic material. In the CGH study by Buerger et al. on 38 DCIS and 6 associated invasive breast cancers,

TABLE 24-1

Chromosomal Aberrations of DCIS and IDC

Low-grade DCIS	Intermediate-grade DCIS	High-grade DCIS
16 q loss	1 q gain 11 q loss	8p,11q,13q,14q loss 1q,5p,8q,17q gain 17q12 and 11q13 amplification

Low-grade IDC	High-grade IDC
16 q loss 1q,16p,8q gain	8p,11q,13q,1p and 8q loss 1q,8q,17q,20q and 16p gain 17q12 and 11q13 amplification

Intermediate-grade DCIS lesions have common features with low- and high-grade IDC.

losses of 16q were exclusively seen in well- and intermediately-differentiated DCIS. A higher frequency of gains of 1q and losses of 11q was observed in intermediately-differentiated DCIS. The poorly-differentiated DCIS displayed complex genomic alterations, including loss of 8p, 11q, 13q, and 14q and gains of 1p, 8q, and 17q. This was characterized by a higher frequency of amplifications of 17q12 and 11q13. Analysis of paired IBC revealed a CGH pattern similar to the DCIS counterpart (33). This data provided further evidence that DCIS are precursor lesions of IBC, but progression from low- and high-grade DCIS to IBC are likely from different genetic pathways (34) (Table 24-1).

In addition, FEA and ADH has morphological overlap with low-grade carcinomas, and ADH is accepted as a precursor lesion for low-grade/noncomedo DCIS. Molecularly, FEA has a genetic profile that overlaps with those of synchronous low-grade DCIS and low-grade invasive carcinomas and has a high rate of LOH at 16q, supporting its precursor role in the evolution to low-grade cancers (11). In another study, FEA exhibited recurrent chromosomal copy number gains and losses (gains on 15p, 16p, and 19; losses on 16q, 17p, and X), which overlap with those observed in both ADH and low-grade DCIS (9).

However, the precursor lesion of high-grade/comedo DCIS is not clear. High-grade DCIS lesions are associated with more complex genetic alterations and overexpression of genes related to mitotic activity and cell cycle processes (35). In a comparison of copy number changes of 21 breast cancer–related genes between laser-microdissected DCIS and adjacent IDC lesions (25), no significant differences existed between DCIS and adjacent IDC. However, low/intermediate-grade DCIS showed on average 6 gains/amplifications versus 8 in high-grade DCIS. Furthermore, alterations of *AURKA* (aurora kinase A) and *CCNE1* (cyclin E1) were exclusively found in high-grade DCIS, and *HER2*, *PRDM14* (PR domain containing 14), and *EMSY* amplification was more frequent in high-grade DCIS than in low/intermediate-grade DCIS. These data indicate that DCIS is genetically as advanced as IBC and support a model in which different histological grades of DCIS are associated with distinct genomic changes that progress to IDC in different routes.

EVOLUTION FROM LOWER TO HIGHER GRADE LESIONS

The significant intratumoral histological and biological diversity within cases of DCIS argues for an evolution of DCIS from lower grade to higher grade (28). In an analysis of 120 consecutive cases of pure DCIS, 45.8% of cases showed areas of diversity in nuclear grades, including 30% with grades I and II, 6.6% with grades II and III, and 9.2% with grades I, II, and III. In addition, about one-third of the cases showing histologic diversity also showed biologic diversity for one or more biomarkers that included ER, GATA3, HER2, CK5/6, CK18, and p53 by immunohistochemistry staining. Similarly, in studies assessing the LOH, DCIS contained many of the same specific genetic defects regardless of histologic differentiation, although the absolute number of defects was found to be higher in higher grade lesions (8). Furthermore, a significant subset of genes expressed at higher levels in grade III DCIS compared to grade I DCIS were further elevated in IDC. In addition, the link between tumor grade and transition from DCIS to IDC is consistent with the clinical observation that grade III DCIS is more likely to be associated with occult invasive disease than grade I DCIS (36).

MOLECULAR MARKERS OF DCIS THAT PREDICT RECURRENCE AND INVASIVE PROGRESSION

The evolution of genetic events that drives the process of breast tumorigenesis is poorly understood. As demonstrated in previous studies, many genetic alterations present in the invasive breast cancer already exist in the earliest phenotypically identifiable lesions such as ADH. However, gene expression profiling, CGH, and candidate gene approach, which are the main technologies used in these studies, are limited in their capacity for detailed genomic interrogation. A comprehensive genomic sequencing study of synchronous preinvasive and invasive cancer in comparison to the normal breast epithelial cells is needed but has not been reported. In this section, we will focus on available data investigating molecular markers that may predict the prognosis of DCIS and potential candidate drivers in cancer progression.

Prognostic Markers

Low ER or PR expression or HER2 amplification is associated with higher grades of DCIS and recurrence (37–41). A molecular signature of lack of ER and PR, HER2 overexpression, accumulation of p53, and high Ki67 expression was proposed to predict recurrence (42). COX-2 and p16 have also been associated with progression or recurrence. In a retrospective study, DCIS lesions that were positive for p16, COX-2, and Ki67 expression were significantly associated with risk of subsequent invasive cancer, whereas DCIS lesions that either lacked ER but were positive for HER2 and Ki67 or that lacked COX2 but were positive for p16 and Ki67 were associated with recurrence of DCIS (43). However, with the exception of ER/PR, none of these molecular markers are routinely assessed in the clinic due to the lack of sufficient evidence or established interventions.

Several other molecular markers, including cell cycle regulation and apoptotic markers (cyclin D1, cyclin A, cyclin E, p21, p27, p53, Bcl-2, Bax, Survivin, c-myc, and Rb), angiogenesis-related proteins (VEGF and heparanase-1), and extracellular matrix-related proteins (CD10, secreted protein acidic and rich in cysteine), have been investigated in molecular epidemiology studies; however, the data have not been conclusive (44).

Candidate Drivers of Invasive Progression

ER is commonly expressed in preinvasive lesions, 95% and 75% in ADH/LCIS and DCIS lesions, respectively (10). Binding

of estrogen to ER stimulates the growth and differentiation of breast epithelium; therefore, prolonged estrogen exposure in preinvasive disease might have a role in the development of breast cancer. Consistent with the important role of estrogen in breast cancer progression, tamoxifen has been shown to be an effective drug for prevention of breast cancer in high risk patients as well as an effective adjuvant hormonal therapy for patients with resected ER+ DCIS.

HER2 overexpression occurs commonly in high-grade lesions (60%) compared to low-grade lesions (10%). In addition, HER2 is not overexpressed in TDLUs, very rarely in ADH, and about 2% in LCIS. The absence of HER2 overexpression in the earliest phase of preinvasive disease and its association with higher grade DCIS and more aggressive clinic behavior suggest HER2 overexpression is a driving event in cancer progression (45). A randomized phase III trial of adjuvant radiotherapy with or without trastuzumab in patients with HER2+ DCIS resected by lumpectomy is ongoing to evaluate the effect of HER2-targeting in ipsilateral breast cancer recurrence (NCT00769379).

As mentioned above, the precise genetic event(s) triggered during the transition from DCIS to IDC is a critical unknown in the study of breast cancer. A few limited studies that compared the IDC with the adjacent DCIS suggested that *c-Myc* or *FGFR1* amplification may be involved in this process because these genetic events occurred more frequently in the IDC compared to the adjacent DCIS lesions (46–48), while *PIK3CA, AKT1,* and *TP53* mutations are early events that appeared to already exist at the DCIS stage (Table 24-2). Knudson et al. confirmed in their study that DCIS present in concert with IBC harbors gene expression profiles similar to IBC; however, when IBC and pure DCIS were compared, the expression differences became clearer (49). Genes associated with epithelial-to-mesenchymal transition and myoepithelial specific genes were enriched in IBC relative to DCIS, particularly in the stromal component. There have been few *in vivo* studies addressing the function of genes in the progression of DCIS to IDC. Using a "mammary intraductal DCIS" xenograft model, Lee et al. studied the progression of DCIS to invasive breast cancer *in vivo* by introducing specific genes in the human DCIS cell line. Four genes, including a protease inhibitor (*CSTA*) and three genes involved in cell adhesion and signaling (*FAT1*, *DST*, and *TMEM45A*), which were usually elevated in clinical samples of DCIS, were found to suppress the progression of DCIS to invasive cancer (50).

THE ROLE OF THE TUMOR MICROENVIRONMENT

The morphogenesis and functional differentiation of mammary epithelium are known to depend on signals from systemic hormones and on cues from the local tissue microenvironment, and epithelial-mesenchymal interactions are important for breast cancer tumorigenesis (51). Multiple lines of evidence point to the potential importance of tumor microenvironment, which is composed of fibroblasts, myoepithelial cells, endothelial cells, and various immune cells or leukocytes during the transition from invasive to metastatic breast cancer (52–54) and from DCIS to IDC (55,56). To analyze the contribution of tumor microenvironment, several groups have performed unbiased high-throughput genomic and transcriptomic analysis on different tissue/cellular compartments of preinvasive and invasive breast cancer. Using cell-type specific antibodies, Allinen et al. isolated different cell types including epithelial cells, myoepithelial cells, myofibroblasts, leukocytes, and endothelial cells from normal breast, DCIS, or invasive breast cancer specimens and performed comprehensive gene expression profile and aCGH analysis of each cell type (55). While genetic changes by CGH were restricted to tumor epithelial cells of DCIS and IDC, gene expression changes are present

TABLE 24-2

Genetic Alterations in the Invasive Breast Cancer Compared to the Adjacent DCIS

Genes	*Method*	*Patient Features*	*Results*
c-Myc(45)	CGH and FISH	n = 12 IBC with large *in situ* component	*c-Myc* is amplified in IBC but not paired DCIS
c-Myc amplification *CDH1* loss(46)	FISH probe panel consisting of oncogenes and tumor suppresor genes, single-cell genetic analyses	n = 13 synchronous DCIS and IDC	*c-Myc* gain and *CDH1* loss were the most frequent changes between DCIS and IDC
FGFR1(47)	FISH performed on selected gene on tissue microarray	n = 179 pure DCIS, n = 438 invasive carcinoma, n = 216 with DCIS component	*FGFR1* amplification is more frequent in invasive carcinoma, associated with decreased overall survival (OS)
PIK3CA(48)	LCM, PCR sequencing for exon 9 and exon 20	n = 125 DCIS, n = 108 IBC	Similar in DCIS and IDC
AKT/PIK3CA(49)	LCM and PCR mutation analysis	n = 81 invasive + *in situ* carcinoma	12/81 *PIK3CA* mutation, 3/78 *AKT* mutation, no difference in DCIS and IBC
TP53(50)	LCM, PCR mutation analyses	n = 32 DCIS, n = 38 IBC, n = 48 mixture	No significant difference in *TP53* mutations in DCIS and IBC

CGH, comparative genomic hybridization; DCIS, ductal carcinoma in situ; FISH, fluorescence in situ hybridization; *FGFR1,* fibroblast growth factor receptor 1; IDC, invasive ductal carcinoma; LCM, laser capture microdissection; PCR, polymerase chain reaction; *PIK3CA,* phosphatidylinositol-4,5-bisphosphate 3-kinase; *TP53,* tumor protein 53.

in all cell types. The most consistent and dramatic gene expression changes occurred in myoepithelial cells from normal breast and those from DCIS samples. Interestingly, a significant fraction of these genes were secreted or cell-surface proteins, including CXCL12 and CXCL14 chemokines, suggesting paracrine interactions between myoepithelial and other cell types. Similarly, in an oligonucleotide microarray study performed on 14 patient-matched normal epithelium, normal stroma, tumor epithelium, and tumor-associated stroma from DCIS and invasive cancer, the transition from DCIS to invasive carcinoma was accompanied by significant increases in the expression of genes encoding extracellular matrix proteins and matrix metalloproteases (MMP2, MMP11, and MMP14) and cell cycle-related genes, in the stroma compartment (56). In contrast, the epithelial compartment demonstrates no or rare gene expression changes during the DCIS to IDC transition. These findings support the notion that stroma-produced MMPs may be key players driving the DCIS-to-IDC transition. Studies indicate the presence of distinct epigenetic changes in tumor-associated stroma cells (57,58). Future studies investigating the mechanisms of epigenetic changes may shed new light on the control of gene expression during breast tumorigenesis and tumor progression.

CLONAL EVOLUTION DURING INVASIVE PROGRESSION

Single-cell genetic analysis and next-generation sequencing studies support the hypothesis that IBC is the result of clonal evolution driven by a combination of an increased mutation rate and selection pressure on cells within the evolving malignant focus. Using a 4-FISH probe panel that targets 8 candidate genes, including oncogenes *COX2, c-Myc, HER2, CCND1,* and *ZNF217* and tumor suppressor genes *DBC2, CDH1,* and *TP53* and 2 centromere probes, single-cell analysis of copy number changes of the 8 genes was performed on 13 cases of synchronous DCIS and IDC (47). Signal patterns were counted in 76 to 220 nuclei per sample. A high degree of chromosomal instability, defined as variability in the signal patterns from one cell to another in a tumor population (Fig. 24-4), was observed in both DCIS and IDC samples. Despite enormous intercellular heterogeneity in DCIS and IDC, nonrandom distribution of genomic imbalances was observed. The progression from DCIS to IDC was commonly accompanied by loss of *CDH1* and gain of *MYC (c-Myc).* Four of 13 DCIS showed identical clonal imbalances in the IBC (see Fig. 24-4, Category I). Six cases revealed a switch, four of which acquired a gain of *MYC* in IDC (see Fig. 24-4, Category II). In one case, the major clone in the IDC was one of several clones in the DCIS (see Fig. 24-4, Category IV), and in another case, the major clone in the DCIS became one of the two major clones in the IDC (see Fig. 24-4, Category III). This data suggest that transition from DCIS to IBC is driven by a selection of clone(s) with a specific repertoire of genetic alterations. This hypothesis was further supported by another study of 13 matched DCIS and IDC pairs by a CGH and Sequenom MassARRAY (59). Although the genomic profiles of matched DCIS and IDCs were similar, amplification of distinct loci (i.e., 1q41, 2q24.2, 6q22.31, 7q11.21, 8q21.2, and 9p13.3) was either restricted to, or more prevalent in, one of the components in 3 pairs. *PIK3CA* mutations were restricted to the DCIS component in two cases, and reduced from 49% in the DCIS to 25% in the IDC component in the third case. Similarly, it is well known that some DCIS harboring *HER2* gene amplification are associated with HER2-negative invasive carcinomas (60,61).

Using newly developed bioinformatic algorithms (62), Nik-Zainal et al. reconstructed the genomic evolution and a model of breast cancer development over molecular time (Fig. 24-5A) based on analysis of NGS data obtained for 21 breast cancers that included ER+ (n = 5), HER2+ (n = 4), triple negative breast cancer (TNBC) (n = 3), *BRCA1* mutant (n = 5), and *BRCA2* mutant (n = 4) cases. An example of the phylogenetic tree constructed for PD4120, which was sequenced to 188-fold depth is shown in Figure 24–5B. The chronological orders of copy number gains in 16 informative breast cancer genomes are shown in Figure 24-5C. A key milestone in this evolutionary process is the appearance of the "most-recent common ancestor"—the cell with the full range of somatic mutations found in all tumor cells, which demarcates the point when divergent subclones branch out from the initial clone (see Fig. 24-5A,B) (63,64). Strikingly, many oncogenic events, including several driver mutations such as mutations in *PIK3CA* and *TP53*, amplifications of *ERBB2, MYC,* and *CCND1,* and somatic loss of the *BRCA1* and *BRCA2* alleles, accumulated before the emergence of the most-recent common ancestor and were identified in all tumor cells among the 21 breast cancers studied. Another important finding from the study was that all of the tumors contained a dominant subclonal lineage, accounting for more than 50% of cancer cells in the sample and carrying many hundreds or thousands of point mutations. Using PD4120a as an example, 26,762 of the 70,690 somatic substitutions genome-wide were present in all tumor cells, and 4 major subclones were present by statistical modeling of the distribution of clonal and sublonal mutations, with the dominant clone composed of an estimated 70% of the cells in the tumor sample (35% of sequencing reads reported this variant) (Fig. 24-5D). Chromosomal instability was found to be common throughout the history of the cancer although not usually the earliest genomic event. This results in the clonal acquisition of many recurrent abnormalities, such as gains of 1q and 8q and losses of 17p, and considerable divergence among subclones. Similarly, other mutations accumulate during the tumor's development. Once again, it is not clear what triggers the development of the dominant clone. One theory is that this involves an event referred to as chromotripsis (Greek; *chromos* for *chromosome, tripsis* for *shattered into pieces*). Chromotripsis describes a cataclysmic event in which tens to hundreds of genomic rearrangements interspersed with widespread losses of sequence fragments occur in a one-off cellular crisis (65). This is accompanied occasionally by the formation of small circular DNA molecules (double-minute chromosomes), which could become amplified with oncogenes. Strikingly, this genomic rearrangement has been found to be limited to one or a few chromosomes, with affected regions criss-crossing back and forth and showing the characteristic pattern of copy number oscillations between two copy number states. This phenomenon was recently discovered amidst a flood of information from the NGS, in which both ends of 50 to 100 million genomic DNA fragments per sample are sequenced and aligned to a reference genome. In the initial analysis of 10 chronic lymphocytic leukemia (CLL) cases, chromotripsis was detected in one sample (Fig. 24-6) (65). Chromotripsis was identified in 18 of 746 (2.4%; 95% CI, 1.5%–3.9%) cancer cell lines subsequently analyzed using the high-resolution single nucleotide polymorphism (SNP) array data (65). The affected cell lines were across many different tumor types including melanoma; small-cell lung cancer; glioma; non-small–cell lung cancer; synovial sarcoma; and esophageal, colorectal, renal, and thyroid cancers. Additionally, a similar proportion of cases demonstrated evidence of chromotripsis in the analysis of SNP array data from 2,792 cancer specimens that composed 80% of primary tumors. This phenomenon

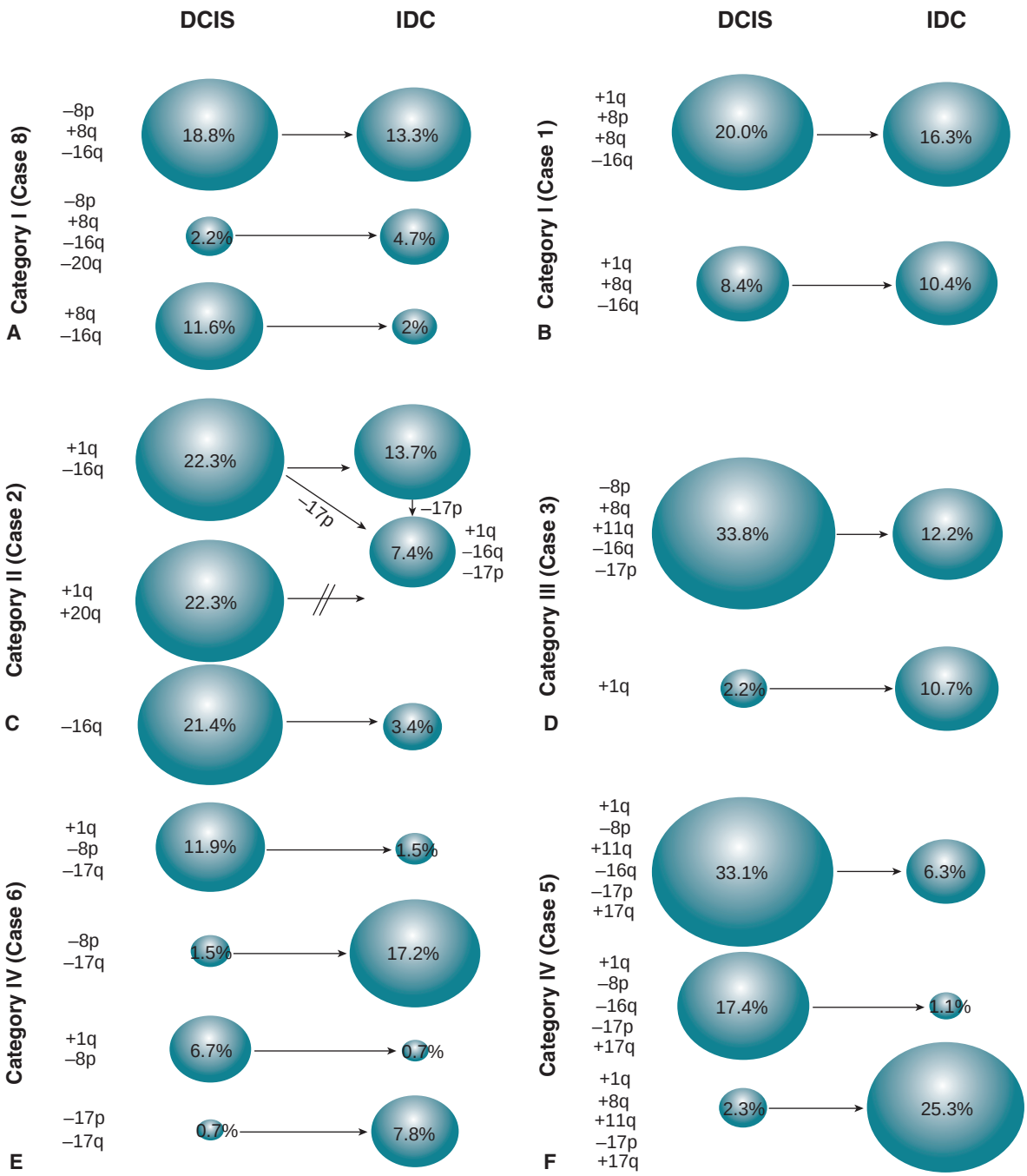


FIGURE 24-4 Schematic presentation of examples of clonal evolution in categories I **(A and B)**, II **(C)**, III **(D)**, and IV **(E and F)** based on the presence of imbalance clones. In case 8 (A) the major clone in DCIS [an 18.8% gain of *MYC* (+8q), losses of *DBC2* (–8p) and *CDH1* (–16q)] was also the major clone in IDC (13.3%). A rare clone in the DCIS (a gain of *MYC*, losses of *DBC2, CDH1,* and *ZNF217*) expanded to become the second largest clone, whereas the second largest clone in DCIS (a gain of *MYC*, a loss of *CDH1*) became rare in the IDC. The text on the left of each panel denotes whether specific chromosome arms are gained (+) or lost (–). The sizes of the circles reflect the frequency with which a clone occurred, which is specified by the percentages in the circles as well. In (C), the clone that occurred in 7.4% of the IDC could have emerged by losses of 17p from either the major clone in the DCIS (+1q, –16q) or the IDC clone present in 13.7% of the cells. Note that one of the major clones in the DCIS (+1q, +20q) vanished in the IDC. (From Heselmeyer-Haddad K, et al. Single-cell genetic analysis of ductal carcinoma in situ and invasive breast cancer reveals enormous tumor heterogeneity yet conserved genomic imbalances and gain of MYC during progression. *Am J Pathol* 2012;181:1807–1822.)

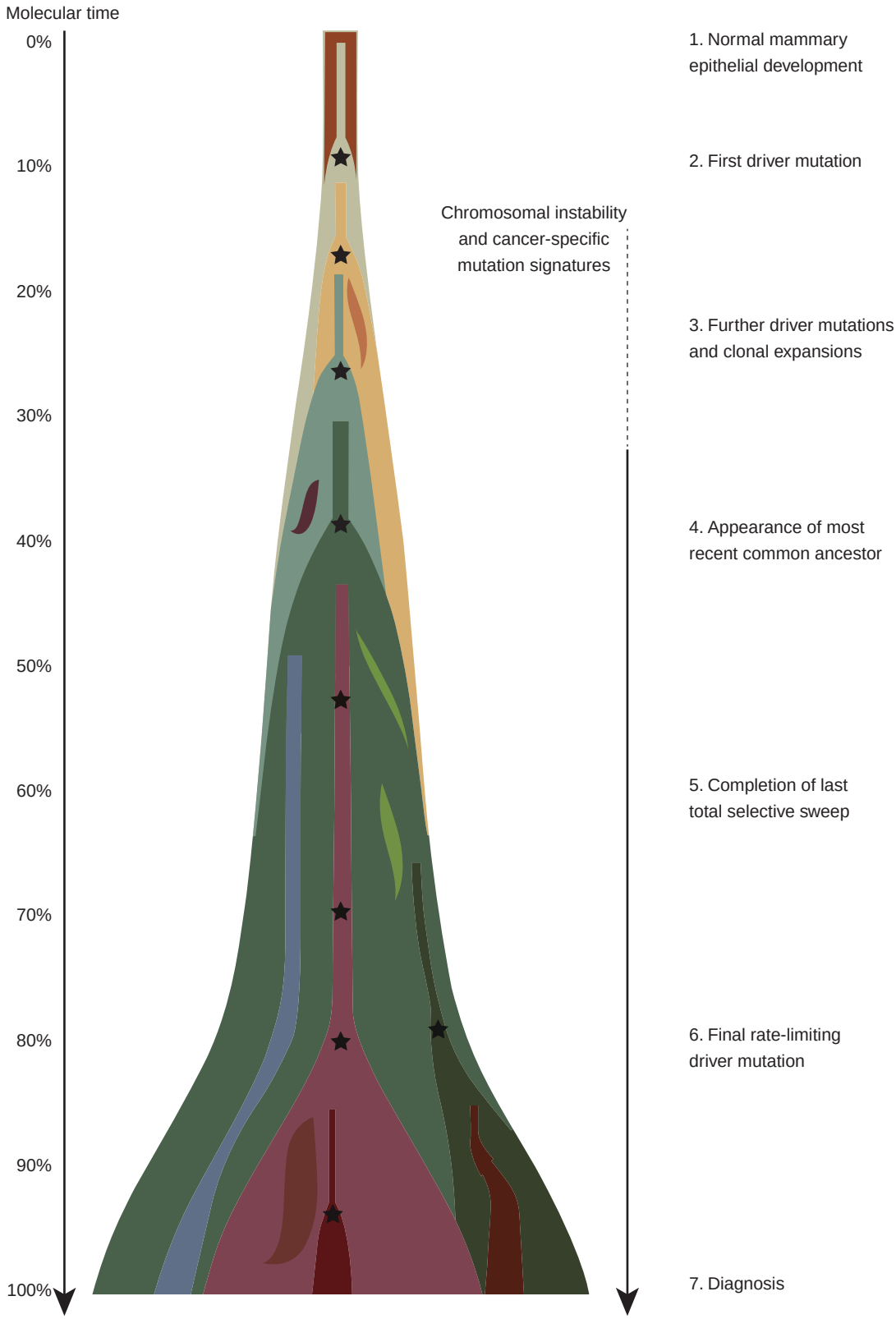


FIGURE 24-5 **(A)** A model for breast cancer development over molecular time. The cancer evolves through acquisitions of driver mutations (*black stars*), which produce clonal expansions. These driver mutations occur only infrequently in long-lived lineages of cells, which passively accumulate many mutations without expansion.

has been found to be particularly common in bone cancers (9 or 20 tumors identified). The argument that the chromotriptic changes are a result of a single catastrophic event was based on the observation of the coordinated gene arragement, with the restriction of two copy number and preservation of LOH of involved regions and was supported by a statistical analysis using Monte Carlo simulations of the progressive model of gradual accumulation of random alterations (65). The mechanisms underlying chromotripsis are unknown. One hypothesis is that chromosomes can be "pulverized" or undergo premature chromosome compaction (66), a phenomon observed during cell-fusion experiments, in which incompletely replicated chromosomes from the S phase nucleus shatter when induced to undergo chromosomal condensation by signals from the host cell in mitosis (67,68). But how this process involves only one or two chromosomes or a single chromosome arm remains to be explained. A lack of sequence homology between joined segments of the regions affected argues that the nonhomologous end-joining DNA repair system is involved after the massive DNA fragmentation. The end results of chromotripsis are the survival advantage that could be offered when tumor suppressors are lost and the generation of new fusion genes in the disrupted chromosome, as well as amplified oncogenes occurring on the derivative chromosomes. Examples include the identification of a normal copy of chromosome 8 as well as a large number of double-minute chromosomes that are composed of 15 distinct segments of chromosome 8, leading to amplification of the *MYC* oncogene in a small-cell lung cancer cell line and the identification of simultaneous loss of several tumor suppressor genes including *CDKN2A, WRN,* and *FBXW7* in a chordoma sample (65).

SEQUENCING OF A BREAST CANCER PRIMARY AND METASTASIS

In 2009, Shah et al. described the mutational evolution of a lobular breast carcinoma (69). The DNA sequence of a metastatic, lobular breast carcinoma was obtained using next-generation DNA sequencing and comparison was made to the patient's original primary breast cancer, which was resected 9 years previously. The metastasis contained 32 somatic, protein-coding mutations. Of these, five mutations were prevalent in the primary cancer, six were present at lower frequency in the primary cancer (between 1% and 13%) and were more prevalent in the metastasis, and nineteen mutations could not be detected at all in the primary. Another study, conducted by Ding et al., investigated the genomic differences between DNA derived from a primary

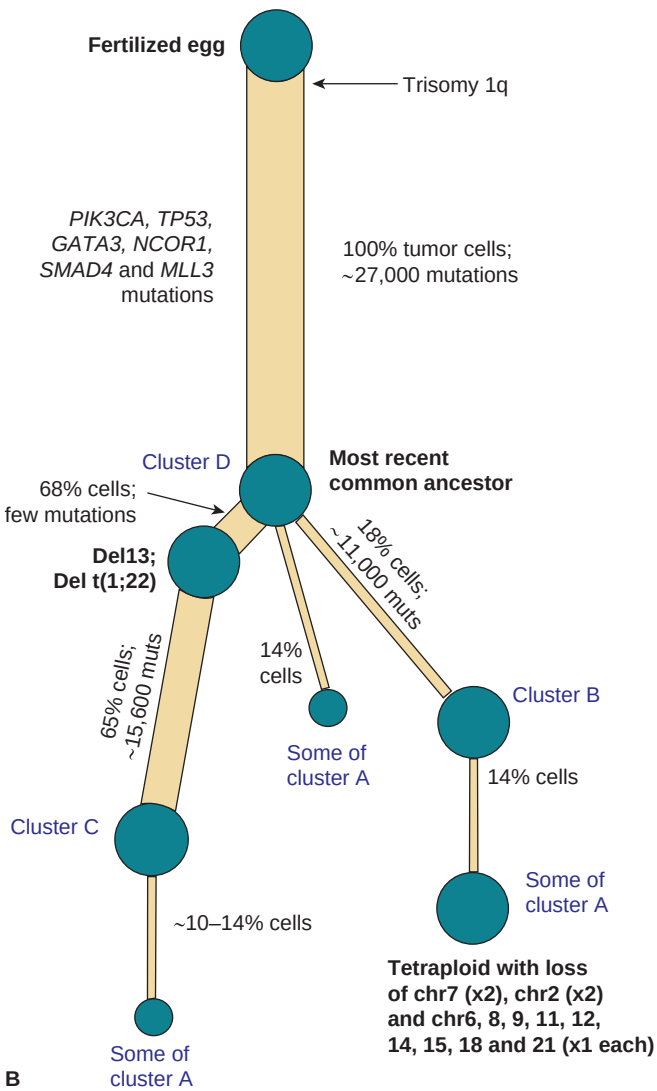


FIGURE 24-5 *(Continued)* **(B)** Reconstruction of the phylogenetic tree for PD4120a. The thickness of the branches reflects the proportion of tumor cells comprising that lineage. The length of the branches reflects the number of mutations specific to that lineage.

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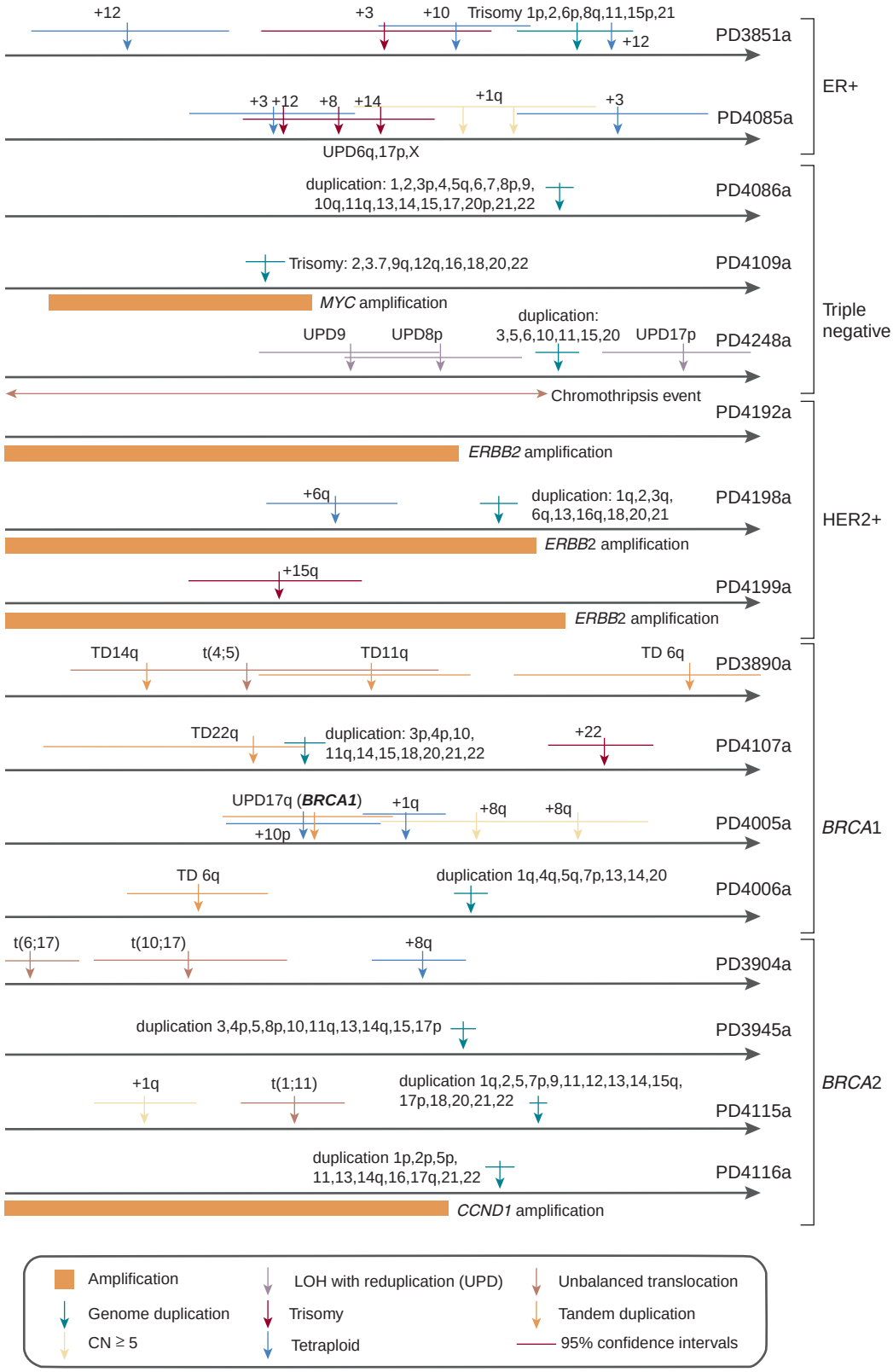

C

FIGURE 24-5 *(Continued)* **(C)** Timing of copy number gains in 16 informative breast cancer genomes from the ploidy of mutations. The point estimates of timing for specific copy number gains are shown as arrows colored by the type of chromosomal aberration, with 95% confidence intervals generated by bootstrapping shown as horizontal lines. Molecular time is shown as an *arrow*, with the timing estimated as a fraction of point mutation time.

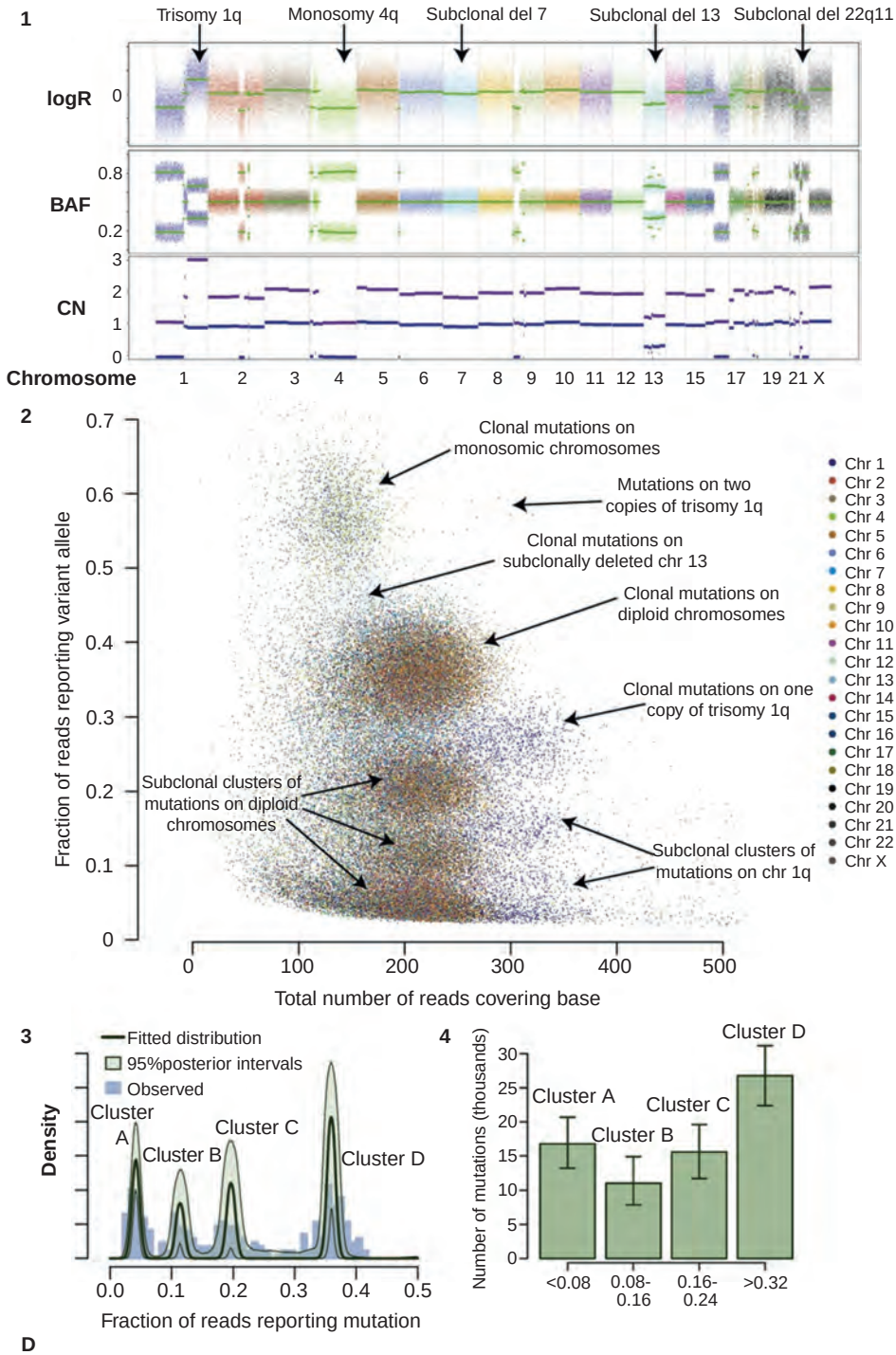

FIGURE 24-5 *(Continued)* **(D)** Genomic architecture of PD4120a, a breast cancer genome sequenced to 188-fold coverage: (1) Copy number profile of the sample, with the upper panel showing the logR of intensity, and the middle panel showing the B allele fraction (BAF) of germline heterozygous SNPs. Genomic segments of constant logR and BAF value were identified by the ASCAT algorithm (*green lines*). These were interpreted to give estimated overall copy number (*purple lines*) and copy number of the minor allele (*blue lines*) across the genome (*lower panel*). (2) Distribution of 70,690 somatically acquired base substitutions according to the total number of reads across that base (x-axis) and the fraction of those reads reporting the variant (y-axis). Points are colored according to the chromosome the mutation derives from. (3) Statistical modeling of the distribution of clonal and subclonal mutations by a Bayesian Dirichlet process. The empiric histogram of mutations is shown in pale blue, with the fitted distribution as a dark green line. Also shown are the 95% posterior confidence intervals for the fitted distribution (*pale green area*). Four separate clusters of mutations, named A–D, are identified. (4) Estimated number of mutations found in clusters A–D, with the error bars representing the 95% posterior confidence intervals. (From Nik-Zainal S, Alexandrov LB, Wedge DC, et al. The life history of 21 breast cancers. *Cell* 2012;149:994–1007.)

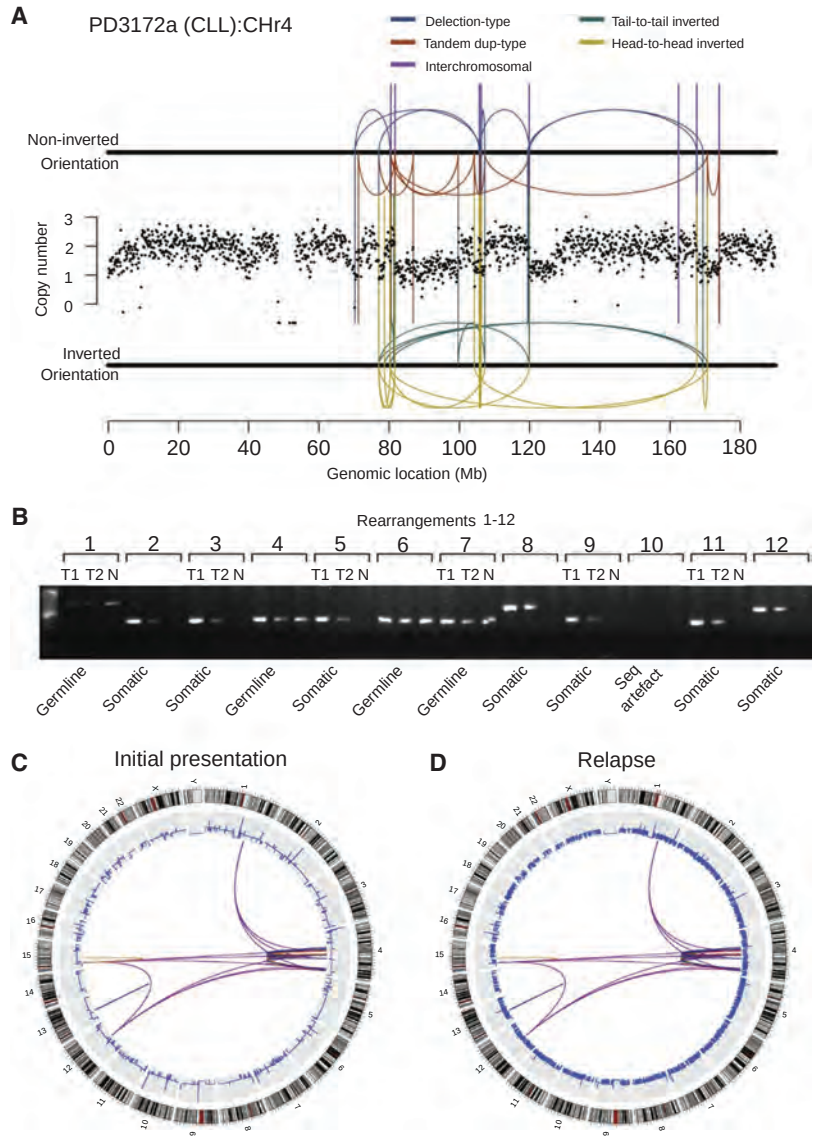

FIGURE 24-6 Clustered rearrangements on chromosome 4q in a patient with chronic lymphocytic leukemia. **(A)** Copy number between 70 Mb and 170 Mb of the chromosome oscillates between a copy number of 1 and 2, demarcated by back-and-forth intrachromosomal rearrangements of all four possible orientations, as well as several interchromosomal rearrangements. **(B)** PCR gel of 12 putative genomic rearrangements identified by sequencing. PCR across the breakpoint is performed for each rearrangement on tumor DNA for samples taken at initial presentation (T1) and relapse (T2) as well as germline DNA (N). **(C)** Genome-wide profile of rearrangements in a sample taken before chemotherapy. Chromosomes range around the outside of the circle, copy number changes are shown by the blue line in the inner ring, and somatically acquired genomic rearrangements are shown as arcs linking the two relevant genomic points. **(D)** Genome-wide profile of rearrangements from the same patient 31 months later, at relapse after therapy, which showed all rearrangements present at initial presentation were present at relapse, and the striking copy number profile persisted. There were no new genomic rearrangements, suggesting that the process generating this complex regional remodeling had resolved before the patient was first diagnosed. (From Stephens PJ, Greenman CD, Fu B, et al. Massive genomic rearrangement acquired in a single catastrophic event during cancer development. *Cell* 2011;144:27–40.)

tumor, a metastasis, and a xenograft sample from the same patient (70). The samples were obtained from a 44-year-old African American woman with triple-negative breast cancer resistant to initial chemotherapy. The primary breast cancer contained 48 somatic, protein-coding mutations, which had a wide range of variant allele frequencies. The metastasis contained all 48 of these mutations, but about half of these mutations showed higher variant allele frequency in the metastasis, indicating enrichment or clonal selection in the metastasis. This enrichment was also seen in the xenograft that was derived from the primary cancer, and, because the sample to establish the xenograft was obtained prior to any cancer treatment, this argues that this enrichment or clonal selection is an intrinsic property of the cancer and not due to the effects of treatment. Further, two new mutations and one large DNA deletion were present in the metastasis but not in the primary cancer, indicating that there was some degree of genomic evolution in the cells making up the metastasis.

Studies of other cancer types also provide guidance about the type of genomic progression that can occur in breast cancer. Sequencing of a renal cell cancer that had metastasized to the lung and chest wall showed substantial intratumor genomic heterogenity (71). The researchers sampled 9 different areas within the primary tumor and 3 metastases (1 from the perinephric fat metastasis; 2 from the chest wall metastasis) and found that only 31% to 37% of the mutations were common to all samples. They constructed a phylogenetic tree based on these results (Fig. 24-7) and proposed that the shared mutations are found in the trunk of this tree (ubiquitous mutations, indicated in blue) whereas the remainder of mutations (63% to 69%) are located in the branches of the tree (indicated in yellow, green, or red). Based on these cases, a schema of clonal evolution in both the primary tumor and metastasis can be proposed (Fig. 24-8) (72). Because of genomic instability in the cancer cells, heterogenity and different subclones develop within the primary tumor. Metastases can develop either early or late in the cancer and are an opportunity for one or several subclones to grow at a distant site. The metastasis can derive from a dominant clone or a minor clone of the primary cancer, which will influence how similar the metastasis and primary cancer are in mutation pattern or even in response to treatment. The ability to sequence individual cancer cells (73) is providing further information about this clonal evolution process and will likely lead to future advances in this area.

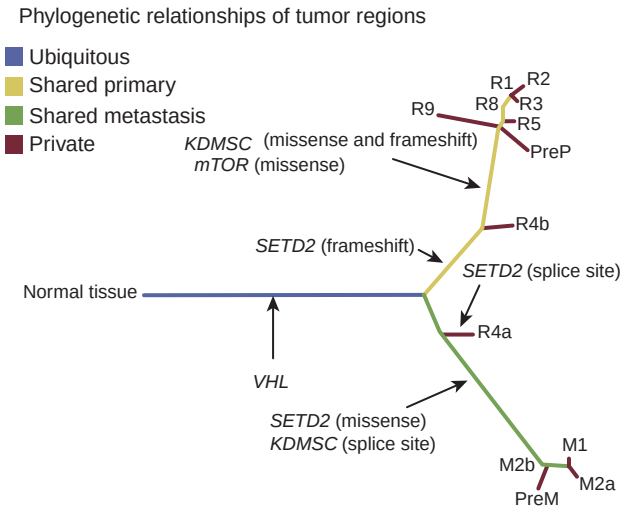

FIGURE 24-7 Phylogenetic relationships of the different renal cell cancer regions and metastases. A single renal cell cancer was subdivided into 9 regions (labeled R1–R9). Additionally, a perrinephric metastasis (M1) and a chest wall metastasis (subdivided into two halves, M2a and M2b) were sequenced. R4a and R4b are the subclones detected in R4. A question mark indicates that the detected SETD2 splice-site mutation probably resides in R4a, whereas R4b most likely shares the SETD2 frameshift mutation also found in other primary-tumor regions. Branch lengths are proportional to the number of nonsilent mutations separating the branching points. Potential driver mutations were acquired by the indicated genes in the branch (arrows). (From Gerlinger M, Rowan AJ, Horswell S, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. *N Engl J Med* 2012;366:883–892.)

COMPARISON OF THE CLONAL EVOLUTION MODEL AND THE CANCER STEM CELL MODEL

In addition to the clonal evolution model discussed extensively up to this point, the cancer stem cell model also offers an explanation for tumor heterogeneity and cancer progression. The cancer stem cell hypothesis proposes that there is a subpopulation of cells within the tumor that are capable of self-renewal and multi-lineage differentiation (74,75). These cells can be isolated based on low expression of the heat stable antigen (CD24), high level expression of the hyaluronic acid receptor (CD44), and expression of aldehyde dehydrogenase (ALDH1) (76–78). In the cancer stem cell model, only mutations in these cells are propagated, and the clonal evolution in them gives rise to the genomic heterogenity in the cancer (Fig. 24-9). Data to support this concept come from Nik-Zainal et al., where 21 primary breast cancer samples were sequenced and their clonal evolution was analyzed with bioinformatic algorithms as described earlier (63). They observed that all tumors contained a dominant subclone that accounted for more than 50% of cancer cells in the sample. They postulated that this expansion of a dominant clone is the final step in the development of a tumor that is responsible for triggering diagnosis, due to the emergence of a palpable mass. As there is minimal evidence of clonal expansion before the accumulation of all mutations in the dominant subclone, they suggest that the dominant clone becomes a cancer-initiating population, which is conceptually similar to a cancer stem cell (79). Similarly, Shah et al. performed deep sequencing, to a depth of 20,000X, on 104 triple-negative breast cancers (80). They observed that groups of mutations within individual cases have different clonal frequencies, indicative of distinct clonal genotypes. These triple-negative breast cancers had a wide range of clonal frequencies in the mutations sequenced, with some cases showing only one or two clonal populations (indicating a smaller number of clonal genotypes), whereas other tumours exhibited more extensive clonal evolution. The findings that many breast cancers have a dominant clone could be the result of this clone having a competitive advantage and taking over the tumor (the clonal evolution model) or could result from one or a few clones in the cancer stem cells, which then propagate and fill the tumor with their progeny.

The cancer stem cell model has also been proposed to explain the existence of the intrinsic molecular subtypes of breast cancer defined by gene expression (Fig. 24-10) (81,82). With the comprehensive genomic sequencing analysis of hundreds and thousands of invasive breast cancers in recent years, it is well established that the profound difference in the gene expression patterns among the various molecular subtypes is accompanied by subtype-specific genetic alterations (Table 24-3) (80,83–90). This suggests that the molecular subtypes are mechanistically different and perhaps derived from progenitor cells (or stem cells) at different stages of differentiation (81,91,92). Lim et al. isolated and funtionally characterized the 4 populations of breast cells by fluorescence-activated cell sorting (FACS) analysis of EpCAM and CD49f (81). Using transplation assays in immunocompromised mice, the $CD49f^{hi}EpCAM^{-}$ subpopulation was enriched with bipotent (ability to derive luminal and myoepithelial progenitors) mammary stem cell progenitors (MaSC), the $CD49f^{+}EpCAM^{+}$ subpopulation was enriched for luminal progenitor, the $CD49f^{-}EpCAM^{+}$ subpopulation were committed luminal cells, and the $CD49f^{-}EpCAM^{-}$ subpopulation were stromal cells. The data comparing the gene expression profiles of these different subpopulations of cells and that of invasive breast cancers suggest that Luminal A, Luminal B, and HER2-enriched breast cancers are likely derived from the more mature luminal cells, while basal-like tumors are derived from the less differentiated "luminal restricted progenitor" cells, and the claudin-low tumors are derived from the pluripotent or bipotent stem cell population (see Fig. 24-10) (81,82,91–93).

EFFECTS OF TREATMENT ON CLONAL EVOLUTION

The development of endocrine therapy resistance or chemotherapy resistance in advanced breast cancers contributes significantly to patient mortality. Cancer treatment imposes a selective pressure on a tumor that can create an evolutionary bottleneck (Fig. 24-11). Drug resistant clones, which already existed as a minor population within the cancer, can be selected for and expand after cancer treatment (72,94). Genomic studies investigating the effects of treatment on breast cancer cells are still in progress, but evidence for this phenonemon comes from other cancer types. *BRCA2* mutant ovarian cancers are sensitive to cisplatin and PARP inhibitors, but secondary mutations in the *BRCA2* gene have been identified which give rise to resistance to these drugs (95,96). Similarly, resistance to imatinib in chronic myelogenous leukemia (CML) arises from secondary mutations in the BCR-ABL fusion protein (97). Chemotherapy or radiation therapy can itself induce mutations through DNA damage. Temozolomide treatment of glioblastoma multiforme

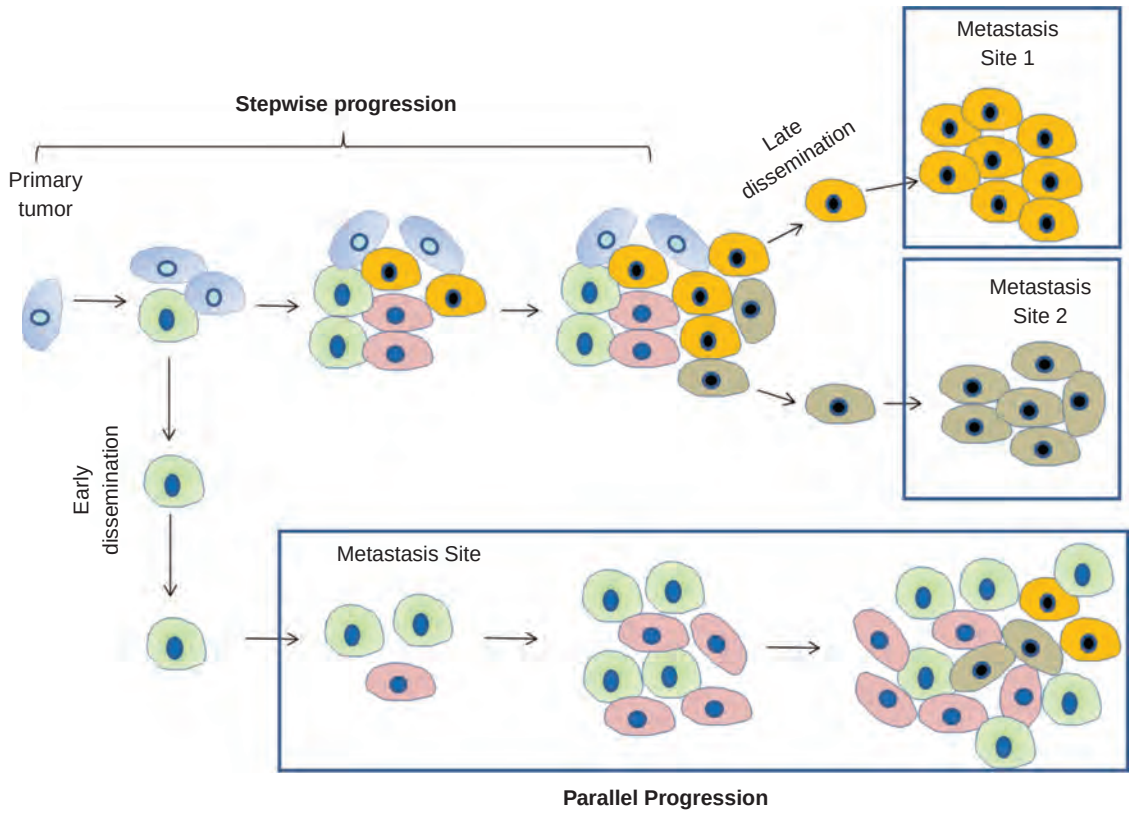

FIGURE 24-8 Tumor heterogeneity in the primary tumor and metastases. Two models of clonal evolution are diagrammed here, with either early or late dissemination of cancer cells.

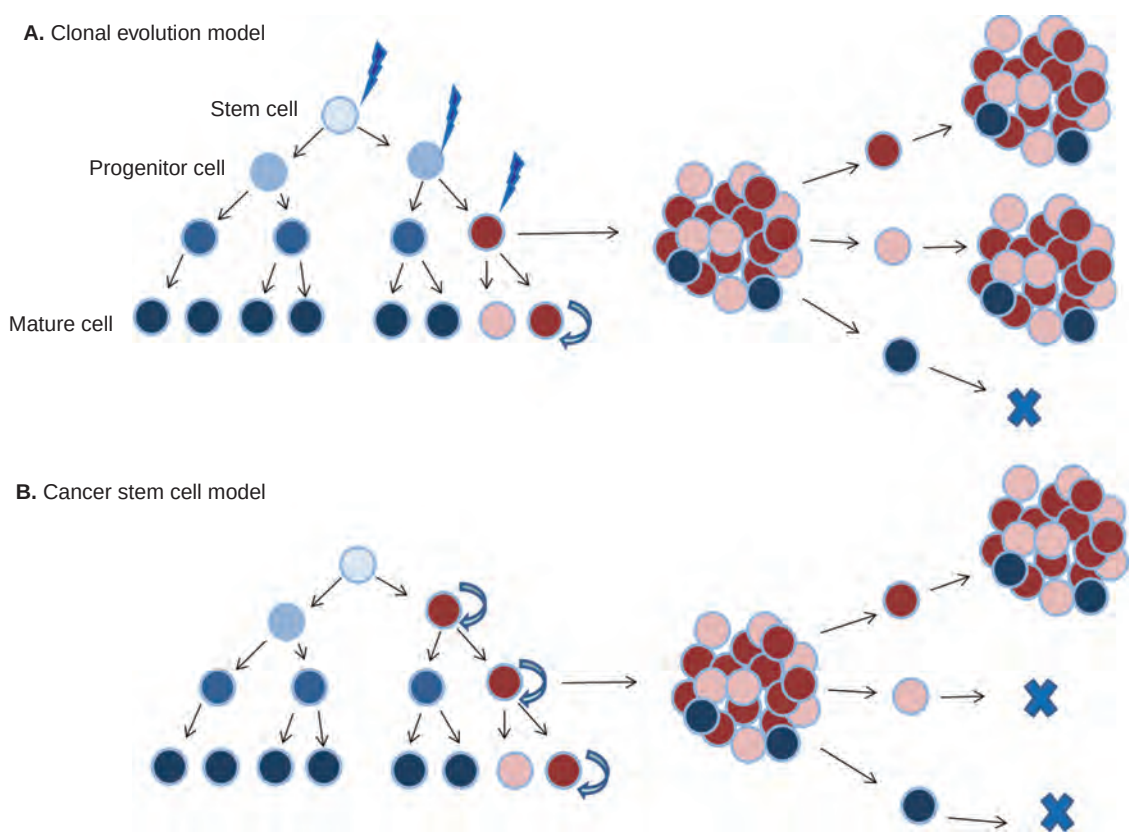

FIGURE 24-9 Comparison of the clonal evolution and cancer stem cell models. In the clonal evolution model, mutations can occur in any cell within the tumor.

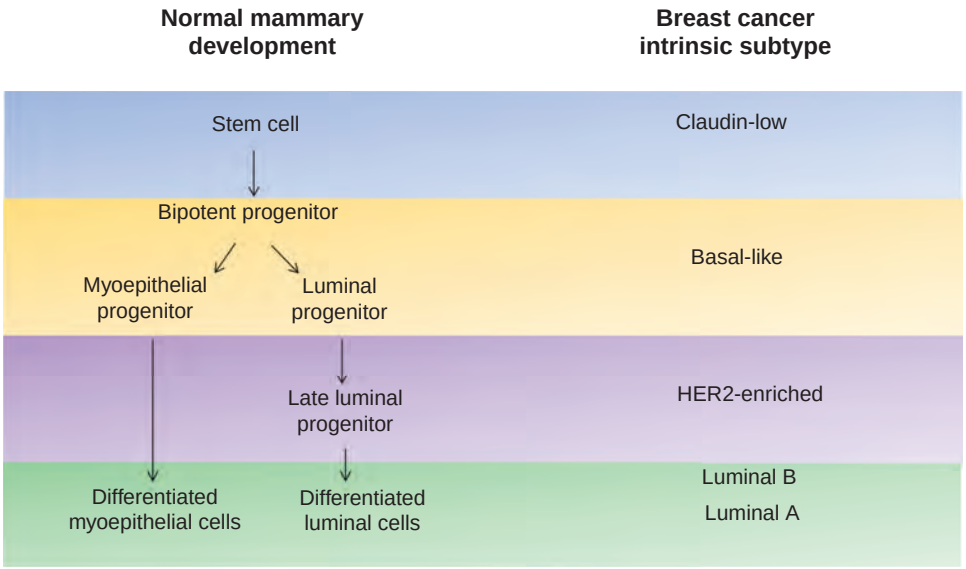

FIGURE 24-10 Breast cancer intrinsic subtype in correlation to stages of normal mammary development.

TABLE 24-3

Highlights of Genomic, Clinical, and Proteomic Features of Subtypes[a]

Subtype	*Luminal A*	*Luminal B*	*Basal-like*	*HER2E*
ER+/HER2– (%)	87	82	10	20
HER2+ (%)	7	15	2	68
TNBCs (%)	2	1	80	9
TP53 pathway	*TP53* mut (12%); gain of *MDM2* (14%)	*TP53* mut (32%); gain of *MDM2* (31%)	*TP53* mut (84%); gain of *MDM2* (14%)	*TP53* mut (75%); gain of *MDM2* (30%)
PIK3CA/PTEN pathway	*PIK3CA* mut (49%); *PTEN* mut/loss (13%); INPP4B loss (9%)	*PIK3CA* mut (32%); *PTEN* mut/loss (24%); INPP4B loss (16%)	*PIK3CA* mut (7%); *PTEN* mut/loss (35%); INPP4B loss (30%)	*PIK3CA* mut (42%); *PTEN* mut/loss (19%); INPP4B loss (30%)
RB1 pathway	*Cyclin D1* amp (29%); CDK4 gain (14%); low expression of CDKN2C; high expression of RB1	*Cyclin D1* amp (58%); CDK4 gain (25%)	*RB1* mut/loss (20%); *cyclin E1* amp (9%); high expression of CDKN2A; low expression of RB1	*Cyclin D1* amp (38%); CDK4 gain (24%)
mRNA expression	High ER cluster; low proliferation	Lower ER cluster; high proliferation	Basal signature; high proliferation	*HER2* amp signature; high proliferation
Copy number	Most diploid; many with quiet genomes; 1q, 8q, 8p11 gain; 8p, 16q loss; 11q13.3 amp (24%)	Most aneuploid; many with focal amp; 1q, 8q, 8p11 gain; 8p, 16q loss; 11q13.3 amp (51%); 8p11.23 amp (28%)	Most aneuploid; high genomic instability; 1q, 10p gain; 8p, 5q loss; *MYC* focal gain (40%)	Most aneuploid; high genomic instability; 1q, 8q gain; 8p loss; 17q12 focal *ERRB2* amp (71%)
DNA mutations	*PIK3CA* (49%); *TP53* (12%); *GATA3* (14%); *MAP3K1* (14%)	*TP53* (32%); *PIK3CA* (32%); *MAP3K1* (5%)	*TP53* (84%); *PIK3CA* (7%)	*TP53* (75%); *PIK3CA* (42%); *PIK3R1* (8%)
DNA methylation	—	Hypermethylated phenotype for subset	Hypomethylated	—
Protein expression	High estrogen signaling; high MYB; RPPA reactive subtypes	Less estrogen signaling; high FOXM1 and MYC; RPPA reactive subtypes	High expression of DNA repair proteins; PTEN and INPP4B loss signature (pAKT)	High protein and phosphoprotein expression of EGFR and HER2

[a]Percentages are based on a 466 tumor overlap list.
Amp, amplification; mut, mutation.
From The Cancer Genome Atlas Research Network. Comprehensive molecular portraits of human breast tumors. *Nature* 2012;490:61–70.

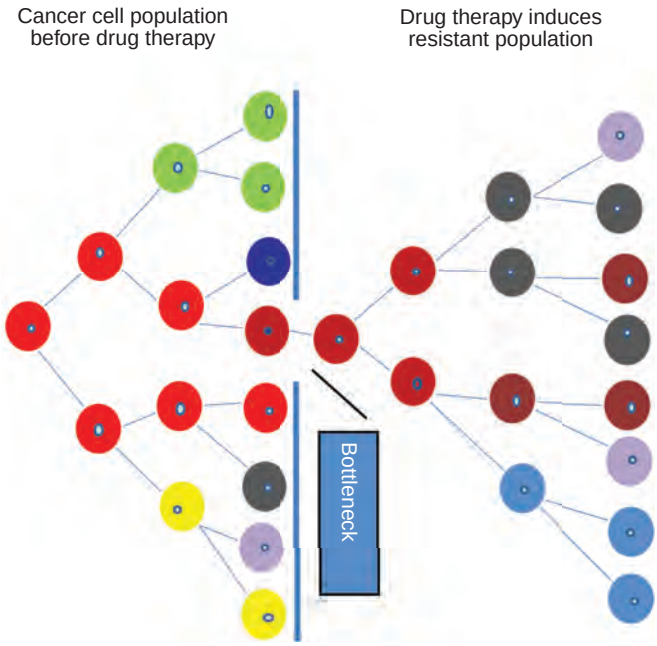

FIGURE 24-11 Tumor heterogeneity during progression and treatment.

produces a statistically significant increase in patient survival, but subsequent recurrence and drug resistance in the cancer is frequently seen. Hunter et al. sequenced two recurrent glioma that had been treated with temozolomide and identified large numbers of somatic mutations in a pattern that was consistent with alkylating agent–induced mutations (98). They identified inactivating somatic mutations of the mismatch repair gene MSH6 in both of these cancers, and they proposed that these MSH6 mutations both conferred resistance to alkylating agents and triggered accelerated mutagenesis in the resistant clones. Accelerating mutagenesis will result in more clonal heterogenity in the cancer and has the potential to give rise to cancers that more difficult to treat. In 1976, Nowell proposed that more research should be directed toward understanding and controlling the evolutionary process in tumors (2). Next-generation DNA sequencing provides a higher volume of data to understand this process, but the ability to control or reduce clonal evolution in cancer is still beyond our current capabilities.

CONCLUSIONS

Despite recent advances, it remains clear that insufficient effort has been placed on acquiring samples from patients with a range of premalignant lesions in order to determine the molecular landscape of precursor lesions. Similarly, at the other end of the scale, we still do not have a comprehensive catalog of the genomic landscape of advanced breast cancer. A comprehensive effort should be made to longitudinally sample the disease so that we can understand the genome dynamics of disease progression. It does appear that the process cannot be described as linear with a series of checkpoints, as Vogelstein imagined; this process is much more chaotic and complex than that, with any one tumor containing a spectrum of dominant and subdominant clones that constantly evolve in response to environmental and therapeutic stresses. Despite this, breast cancer is a curable illness in the majority of cases, which means that heterogenity can be successfully overcome with the right treatment. However, for many patients who are not cured, genomic heterogenity and Darwinian evolution at the cellular level is the root cause of their incurability.

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CHAPTER 25

Pathology of Invasive Breast Cancer

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CHAPTER CONTENTS

Invasive breast cancers constitute a heterogeneous group of lesions that differ with regard to their clinical presentation, radiographic characteristics, histopathologic and molecular features, and biological potential. The most widely used classification of invasive breast cancers, and that used in this chapter (with minor modifications), is that of the World Health Organization (1). This classification scheme is based on the growth pattern and cytologic features of the invasive tumor cells and does not imply histogenesis or site of origin within the mammary duct system. For example, although the classification system recognizes invasive carcinomas designated "ductal" and "lobular," this is not meant to indicate that the former originates in extralobular ducts and the latter in lobules. In fact, subgross whole organ sectioning has demonstrated that most invasive breast cancers arise in the terminal duct lobular unit, regardless of histologic type (2).

The most common histologic type of invasive breast cancer by far is invasive (infiltrating) ductal carcinoma. In fact, the diagnosis of invasive ductal carcinoma is a diagnosis by default, since this tumor type is defined as a type of cancer not classified into any of the other categories of invasive mammary carcinoma (1). To further emphasize this point, and to distinguish these tumors from invasive breast cancers with specific or special histological features (such as invasive lobular, tubular, mucinous, papillary, and other rare types), some authorities prefer the term *invasive* or *infiltrating ductal carcinoma, not otherwise specified (NOS)* or of *no special type (NST)*. In this chapter, the terms *invasive ductal carcinoma, infiltrating ductal carcinoma,* and *infiltrating or invasive carcinoma of no special type* are used interchangeably.

The distribution of histologic types of invasive breast cancer has varied among published series (Table 25-1). These differences may be related to a number of factors including the nature of the patient population and variability in the confines of definition for the different histological types. In general, special type cancers comprise approximately 20% to 30% of invasive carcinomas, and at least 90% of a tumor should demonstrate the defining histological characteristics of a special type cancer to be designated as that histological type (6).

The widespread use of screening mammography has had a dramatic impact on the nature of invasive breast cancers encountered in clinical practice. The value of mammography in detecting more cases of ductal carcinoma *in situ*, smaller invasive breast cancers, and fewer cancers with axillary lymph node involvement is well recognized. However, mammography has also resulted in a change in the distribution of the histological features of the invasive breast cancers detected. In particular, special type cancers (particularly tubular carcinomas) and cancers of lower histological grade are more frequently observed in mammographically screened populations than in patients who present with a palpable mass, particularly in the prevalent round of screening.

Most invasive breast cancers have an associated component of *in situ* carcinoma, although the extent of the *in situ* component varies considerably. The prevailing view has long been that the invasive carcinomas derive from the *in situ* component. This is based not only on the frequent coexistence of the two lesions, but on the histological similarities between the invasive and *in situ* components within the same lesion. For example, a number of studies have

TABLE 25-1

Histologic Types of Invasive Breast Cancer in Four Large Series before the Widespread Use of Mammographic Screening

		Histologic Type (%)							
Study	*No. of Cancers*	*Ductal*[a]	*Lobular*	*Medullary*	*Mucinous*	*Tubular*	*Tubular Mixed*	*Mixed*	*Other*
Fisher et al. (3)	1,000	53	5	6	2	1	—	32	—
Rosen (4)	857	75	10	9	2	2	—	—	—
Ellis et al. (6)	1,547	49	16	3	1	2	14	14	2
Edinburgh (5)	Not stated	70	10	5	2	3	—	2	8

[a]In some series, designated "not otherwise specified" (NOS) or "no special type" (NST).

clearly documented that low-grade invasive cancers are most often associated with low-grade ductal carcinoma *in situ*, and high-grade invasive cancers with high-grade *in situ* lesions (7). In addition, studies evaluating profiles of biological markers and genetic abnormalities have shown that coexisting invasive and *in situ* carcinomas often share the same immunophenotype and genetic alterations. Gene expression profiling studies have confirmed this observation (8).

The routine pathologic examination of invasive breast cancers has extended beyond simply determining and reporting the histologic type of the tumor. Although histologic typing provides important prognostic information in and of itself, other morphologic features that are evaluable on routine histologic sections are also of prognostic value. In this chapter, the various histologic types of invasive breast cancer will be discussed as will pathologic features important in the assessment of prognosis (prognostic factors) and response to therapy (predictive factors). Characteristic molecular and immunophenotypic features will also be noted where appropriate.

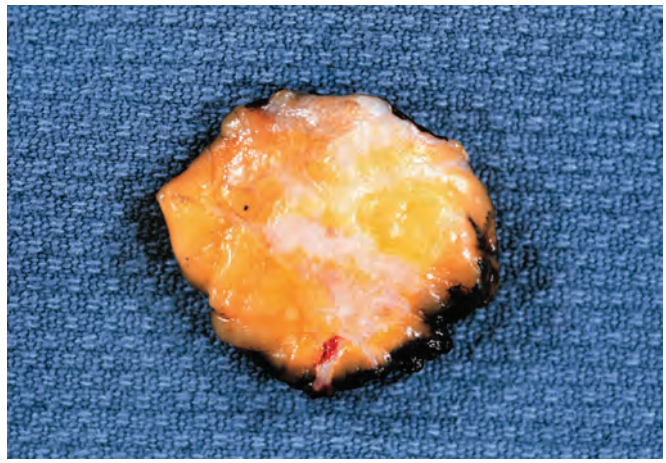


FIGURE 25-1 **Cut surface of an excision specimen containing an invasive ductal carcinoma.** The tumor appears as an irregular area of whitish tissue.

INVASIVE (INFILTRATING) DUCTAL CARCINOMA

Invasive ductal carcinomas represent the single largest group of invasive breast cancers. Although these tumors are most commonly encountered in pure form, a substantial minority exhibit admixed foci of other histologic types. The classification of tumors composed primarily of invasive ductal carcinoma with a minor component consisting of one or more other histological types is problematic. Some authorities categorize such lesions as invasive ductal carcinomas (or invasive carcinomas of no special type) and simply note the presence of the other types, whereas others classify them as "mixed."

Clinical Presentation

Invasive ductal carcinomas most often present as a palpable mass and/or mammographic abnormality. There are no clinical or mammographic characteristics that distinguish invasive ductal carcinomas from other histologic types of invasive cancer. Rarely, these lesions present with Paget disease of the nipple.

Gross Pathology

The classic macroscopic appearance of invasive ductal carcinoma is that of a scirrhous carcinoma, characterized by a firm, sometimes rock-hard, mass that on cut section has a gray-white gritty surface (Fig. 25-1). This consistency and appearance is due to the desmoplastic tumor stroma and not the neoplastic cells themselves. Some invasive ductal carcinomas are composed primarily of tumor cells with little desmoplastic stromal reaction, and such lesions are grossly tan and soft. Although most invasive ductal cancers have a stellate or spiculated contour with irregular peripheral margins, some lesions have rounded, pushing margins, and still others are grossly well circumscribed.

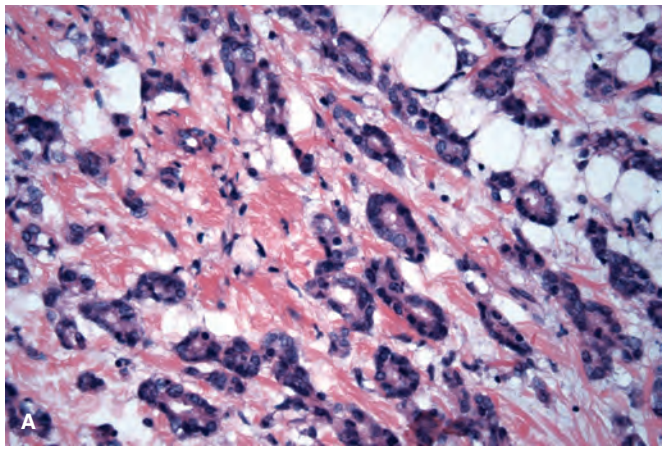
Histopathology

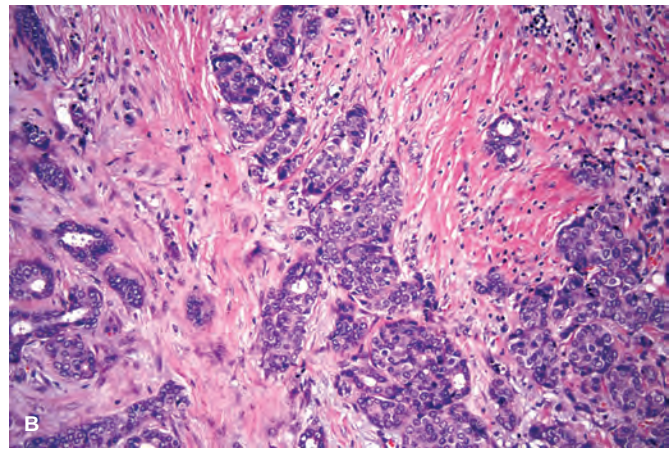
The microscopic appearance of invasive ductal carcinomas is highly heterogeneous with regard to growth pattern, cytologic features, mitotic activity, stromal desmoplasia, extent of the associated ductal carcinoma *in situ* (DCIS) component, and contour. Variability in histologic features may even be seen within a single case. The tumor cells may be arranged as glandular structures; as nests, cords, or trabeculae of various sizes; or as solid sheets. Foci of necrosis are evident in some cases and may be extensive. Cytologically, the tumor cells range from those that show little deviation from normal breast epithelial cells to those exhibiting marked cellular pleomorphism and nuclear atypia. Mitotic activity can range from imperceptible to marked. Stromal desmoplasia is inapparent to minimal in some cases. At the other end of the spectrum, some tumors show such prominent stromal desmoplasia that the tumor cells constitute only a minor component of the lesion. Similarly, some invasive ductal carcinomas have no identifiable component of DCIS, whereas in others, the *in situ* carcinoma is the predominant component of the tumor. An associated lymphocytic or lymphoplasmacytic infiltrate may or may not be present. Finally, the microscopic margins of the cancer may be infiltrating, pushing, circumscribed, or mixed.

Recognizing that invasive ductal carcinomas are a histologically diverse group of lesions, many investigators have attempted to stratify them based upon certain microscopic features. The most common method to subclassify invasive ductal carcinomas is grading, which may be based solely on nuclear features (nuclear grading) or on a combination of architectural and nuclear characteristics (histologic grading). Histologic grading is the method of grading most often used in current practice. The histologic grading system currently in most widespread use is that of Elston and Ellis (reviewed in detail in reference 9). This system is a modification of the grading system proposed by Bloom and Richardson in 1957, but provides strictly defined criteria that are lacking in the original description. Tubule formation, nuclear pleomorphism, and mitotic activity are each scored on a 1 to 3 scale. The sum of the scores for these three parameters provides the overall histologic grade, such that tumors in which the sum of the scores is 3 to 5 are designated grade 1 (well differentiated), those with score sums of 6 and 7 are designated grade 2 (moderately differentiated), and those with score sums of 8 and 9 are designated grade 3 (poorly differentiated) (Fig. 25-2; Table 25-2). The prognostic significance of histologic grading is discussed below (see section on prognostic factors).

Biomarkers

The expression of biologic markers, such as estrogen and progesterone receptors, growth factors, oncogene and tumor suppressor gene products, and other markers is





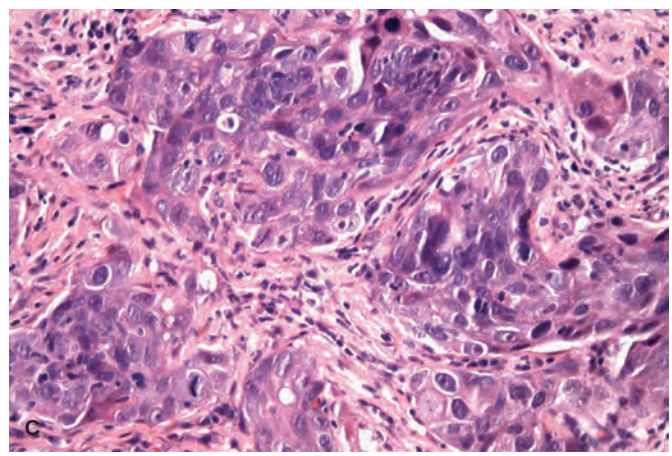


FIGURE 25-2 **Invasive ductal carcinoma. (A)** Histologic grade 1. **(B)** Histologic grade 2. **(C)** Histologic grade 3.

TABLE 25-2

Histologic Grading System for Invasive Breast Cancers (Elston and Ellis Modification of Bloom and Richardson Grading System)

Components of Grade	*Score*
Tubules	
>75% of tumor composed of tubules	1 point
10%–75% of tumor composed of tubules	2 points
<10% of tumor composed of tubules	3 points
Nuclear grade	
Nuclei small and uniform	1 point
Moderate variation in nuclear size and shape	2 points
Marked nuclear pleomorphism	3 points
Mitotic rate	
Dependent on microscope field area	1–3 points
Histologic Grade	**Total points**
1 (well differentiated)	3–5
2 (moderately differentiated)	6–7
3 (poorly differentiated)	8–9

Adapted from Ellis IO. Assessment of histologic grade. In: Elston CW, Ellis IO, eds. *The breast*. Edinburgh, Scotland: Churchill Livingstone, 1998:365–384.

highly variable in invasive ductal carcinomas as might be anticipated from their histologic heterogeneity. Although a large number of biomarkers have been studied in invasive ductal carcinomas, only estrogen receptor, progesterone receptor, and HER2 are reported in routine clinical practice at this time. Overall, 70% to 80% of invasive ductal carcinomas are estrogen receptor positive and approximately 15% are HER2 amplified and overexpressed.

Invasive ductal carcinomas also display a wide variety of genetic and genomic alterations. In gene expression profiling studies, invasive ductal carcinomas may be found within all major molecular subtypes (24).

Clinical Course and Prognosis

The prognosis of invasive ductal cancer varies according to tumor size, histologic grade, lymph node status, and presence of lymphovascular invasion as well as expression of hormone receptors and HER2 (see section on prognostic factors). However, even within this group prognostically favorable specialized tumor types can be identified, as discussed below.

INVASIVE (INFILTRATING) LOBULAR CARCINOMA

Invasive lobular carcinomas constitute the second most frequent type of invasive breast cancer, in most series accounting for approximately 5% to 15% of cases. Although some of this variability may be related to differences in patient populations, much of it appears to be due to differences in diagnostic

criteria. In particular, since the "classical" form of invasive lobular carcinoma was first described by Foote and Stewart (11), a variety of authors have described invasive breast cancers that they consider variants of invasive lobular carcinoma, thereby expanding the spectrum of this histologic type and accounting for a higher incidence of invasive lobular carcinoma in more recent series than in the past. In addition, recent studies have suggested that the increase in the frequency of infiltrating lobular carcinoma may be in part related to the use of postmenopausal hormone replacement therapy (14).

Invasive lobular carcinomas are characterized by multifocality in the ipsilateral breast and appear to be more often bilateral than other types of invasive breast cancer. Lobular carcinoma *in situ* coexists with invasive lobular carcinoma in the majority of cases, with 70% to 80% of cases of invasive lobular carcinoma associated with foci of lobular carcinoma *in situ*.

Clinical Presentation

Invasive lobular carcinoma may present as a palpable mass or a mammographic abnormality with characteristics similar to those of invasive ductal carcinomas (i.e., discrete, firm mass on palpation; spiculated mass on mammogram). However, both the findings on physical examination and the mammographic appearance of invasive lobular carcinomas may be quite subtle. On physical examination, there may be only a vague area of thickening or induration, without definable margins. Mammographic findings may be equally subtle, with many invasive lobular carcinomas appearing as poorly defined areas of asymmetric density with architectural distortion and others revealing no mammographic abnormalities, even in the presence of a palpable mass. In fact, the extent of the tumor may be substantially underestimated by both physical examination and mammography.

Gross Pathology

Some invasive lobular carcinomas appear as firm, gritty, gray-white masses, indistinguishable from invasive ductal carcinomas. However, in other cases, no mass is grossly evident and the breast tissue may have only a rubbery consistency. In still other cases, no abnormality is evident on visual inspection or upon palpation of the involved breast tissue and the presence of carcinoma is revealed only upon microscopic examination.

Histopathology

Invasive lobular carcinomas as a group show distinctive cytologic features and patterns of tumor cell infiltration of the stroma. The *classical form* is characterized by small, relatively uniform neoplastic cells that invade the stroma singly and in a single-file pattern which results in the formation of linear strands (Fig. 25-3). These cells frequently encircle mammary ducts in a targetoid manner. Furthermore, the tumor cells may infiltrate the breast stroma and adipose tissue in an insidious fashion, invoking little or no desmoplastic stromal reaction. This feature accounts for the difficulty in detecting some invasive lobular carcinomas on physical examination, mammography and gross pathologic examination. The nuclei of the neoplastic cells are usually small, show little variation in size, and are often eccentric. Mitotic figures are infrequent. The cells may contain intracytoplasmic lumina which, in some, may be large enough to impart a signet ring cell appearance. However, in the classical form of invasive lobular carcinoma, cells with a signet ring configuration comprise only a small proportion of the tumor cell population.

Many examples of invasive lobular carcinoma (as well as lobular carcinoma *in situ*) are characterized histologically by tumor cells that are loosely cohesive. This phenotype may be, at least in part, related to the fact that both *in situ* and invasive lobular carcinomas typically show loss of expression of the adhesion molecule E-cadherin. This is associated, in many cases, with mutations in the gene encoding this protein (17) or to loss of heterozygosity on chromosome 16q22.1, the region of the E-cadherin gene (18). Although loss of E-cadherin expression characterizes lobular carcinomas and distinguishes them from ductal-type carcinomas, a subset of lobular carcinomas are reported to be E-cadherin positive (19). Thus, membrane expression of E-cadherin in an invasive carcinoma with morphologic characteristics of invasive lobular carcinoma is not, by itself, sufficient for classification as invasive ductal carcinoma.

Variant forms of invasive lobular carcinoma differ from the classical form with regard to architectural and/or cytologic features. In the solid and alveolar variants, the cells comprising the tumor have features characteristic of the classical form of invasive lobular carcinoma, but differ from the classical form with regard to the growth pattern of the tumor cells (10). In the *solid form*, the neoplastic cells grow in large confluent sheets with little intervening

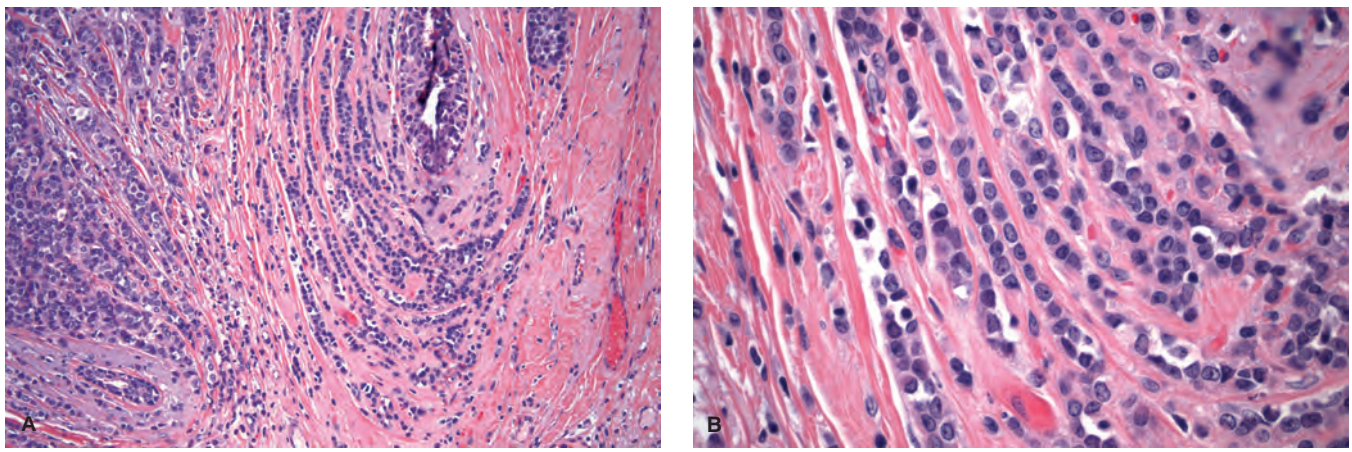


FIGURE 25-3 **Invasive lobular carcinoma, classic type. (A)** Linear strands of tumor cells infiltrate the stroma. **(B)** Higher-power view to demonstrate cytologic detail. The tumor cells have small, relatively uniform nuclei.

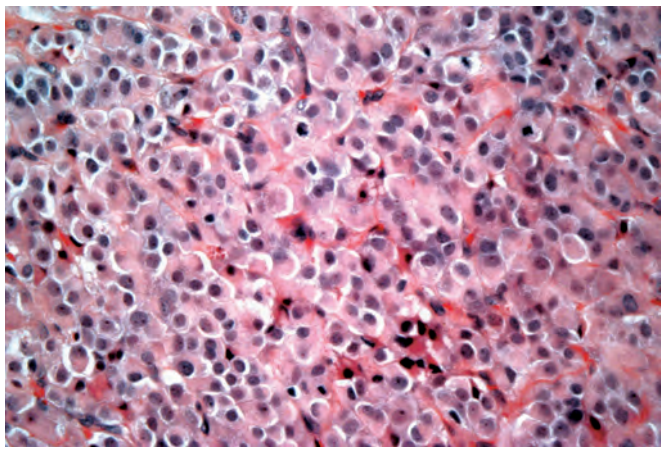


FIGURE 25-4 **Invasive lobular carcinoma, solid type.** The tumor cells grow in a confluent sheet with little intervening stroma.

stroma (Fig. 25-4). The *alveolar form* is characterized by tumor cells that grow in groups of 20 or more cells. These cellular aggregates are separated from one another by a delicate fibrovascular stroma (Fig. 25-5). Although a *trabecular variant* has also been described (10), there is considerable overlap between this pattern and that seen in the classical form of invasive lobular carcinoma. In the *pleomorphic variant,* the neoplastic cells are larger, exhibit more nuclear variation than that seen in the classical form, and may show apocrine features (13) (Fig. 25-6). Although signet ring cells can be seen in the classical type of invasive lobular carcinoma as well as in some examples of invasive ductal carcinoma, tumors that are composed of a prominent component of signet ring cells that otherwise have the characteristic features of invasive lobular carcinoma are considered to represent the *signet ring cell variant* of invasive lobular carcinoma (12). *Histiocytoid carcinoma* is an apocrine variant of invasive lobular carcinoma in which the tumor cells have a histiocyte-like appearance with abundant foamy pale eosinophilic cytoplasm and mild nuclear atypia (20). Some authors have recognized a "mixed" category of invasive lobular carcinoma. This term is generally used to designate lesions in which no single pattern comprises more than 80% to 85% of the lesion (21).

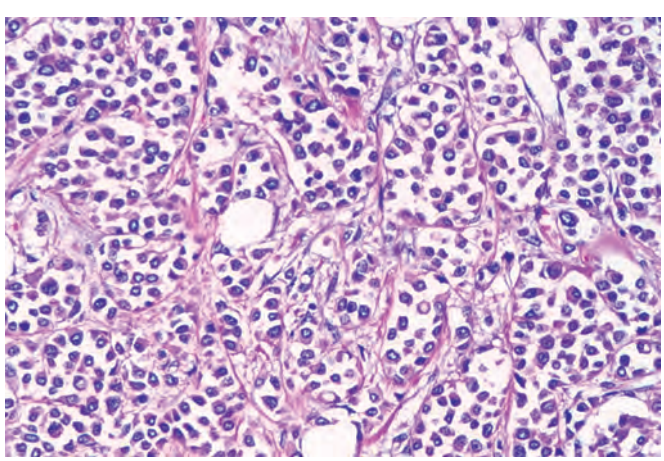


FIGURE 25-5 **Invasive lobular carcinoma, alveolar type.** Loosely cohesive tumor cell aggregates are separated by delicate fibrous septa.

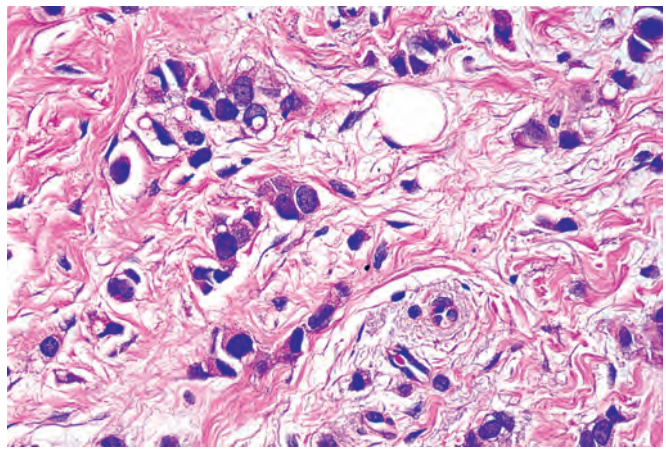


FIGURE 25-6 **Invasive lobular carcinoma, pleomorphic type.** The tumor cells infiltrate the stroma in linear strands, similar to those seen in the classic type of invasive lobular carcinoma. However, the cells in this lobular variant show considerable nuclear pleomorphism, in contrast to the small, monomorphic nuclei characteristic of the classic type of invasive lobular carcinoma (compare with Fig. 25-3B).

The relative frequency of the various lobular subtypes is difficult to discern since not all subtypes have been recognized in all series. In addition, patient selection criteria have varied among these studies. In the series of Dixon et al., among 103 invasive lobular carcinomas, 30% were of the classical type, 22% were solid, 19% were alveolar, and 29% were mixed lesions (15). In the experience of Ellis et al., 40% of invasive lobular carcinomas were of the classical type, 10% were solid type, 4% were alveolar, and 40% were mixed (6). In contrast, in a study from Memorial Sloan-Kettering Cancer Center, 176 of 230 invasive lobular carcinomas (77%) were of the classical type and the remainder were variants: 4% solid, 6% alveolar, and 13% mixed (16) (Table 25-3).

Biomarkers

Classical invasive lobular carcinomas typically show expression of estrogen and progesterone receptors and rarely show HER2 overexpression or amplification. Although pleomorphic lobular carcinomas are also frequently estrogen receptor and progesterone receptor positive, they may also show overexpression and amplification of HER2 (23). Gross cystic disease fluid protein 15 is seen in about one-third of all invasive lobular carcinomas, but is present in the vast majority of lesions that show prominent signet ring cell features (22).

In gene expression profiling studies, most invasive lobular carcinomas are classified as luminal A subtype; however, some cases fall within the luminal B, HER2 and basal-like groups (24). Chromosomal analysis shows characteristic loss of 16q and gain of material on 1q and 16p (18).

Clinical Course and Prognosis

There are several aspects of the clinical course of invasive lobular carcinomas that merit consideration. First, a number of studies have noted differences in the pattern of metastatic spread between invasive lobular and invasive ductal carcinomas. In particular, metastases to the lungs, liver, and brain parenchyma appear to be less common in patients with lobular than ductal cancers (25,26). In contrast, lobular carcinomas have a greater propensity to metastasize to the

TABLE 25-3

Frequency of Invasive Lobular Carcinoma Subtypes in Series with More Than 100 Patients

Study	*No. Invasive Lobular Carcinomas*	*Subtypes*				
		Classic	*Solid*	*Alveolar*	*Tubulolobular*	*Mixed*
Dixon et al. (15)	103	30	22	19	Not included	29
Ellis et al. (6)	243	40	10	4	6	40
DiCostanzo et al. (16)	230	77	4	6	Not included	13

leptomeninges, peritoneal surfaces, retroperitoneum, gastrointestinal tract, and reproductive organs and bone (25). In fact, the majority of cases of carcinomatous meningitis in patients with metastatic breast cancer occur in patients with lobular cancers (98,26). Peritoneal metastases may appear as numerous small nodules studding the peritoneal surfaces in a manner similar to that seen in ovarian carcinoma (25,26). Metastases to the stomach can produce an appearance that simulates an infiltrative (linitis plastica) type of primary gastric carcinoma (27). Involvement of the uterus may result in vaginal bleeding (28), whereas metastatic tumor in the ovary may produce ovarian enlargement and the appearance of a Krukenberg tumor.

Whether or not invasive lobular carcinomas differ in overall prognosis from invasive ductal carcinomas is difficult to determine due in large part to variations in the application of histologic criteria for the diagnosis of invasive lobular carcinoma. However, the prognosis of patients with invasive lobular carcinoma as a group has not consistently been shown to differ from that of patients with invasive ductal carcinoma. Several studies have suggested that the prognosis for the classical form of invasive lobular carcinoma is better than variant types and than invasive ductal carcinomas (6,15,16). Available evidence suggests that the pleomorphic variant and the signet ring cell variant (when defined as lesions in which greater than 10% of the neoplastic cells are of the signet ring cell type) appear to be associated with a particularly poor clinical outcome (13).

Numerous clinical follow-up studies have indicated that patients with invasive lobular carcinoma can be adequately treated with conservative surgery and radiation therapy following complete gross excision of the tumor, with local recurrence rates comparable to those seen in patients with invasive ductal carcinoma (reviewed in reference 29).

INVASIVE CARCINOMAS WITH DUCTAL AND LOBULAR FEATURES

A small proportion of invasive breast cancers, up to 5% in most studies, are not readily classifiable as either ductal or lobular (6). Invasive cancers may be difficult to classify definitively as either ductal or lobular either because they show distinct features of both or have features that are indeterminate. Cancers that show distinct areas of invasive ductal carcinoma and invasive lobular carcinoma are best classified as mixed invasive ductal and invasive lobular carcinoma. *Tubulolobular carcinoma* is a distinctive type of low-grade invasive breast cancer that is E-cadherin positive but shows both ductal and lobular morphologic features. In this variant, some of the tumor cells invade the stroma in linear strands characteristic of the classical form of invasive lobular carcinoma whereas others form small tubules with round to ovoid contours. These tubules are smaller and less angulated than those seen in tubular carcinoma (see below). Some invasive cancers have both cytologic and architectural features that are intermediate between those of invasive ductal and invasive lobular carcinomas. Immunohistochemical staining for E-cadherin and cytokeratin 8 has been proposed as a useful adjunct in making the distinction between ductal and lobular carcinomas in histologically problematic or indeterminate cases (30). The fact that it may be difficult for the pathologist to categorize a given lesion as ductal or lobular in some cases should not be surprising in view of reports suggesting that some invasive ductal carcinomas exhibit cytogenetic alterations that are similar to those seen in invasive lobular carcinomas (18).

Given the heterogeneous nature of the lesions included in this group, data on clinical features and outcome of patients with invasive carcinomas with ductal and lobular features are difficult to interpret. However, these lesions do not appear to be distinctive in their rate of local recurrence or distant failure when compared with patients with invasive ductal or invasive lobular carcinomas.

TUBULAR CARCINOMA

Tubular carcinoma is a special type cancer that is associated with limited metastatic potential and an excellent prognosis. Prior to the widespread use of screening mammography, tubular carcinomas accounted for less than 4% of all breast cancers (31). However, these tumors account for a much higher proportion of cancers detected in mammographically screened populations.

Clinical Presentation

The mean age at presentation for patients with tubular carcinoma is in the early sixth decade (31,32). Historically, the majority of tubular carcinomas were detected as palpable lesions; however, the majority (60% to 70%) now present as nonpalpable mammographic abnormalities. Not infrequently, tubular carcinomas are discovered incidentally in biopsies performed for unrelated reasons. Rare examples of tubular carcinoma have been reported in men.

Mammographic abnormalities, in the absence of a palpable mass, have been reported in the majority (80%) of patients with tubular carcinomas; however, mammographically occult tubular carcinomas are not infrequent. When a mammographic abnormality is present, it is usually a mass lesion, occasionally associated with microcalcifications. The mass may be irregular, round, oval, or lobulated. The majority of tubular carcinomas have spiculated margins, and cannot be distinguished radiologically from infiltrating ductal carcinomas.

Gross Pathology

Tubular carcinomas are typically small, with an average diameter less than 1.0 cm in most series (32). Tubular carcinomas detected by screening mammography are typically smaller than palpable lesions. Grossly tubular carcinomas are firm, spiculated lesions that are indistinguishable from infiltrating ductal carcinomas.

Histopathology

Tubular carcinomas are characterized by a proliferation of well-formed glands or tubules formed by a single layer of epithelial cells without surrounding myoepithelial cells. These tubules tend to be ovoid in shape and have sharply angular contours with tapering ends, and open lumens. The cells comprising these tubules are characterized by low-grade nuclear features and are usually polarized toward the lumen, often exhibiting apical cytoplasmic "snouts" (Fig. 25-7). The stroma of tubular carcinomas usually has desmoplastic features, and prominent elastosis may be present. There is now general agreement that more than 90% of the tumor should exhibit this characteristic morphology to be categorized as a "pure" tubular carcinoma (1); however, the proportion required for this diagnosis in published studies has varied from 75% to 100%.

The majority of tubular carcinomas have an associated intraductal component. The DCIS seen in association with tubular carcinoma is usually of low nuclear grade, with cribriform and micropapillary patterns, and does not typically comprise a large proportion of the tumor mass. In addition, flat epithelial atypia may be found in the vicinity of tubular carcinomas (36). Lobular carcinoma *in situ* may also be observed in association with tubular carcinoma. The frequency of multifocality and multicentricity in tubular carcinoma is difficult to determine due to varying definitions and methods of specimen sampling employed by different investigators. In one report in which 17 mastectomy specimens with tubular carcinomas were examined using the Egan serial subgross method (37), Lagios et al. (33) found a 56% incidence of multicentricity, defined in that study as carcinoma of any type present 5 cm from the index lesion. This incidence was significantly greater than a control group comprised of mastectomy specimens containing breast cancers of other types (33).

Because these lesions are extremely well differentiated, several benign entities such as sclerosing adenosis, radial scars, complex sclerosing lesions, and microglandular adenosis may enter into the differential diagnosis. In such cases, the use of immunohistochemical stains may be necessary in order to arrive at the correct diagnosis.

Biomarkers

The expression of various biologic markers in tubular carcinomas generally reflects the well-differentiated nature and favorable prognosis associated with these lesions. Tubular carcinomas are strongly positive for estrogen receptor and usually positive for progesterone receptor. In addition, these lesions are almost always diploid, have a low proliferative rate and no HER2 overexpression or amplification (38). When compared to invasive carcinomas of no special type, tubular carcinomas exhibit fewer overall chromosomal changes, more often show losses of 16q and less often show losses of 17p (39). On gene expression profiling studies, tubular carcinomas fall into the luminal A category (24).

Clinical Course and Prognosis

The reported incidence of axillary lymph node metastases in patients with tubular carcinomas is up to 29% (31,32); however, there is considerable variation in the histologic definitions employed in these studies. A number of studies have shown an inverse relationship between the degree of tubular differentiation and the incidence of lymph node metastases (34). Nevertheless, even patients with "pure" tubular carcinomas (over 90% tubules) have nodal metastases in up to 15% of cases (35). However, as with other types of breast cancer, the size of the tumor strongly influences the likelihood of axillary metastases. Winchester reported that 67% of tubular carcinomas associated with nodal metastases were greater than the median size of 1.0 cm (35). The relative infrequency of nodal disease in patients with small tubular carcinomas has led some investigators to advocate abandoning axillary lymph node dissection in these patients.

With regard to survival, patients with tubular carcinoma have an excellent prognosis, equivalent in some series to age-matched women without breast cancer (40). In the randomized prospective NSABP-B06 trial, 1090 node-negative and 651 node-positive patients were classified with regard to histologic type, and the "favorable" category included 120 patients with tubular carcinoma (43). Both node-negative and node-positive patients in the "favorable" category

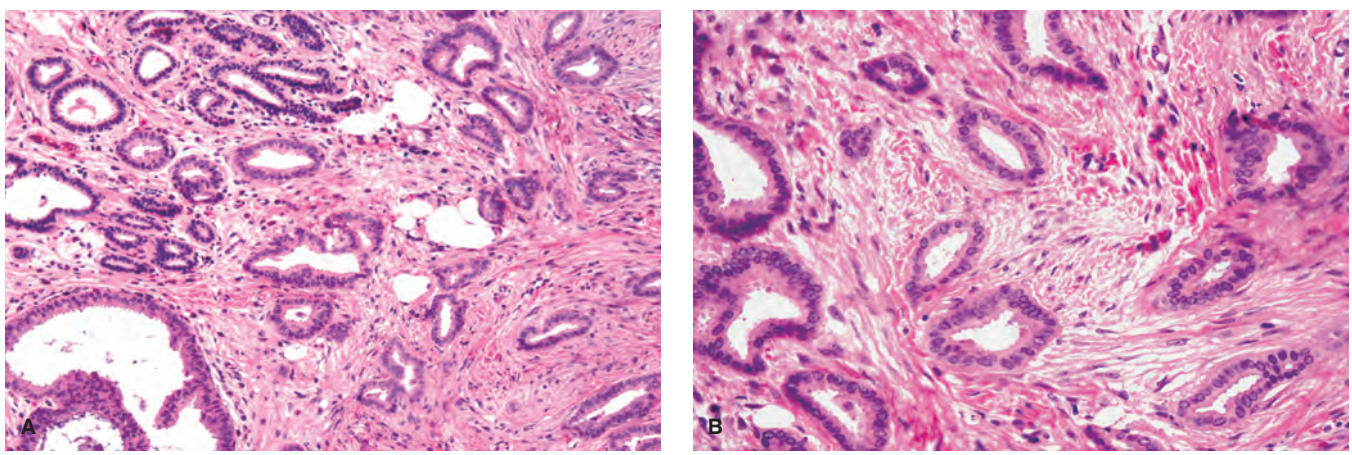


FIGURE 25-7 **Tubular carcinoma. (A)** This tumor is composed of well-formed glandular structures in a desmoplastic stroma. **(B)** The glands, or tubules, are elongated, and some have tapering ends. Numerous cytoplasmic "snouts" are evident at the luminal aspect of the tumor cells.

experienced significantly greater overall survival at 10 years compared to other patients in a univariate analysis, and "favorable" histology proved to be an independent predictor of survival in node-negative patients by multivariate analysis (43). Similar improved survival rates in patients with tubular carcinoma were reported in a series of 1,621 patients, although these patients were not stratified by node status (6). In this latter study, even patients with "tubular mixed" tumors (which were defined as stellate cancers composed of cells typical of invasive ductal carcinoma but with central tubules identical to tubular carcinoma) experienced significantly better overall survival compared to patients with invasive ductal carcinoma (6). In addition, two series, one examining node-negative early stage breast cancer patients treated with mastectomy, and the other examining early stage patients treated with breast-conserving therapy, both reported that patients with tubular carcinoma had significantly lower rates of distant recurrences compared to patients with invasive ductal carcinoma (41,42).

Other investigators have suggested that even patients with node-positive tubular carcinomas have a good prognosis. When tubular carcinoma does metastasize to axillary lymph nodes, usually one and seldom more than three nodes are involved. Several investigators have concluded that the presence of nodal disease in patients with tubular carcinoma does not affect disease-free or overall survival in these patients (35).

Reports examining the use of conservative surgery and radiation therapy in patients with tubular carcinoma show no significant differences in local recurrence rates when patients with tubular carcinomas are compared to patients with invasive ductal carcinoma (42). Although it is tempting to speculate that at least some patients with tubular carcinoma may be adequately treated with local excision alone (i.e., without radiation therapy), there are currently insufficient data to consider this a standard treatment option.

MUCINOUS CARCINOMA

Mucinous carcinoma (also known as colloid carcinoma) is another special type cancer that is associated with a relatively favorable prognosis. The reported incidence of mucinous carcinoma varies depending on the histologic criteria. Most studies have indicated that less than 5% of invasive breast carcinomas have a mucinous component and of these, less than half represent pure mucinous carcinomas (44).

Clinical Presentation

The mean age at presentation for patients with mucinous carcinoma is in the seventh or early eighth decade in most studies, and is greater than that for patients with breast cancers of no special type. Many patients with mucinous carcinoma present with palpable tumors. However, with widespread screening mammography, a substantial proportion (30% to 70%) present with nonpalpable mammographic abnormalities, most often poorly defined or lobulated mass lesions that are rarely associated with calcification (46). Wilson and coworkers reported that pure mucinous carcinomas were more often associated with a circumscribed, lobulated contour than the irregular borders characteristic of tumors with a mixture of mucinous and nonmucinous components (mixed mucinous tumors) (46). In addition, mammographically occult mucinous carcinomas are not infrequent.

Gross Pathology

Mucinous carcinomas average approximately 3 cm in size, with a wide range reported in the literature (47). Mucinous carcinomas have a distinctive gross appearance. These lesions are typically circumscribed and have a variably soft, gelatinous consistency, and a glistening cut surface. However, lesions with a greater amount of fibrous stroma may have a firmer consistency.

Histopathology

The hallmark of mucinous carcinomas is extracellular mucin production. However, the extent of extracellular mucin varies from tumor to tumor. Typically, tumor cells in small clusters are dispersed within pools of extracellular mucin (Fig. 25-8). This characteristic histology should comprise at least 90% of the tumor (or 100% according to some) (6) to qualify for the diagnosis of mucinous carcinoma. The cells comprising mucinous carcinomas are usually of low or intermediate nuclear grade. Mucinous neoplasms intermixed with other non-mucinous histologic features are classified as "mixed" mucinous tumors. The cellularity of mucinous carcinomas is variable, with some tumors being highly cellular (type B) and others relatively paucicellular (type A). For paucicellular type A mucinous carcinomas, the differential diagnosis may

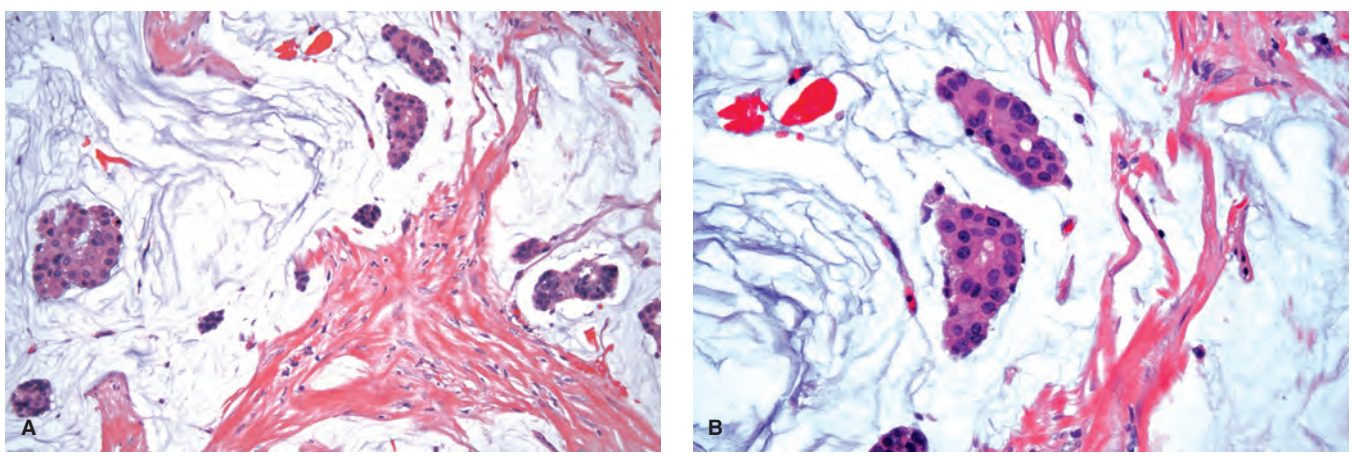


FIGURE 25-8 **Mucinous carcinoma. (A)** The tumor is composed of clusters of neoplastic cells dispersed in mucous pools. **(B)** In this specimen, the neoplastic cells have intermediate-grade nuclei.

include mucocele-like lesions, benign lesions characterized by cystically dilated ducts associated with rupture and extravasation of mucin into the stroma. Type B mucinous carcinomas may show endocrine differentiation, including immunoreactivity for chromogranin or synaptophysin (48). Mucinous carcinomas are often accompanied by a DCIS component which may have a papillary, micropapillary, cribriform, or solid pattern. In some cases, the DCIS may also exhibit prominent extracellular mucin production (47).

Biomarkers

The expression of various biological markers in mucinous carcinomas reflects the good prognosis associated with these lesions. Mucinous carcinomas are generally estrogen receptor positive. The majority of cases (about 70%) are also progesterone receptor positive. In addition, mucinous carcinomas usually do not overexpress the HER2 protein or show HER2 amplification (38). Mucinous carcinomas show relatively little genomic instability, with substantially fewer chromosomal gains and losses than invasive carcinomas of no special type (49). In gene expression studies, mucinous carcinomas generally cluster within the luminal A subtype. Type B mucinous carcinomas are distinct from type A mucinous carcinomas and cluster with other breast carcinomas showing neuroendocrine differentiation (50).

Clinical Course and Prognosis

Only 12% of patients presented with axillary lymph node metastasis in the SEER database review of over 11,000 patients with pure mucinous carcinoma (45). This is significantly less than the incidence of node positivity seen in mixed mucinous tumors or invasive breast cancers of no special type. Lymph node involvement is related to tumor size and is extremely rare in mucinous carcinomas measuring less than 1 cm (38).

With regard to survival, 38 patients with mucinous carcinoma were enrolled in the NSABP-B06 trial, and they experienced the same significantly increased survival as patients with tubular carcinoma, particularly in the node-negative group (43). Similar results were reported by Ellis and coworkers in their retrospective series; however, these patients were not stratified by nodal status (6). A report utilizing the SEER database compared 20-year survival data from 11,422 patients with mucinous carcinoma and patients with invasive ductal carcinoma diagnosed between 1973 and 2002 (45). Similar to the studies cited above, this report indicated that the patients with mucinous carcinoma present most often with localized disease (86%), with only 12% having regional lymph node involvement and 2% with distant metastases at the time of diagnosis. Although there were no significant differences in overall survival, survival at 10, 15, and 20 years for mucinous carcinoma was 89%, 85%, and 81%, respectively, compared with 72%, 66%, and 62% for invasive ductal carcinoma. The most significant prognostic factors in multivariate analyses were nodal status, then age, tumor size, progesterone receptor status, and nuclear grade (45). In addition, two series, one examining node-negative early stage breast cancer patients treated with mastectomy (with 20-year follow-up), and the other examining early stage patients treated with breast-conserving therapy (with 10-year follow-up), both reported that patients with mucinous carcinoma had significantly lower rates of distant recurrences compared to patients with invasive ductal carcinoma (41,42). Several studies have noted that a significant number of late recurrences are seen in patients with mucinous carcinoma, with one report documenting a recurrence 30 years after initial treatment (51).

Several studies have examined the use of conservative surgery and radiation therapy in patients with mucinous carcinoma, and report no significant differences in local recurrence rates compared to patients with invasive ductal carcinoma (42). Given the relatively good prognosis in patients with mucinous carcinoma, some authors have raised the question of whether radiation therapy can be safely omitted after breast-conserving surgery in patients with this tumor type; however, at this time, there are insufficient data on which to base such a recommendation.

Mucinous carcinomas have rarely been associated with unusual metastatic manifestations, including mucin embolism resulting in fatal cerebral infarcts and pseudomyxoma peritonei (52,53).

CARCINOMAS WITH MEDULLARY FEATURES

Classic medullary carcinomas are rare, accounting for less than 1% of all invasive breast cancers. Initial reports indicated that this type of breast cancer had a favorable prognosis despite its aggressive histologic appearance (54,55). However, there is considerable controversy regarding the appropriate histologic definition of medullary carcinoma, as well as the reproducibility of this diagnosis among pathologists. Carcinomas with some but not all of the features of medullary carcinoma have been called “atypical medullary carcinomas,” “invasive carcinomas with medullary features,” and “invasive ductal carcinomas with medullary features.” Given the difficulties in applying the criteria for medullary carcinoma reproducibly, the current WHO classification combines medullary carcinomas, atypical medullary carcinomas and invasive ductal carcinomas with medullary features into a single group designated “carcinomas with medullary features” (1).

Clinical Presentation

Patients with carcinomas with medullary features usually present at a younger age than patients with other breast cancers, owing, at least in part, to the inclusion in this group of patients with inherited *BRCA1* mutations. The majority of patients present with a palpable mass. Of interest, some patients with this tumor type exhibit axillary lymphadenopathy at the time of presentation with histologic examination of the lymph nodes showing only benign reactive changes (59). Rare examples of carcinoma with medullary features have been reported in males.

Most carcinomas with medullary features are associated with a moderately well-defined mass without calcifications (59); however, a significant proportion are associated with an ill-defined margin. Moreover, the majority of mammographically well-circumscribed cancers are infiltrating ductal carcinomas rather than medullary carcinomas (60). On ultrasound examination, medullary carcinomas are generally well-circumscribed, frequently lobulated, and hypoechoic (60).

Gross Pathology

The mean size of medullary carcinomas is similar to that of breast cancers of no special type (47). Grossly, these lesions are well circumscribed, soft, tan-brown to gray tumors that bulge above the cut surface of the specimen. A multinodular appearance may be appreciated in some cases. Areas of hemorrhage, necrosis, or cystic degeneration may be present in tumors of any size, but prominent necrosis is often seen in larger tumors.

Histopathology

Several similar but distinct classification systems for the histologic diagnosis of medullary carcinomas have been proposed (56–58). All three classification schemes recognize the following attributes, but the relative importance and the mandatory nature of each are stressed to a different degree: (i) syncytial growth pattern of the tumor cells in more than 75% of the tumor, (ii) admixed lymphoplasmacytic infiltrate, (iii) microscopic circumscription,(iv) grade 2 or 3 nuclei, and (v) absence of glandular differentiation (Fig. 25-9). Tumors that lack a variable number of these characteristics (depending on the system used) have been classified either as "atypical medullary carcinoma," or invasive ductal carcinoma.

Carcinomas with medullary features may show hemorrhage, tumor necrosis, cystic degeneration, and various types of metaplasia of the tumor cells, most often squamous metaplasia (47). Some tumors exhibit bizarre cytologic features with marked nuclear atypia and multinucleated tumor giant cells. There is usually little or no associated *in situ* carcinoma.

Biomarkers

Carcinomas with medullary features are typically estrogen receptor negative, progesterone receptor negative, and lack HER2 overexpression/amplification ("triple negative") and show a high proliferation rate. They often show a basal-like phenotype, with expression of basal cytokeratins (CK5/6, 14, and 17) and epidermal growth factor receptor (EGFR) and may have *TP53* mutations. Genomic instability is a characteristic feature of these lesions. Most breast cancers in women with germline *BRCA1* mutations show medullary features; however, only about 13% of cancers with medullary features are associated with germline *BRCA1* mutations (61). Many of the sporadic carcinomas show inactivation of *BRCA1* by somatic mutation or promoter hypermethylation (62).

Gene expression profiling studies have compared patterns of gene expression in 22 cancers diagnosed as medullary carcinoma with 44 high-grade invasive ductal carcinomas. Results of these studies showed that 95% of medullary carcinomas displayed a basal-like profile, similar to that seen in the basal group of invasive ductal carcinomas. Compared with the basal group of invasive ductal carcinomas, however, medullary carcinomas showed lower expression of genes involved in smooth muscle differentiation and greater expression of genes on 12p13 and 6p21, regions known to contain genes involved in pluripotency. Together, these findings suggest that carcinomas with medullary features represent a subset of basal-like breast cancers (63). Studies using array comparative genomic hybridization (CGH) have further clarified the similarities and differences between cancers diagnosed as medullary and other basal-like carcinomas. In one study, medullary carcinomas and other basal-like carcinomas were both characterized by 1q and 8q gains and X losses, with medullary carcinomas typically showing greater chromosomal instability and a wider spectrum of chromosomal gains and losses (64).

Clinical Course and Prognosis

Although studies have differed in the histologic criteria employed, most studies indicate that the incidence of axillary lymph node metastases is lower in patients with medullary carcinomas (19% to 46%) than in those with atypical medullary carcinomas (30% to 52%) or invasive ductal carcinomas with medullary features (29% to 65%) (56,57).

Data regarding survival rates in patients with medullary carcinoma and carcinomas with medullary features are difficult to interpret given the different classification systems employed and general lack of reproducibility. Although a number of earlier studies reported a more favorable prognosis for medullary carcinomas, this finding has not been confirmed in all studies. In addition, a number of studies have also questioned the practical applicability of the diagnostic criteria. Thus, although there may be patients with medullary carcinoma who have improved survival compared to patients with breast cancers of no special type, the ability of pathologists to reliably and reproducibly identify this subset of patients is limited at the current time. It is essential that clinicians be aware of these limitations when confronted with a pathology report suggesting the diagnosis of medullary carcinoma or carcinoma with medullary features. Recently, some studies have suggested that features of the associated inflammatory infiltrate may be important in the prognosis of both high-grade medullary-like and non-medullary-like carcinomas (65,66).

The results of the use of breast-conserving therapy in patients with medullary carcinoma have been reported in several studies (42) with no significant differences in local recurrence rates among patients with medullary carcinoma compared to patients with invasive ductal carcinoma. Thus,

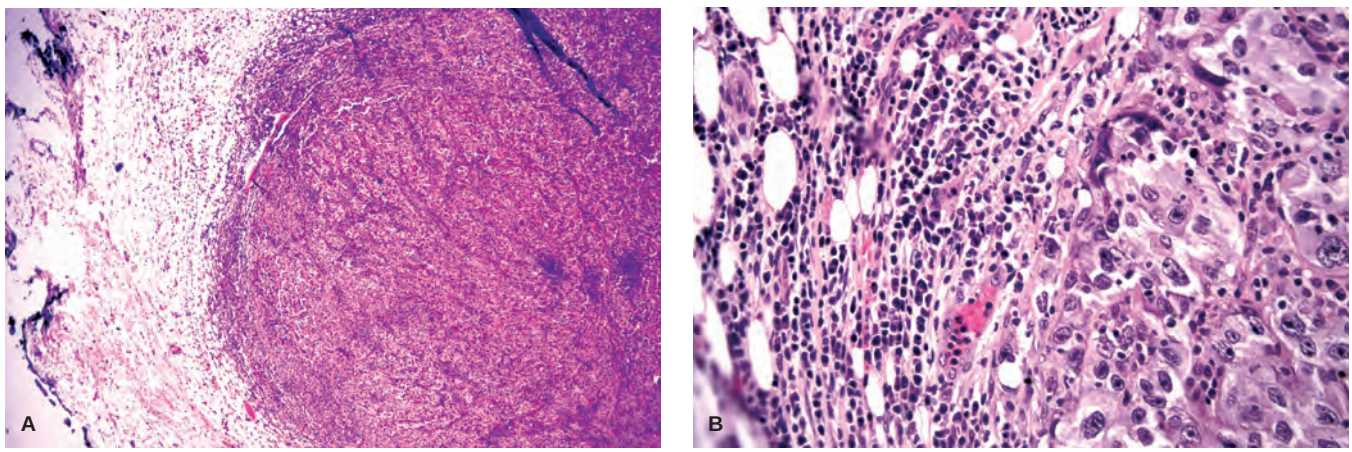


FIGURE 25-9 **Medullary carcinoma. (A)** Low-power photomicrograph demonstrating the well-circumscribed border of the tumor. **(B)** The tumor cells show high-grade nuclear features, and a prominent admixture of lymphocytes and plasma cells is seen.

the available data suggest that conservative surgery and radiation therapy is appropriate local treatment for patients with medullary carcinoma and carcinoma with medullary features.

INVASIVE CRIBRIFORM CARCINOMA

Invasive cribriform carcinoma is a well-differentiated cancer that shares some morphologic features with tubular carcinoma, and is also associated with a favorable prognosis. Invasive cribriform carcinoma accounts for 1% to 4% of invasive breast cancers (67).

Clinical Presentation

The majority of patients with invasive cribriform carcinoma present in the sixth decade (range 19 to 86 years) (67). Tumors may present as a palpable mass, but are often clinically occult and detected by mammography as spiculated masses with or without associated calcifications.

Gross Pathology

No distinctive gross features of invasive cribriform carcinoma have been described.

Histopathology

Invasive cribriform carcinomas are characterized by low- to intermediate-grade tumor cells that invade the stroma in a cribriform or fenestrated growth pattern similar to that seen in the cribriform pattern of DCIS (Fig. 25-10). These tumors often show admixtures of other histologic patterns of invasive breast cancer, particularly tubular carcinoma, which is seen in approximately 20% of cases. The "classic" variant of invasive cribriform carcinoma, described by Page et al. (67), is defined as a tumor composed of an exclusively invasive cribriform pattern, or a tumor with more than 50% invasive cribriform features in which the remainder of the tumor exhibits features of tubular carcinoma. Tumors with any component of nontubular carcinoma were described as "mixed" in that study. Most invasive cribriform carcinomas are associated with DCIS, usually of the cribriform type. The average size of these tumors is relatively large, 3.1 cm (range 1 to 14 cm) for the classical variant of cribriform carcinoma, to 4.2 cm (range 2 to 9 cm) for tumors of mixed histology (67).

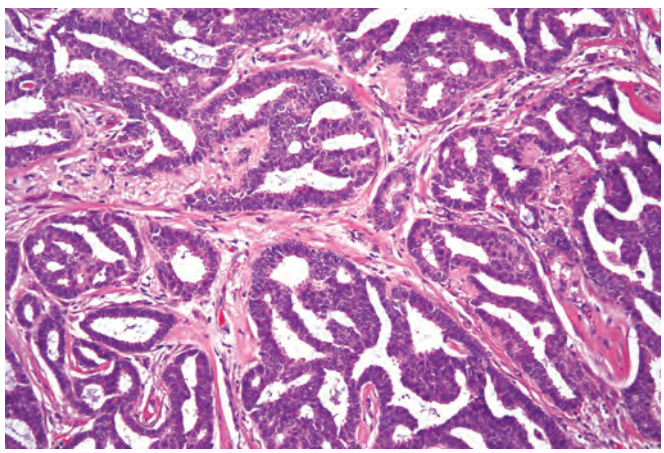


FIGURE 25-10 **Invasive cribriform carcinoma.** The tumor cells invade the stroma in nests that have a fenestrated growth pattern, similar to that seen in the cribriform pattern of ductal carcinoma *in situ*.

The main lesion to distinguish from invasive cribriform carcinoma is the cribriform pattern of DCIS. Invasive cribriform carcinoma ignores normal breast architecture and infiltrates between ducts and lobules, whereas DCIS maintains the normal ductal and lobular architecture. In contrast to cribriform DCIS, where the involved spaces have smooth, rounded contours, the infiltrating glands of invasive cribriform carcinoma often show irregular, sharp, and angulated borders. The stroma in invasive cribriform carcinoma tends to be desmoplastic compared to that associated with cribriform DCIS. Last, the main distinguishing feature is the lack of myoepithelial cells surrounding the glandular islands of invasive cribriform carcinoma, in contrast to their presence in cribriform DCIS. Immunohistochemistry for myoepithelial markers may be useful in distinguishing the two and in determining an accurate size for the invasive component. Also in the differential diagnosis is adenoid cystic carcinoma. Immunohistochemistry for myoepithelial markers can be helpful in documenting the dual epithelial/myoepithelial cell population characteristic of adenoid cystic carcinoma not present in invasive cribriform carcinoma.

Biomarkers

Invasive cribriform carcinomas are positive for estrogen receptor and most are also positive for progesterone receptor. These cancers typically show no overexpression or amplification of HER2. On gene expression profiling studies, invasive cribriform carcinomas fall into the luminal A subtype (24).

Clinical Course and Prognosis

In the series of Page et al. (67), none of the 35 lesions categorized as the classic variant of invasive cribriform carcinoma exhibited lymphatic/vascular space invasion, compared to 3 of 16 (19%) tumors with mixed histology. In that study, axillary lymph node metastases were seen in 14% of patients with classic cribriform carcinoma and 16% of patients with tumors of mixed histology (67). With a median follow-up interval of 14.5 years, Page et al. reported no deaths related to invasive cribriform carcinoma in patients with the classic variant (although one patient recurred in axillary and supraclavicular lymph nodes), but 38% (6 of 16) patients with tumors of mixed histology died of their disease (67). In general, patients with pure invasive cribriform carcinoma have a more favorable prognosis than do patients whose tumors show mixed histologic types (24,67). The excellent prognosis in invasive cribriform carcinoma was confirmed by Ellis and coworkers (6), who reported a 10-year survival of 91% in 13 patients, compared to a 47% 10-year survival for patients with invasive carcinoma of no special type.

INVASIVE PAPILLARY CARCINOMA

Invasive papillary carcinomas are extremely rare. Most published literature concerning papillary carcinomas of the breast includes both invasive and *in situ* papillary lesions. Although published series suggest that these tumors comprise from less than 1% to 2% of invasive breast cancers (68,69), in our experience true invasive papillary carcinomas are even more infrequent than this.

Clinical Presentation

Invasive papillary carcinomas are diagnosed predominantly in postmenopausal patients. Similar to medullary carcinomas, Fisher et al. noted that a significant proportion of patients with invasive papillary carcinoma exhibit axillary

lymphadenopathy suggestive of metastatic disease, but which on pathologic examination is due to benign reactive changes (68).

Mammographically, invasive papillary carcinoma is reportedly characterized by nodular densities which may be multiple, and are frequently lobulated (69,70). These reports should be interpreted with caution, however, as one study noted the difficulty in distinguishing between intracystic papillary carcinoma, intracystic papillary carcinoma with invasion, and invasive papillary carcinoma on imaging (70).

Gross Pathology

Fisher et al. reported that invasive papillary carcinoma is grossly circumscribed in two-thirds of cases (68). Other invasive papillary carcinomas are grossly indistinguishable from invasive breast cancers of no special type.

Histopathology

Of the 1,603 breast cancers reviewed in the NSABP-B04 study, 38 had papillary features, and all but 3 of these were "pure," without an admixture of other invasive histologic types. Microscopically, invasive papillary carcinomas are characteristically circumscribed, show delicate or blunt papillae, and show focal solid areas of tumor growth (Fig. 25-11). The cells typically show amphophilic cytoplasm, but may have apocrine features, and also may exhibit apical "snouting." The nuclei of tumor cells are typically intermediate grade and most tumors are histologic grade 2 (68). Tumor stroma is not abundant in most cases, and occasional cases show prominent extracellular mucin production. DCIS is present in more than 75% of cases, and usually, but not exclusively, has a papillary pattern and may be associated with microcalcifications.

In some lesions in which both the invasive and *in situ* components have papillary features, it may be difficult to determine the relative proportion of each without myoepithelial stains. Many encapsulated papillary carcinomas (also called intracystic papillary carcinomas) have been shown to have absent myoepithelium around the periphery. This finding raises the possibility that these are indolent invasive carcinomas with an expansile growth pattern. However, given their excellent outcome with local therapy alone, the current WHO classification recommends that encapsulated papillary carcinomas be staged and managed as *in situ* lesions (Tis), unless there are areas of frank invasion (1). Areas of invasive ductal carcinoma of no special type may be seen in association with encapsulated papillary carcinoma, solid papillary carcinoma or papillary DCIS. These invasive cancers should be classified according to their individual features and not as invasive papillary carcinoma.

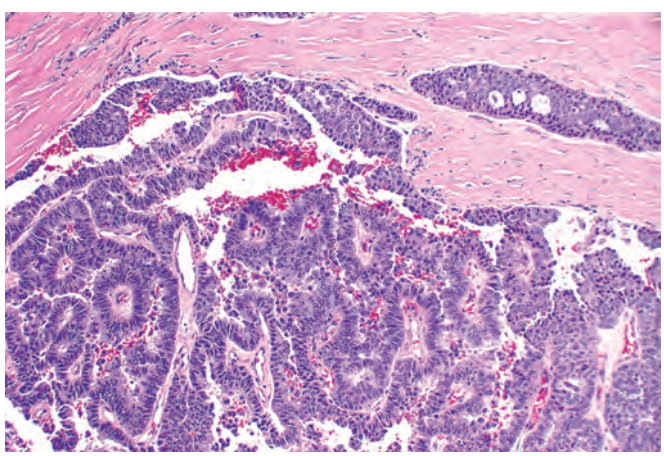


FIGURE 25-11 **Invasive papillary carcinoma.** The tumor cells are organized around fibrovascular cores.

Biomarkers

There is little information on expression of hormone receptors and HER2 in invasive papillary carcinoma; however, the small number of reported cases have been hormone receptor positive and HER2 negative. Based on the rarity of this tumor, metastasis from other sites, including ovary and lung, might be considered in the differential diagnosis, especially for lesions without an *in situ* component.

Clinical Course and Prognosis

There are limited data on the prognostic significance of invasive papillary carcinoma (43,68,71). Among 35 patients with this tumor in the NSABP-B04 trial, after 5 years median follow-up, there were only 3 treatment failures, including 1 patient who died from metastatic papillary carcinoma. These survival data were similar to those reported for patients with pure tubular and mucinous carcinomas in this study (68). A later publication updating the NSABP-B04 results at 15 years revealed that patients with "favorable" histology tumors (including invasive papillary carcinomas) still had significantly better survival in univariate analysis, but tumor histology was not an independent predictor of survival in multivariate analysis (71). However, node-negative patients with invasive papillary carcinomas enrolled in the NSABP-B06 trial experienced improved survival after 10 years follow-up compared to patients with carcinomas of no special type, and tumor histology was an independent predictor of survival in multivariate analysis (43).

INVASIVE MICROPAPILLARY CARCINOMA

Pure invasive micropapillary carcinoma comprises up to 2% of invasive carcinomas of the breast; however, foci of micropapillary carcinoma are more commonly seen mixed with other histologic types, most often invasive ductal carcinoma of no special type. Patients with invasive micropapillary carcinoma often present with axillary lymph node metastases and have a relatively poor prognosis (72–75).

Clinical Presentation

The mean age at presentation for patients with invasive micropapillary carcinoma is 54 to 62 years (72–75). Patients may present with a palpable mass or a mammographically detected lesion, similar to carcinomas of no special type.

Gross Pathology

No distinguishing gross features have been described. The median size was reported as 1.5 cm in one study (range 0.8 to 3 cm), and 4.9 cm in a second study (72,73). A more recent study of 80 cases reported a mean size of 2 cm (range 0.1 to 10 cm) (74). These sizes are significantly larger than invasive carcinomas of no special type (73).

Histopathology

These tumors are characterized by clusters of cells in a micropapillary or tubular-alveolar arrangement that appear to be suspended in a clear space. These micropapillary clusters, unlike true papillary lesions, lack fibrovascular cores (Fig. 25-12). The cell clusters characteristically

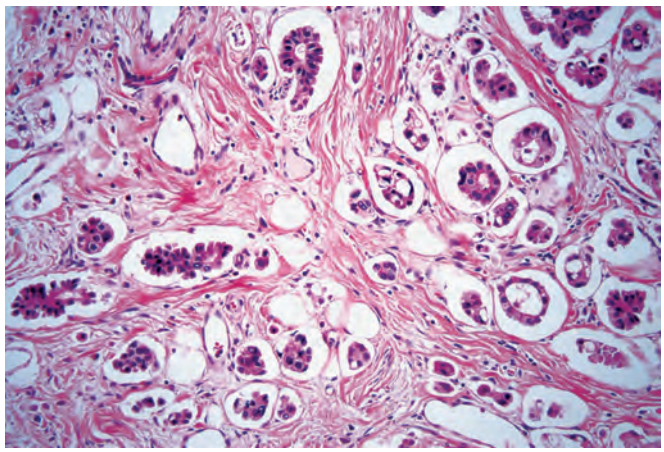


FIGURE 25-12 **Invasive micropapillary carcinoma.** Clusters of neoplastic cells, some forming glands, are present in clear spaces separated by fibrovascular tissue.

have an "inside-out" arrangement, with the apical surface polarized to the outside. This reverse polarity can be demonstrated using immunohistochemistry for epithelial membrane antigen (EMA). The overall appearance of invasive micropapillary carcinoma may mimic serous papillary carcinomas of the ovary, or may simulate lymphatic/vascular space invasion (72). True lymphatic/vascular space invasion has been reported in 33% to 67% of cases, and may be extensive (72–74). Cytologically, the cells comprising the invasive micropapillary carcinoma usually have low to intermediate grade nuclei. The majority of tumors (67% to 70%) are associated with a DCIS component with micropapillary and cribriform patterns (72,73). A minority of cases (33%) have shown calcifications histologically (72).

An invasive micropapillary component is found in approximately 6% of all breast carcinomas (75). However, this component usually makes up a small proportion of the overall tumor, involving less than 20% of the tumor mass in one study (75). In most reported cases, invasive micropapillary carcinomas have been admixed to a variable degree with invasive carcinomas of no special type or, in a minority of cases, with mucinous carcinoma. However, unlike other special type carcinomas, the prognostic implications appear to be the same whether the micropapillary component is present focally or diffusely within the tumor (73,75).

Biomarkers

The majority of invasive micropapillary carcinomas are estrogen receptor positive (72% to 75%), and about half are positive for progesterone receptor. HER2 protein overexpression is reported in up to a third of cases (76,77), with amplification being somewhat less frequent (10% to 30% of cases) (24,78). Immunohistochemical positivity with Wilm's Tumor Antigen 1 (WT-1) and PAX8 are rarely seen in breast cancer and can be useful in distinguishing metastatic micropapillary carcinoma of breast from papillary serous adenocarcinoma of the gynecologic tract in difficult cases.

Array CGH studies have shown recurrent gains of 8q, 17q, and 20q and deletions of 6q and 13q in both pure and mixed micropapillary carcinomas (79). Of interest, similar alterations have been found in both the micropapillary and nonmicropapillary areas in mixed micropapillary carcinomas (78,79). In gene expression profiling studies, invasive micropapillary carcinomas are usually classified as luminal A or luminal B subtype (24).

Clinical Course and Prognosis

In a study of 27 patients with pure invasive micropapillary carcinoma, axillary lymph node metastases were seen in all 27 patients, compared to 66% of patients with invasive carcinoma of no special type (73). Furthermore, four or more lymph nodes were involved in 82% of cases, and on average, nine lymph nodes were positive for metastatic carcinoma. Follow-up information was available for 12 patients, and of these, 6 died an average of 22 months after their initial treatment (73). In a different study of 80 cases of invasive micropapillary carcinoma, 47 (72%) of 65 cases with axillary lymph node dissections had positive lymph nodes (74). Another study that analyzed both pure and mixed invasive micropapillary carcinoma found axillary lymph node metastases present in 77% of cases. The metastases were typically multiple, with 51% of cases having 3 or more positive nodes (75). Importantly, these authors found no significant difference in lymph node status, ER status, tumor size, tumor grade, or lymphatic vascular invasion between tumors with predominant versus focal invasive micropapillary components. Interestingly, the clinical outcome of tumors with invasive micropapillary histology did not differ from infiltrating ductal carcinomas of similar stage and nodal status (75). These findings suggest that while carcinomas with an invasive micropapillary component typically present with higher-stage disease than patients with invasive carcinoma of no special type, when adjusted for stage, the prognosis of these two groups is similar.

METAPLASTIC CARCINOMA

Metaplastic carcinomas represent a morphologically heterogeneous group of invasive breast cancers in which a variable portion of the glandular epithelial cells comprising the tumor have undergone transformation into an alternate cell type—either a nonglandular epithelial cell type (e.g., squamous cell), a mesenchymal cell type (e.g., spindle cell, chondroid, osseous, or myoid), or both. There are numerous published reports describing various aspects of metaplastic carcinomas, and numerous appellations have been applied to the various tumors comprising this group. However, there is no uniformly agreed-upon classification scheme for these tumors. Metaplastic carcinomas are uncommon lesions, representing less than 5% of all breast cancers. The prognostic implications of metaplastic carcinomas are difficult to define, and may relate to some degree to the type of metaplasia present, as discussed below.

Clinical Presentation

Patients with metaplastic carcinoma are similar to patients with invasive carcinoma of no special type with regard to their age at presentation, the manner in which their tumors are detected, and the location within the breast in which these tumors arise (81,82). Most patients present with a single palpable lesion that not infrequently is associated with rapid growth of short duration (82). Skin fixation has been noted in 35% of patients and fixation to deep tissues in 23% of patients in one study (81).

The mammographic appearance of metaplastic carcinoma is not specific. Most are fairly circumscribed, noncalcified lesions, which in many cases appear benign (83). Some show both a circumscribed portion and a spiculated portion, which in one study correlated with the metaplastic and invasive epithelial components, respectively (83,84). Foci of osseous metaplasia may be detected mammographically in a subset of cases.

Gross Pathology

The gross appearance of metaplastic carcinomas is not distinctive, and these tumors can either be well circumscribed or show an indistinct or irregular border. Cystic degenerative changes are not infrequent, particularly in lesions with squamous differentiation. In general, metaplastic carcinomas tend to be relatively large tumors, compared to invasive carcinomas of no special type.

Histopathology

Microscopically, metaplastic carcinomas are highly distinctive, but vary in the types and extent of metaplastic changes. Although there is no universally accepted classification system, current WHO classification (1) includes five subtypes: metaplastic carcinoma with mesenchymal differentiation, spindle cell carcinoma, low-grade adenosquamous carcinoma, fibromatosis-like metaplastic carcinoma, and squamous cell carcinoma.

Metaplastic carcinoma with mesenchymal differentiation most commonly shows chondroid and osseous heterologous elements (Figs. 25-13 and 25-14). In these tumors, the cartilage and bone may appear histologically benign or frankly malignant, resembling chondrosarcoma and osteosarcoma, respectively. If the heterologous metaplastic component of a particular tumor predominates, the differential diagnosis will include a malignant phyllodes tumor with heterologous elements and stromal overgrowth, as well as a pure sarcoma, either primary or metastatic. The correct diagnosis in such cases may require extensive tissue sampling in order to demonstrate epithelial elements. In some cases, immunohistochemical staining for epithelial markers, such as cytokeratin, may be required for proper diagnosis. A panel of cytokeratin antibodies may be necessary, including broad-spectrum and high-molecular weight/basal cytokeratin antibodies, as keratin immunoreactivity may be only focal.

Spindle cell carcinomas may occur as purely spindle cell lesions or mixed with glandular, squamous or heterologous elements (Fig. 25-15). The spindle cells can vary from bland to highly pleomorphic and can show fascicular, fasciitis-like, storiform or haphazard growth patterns. The borders are typically infiltrating, with entrapped normal ducts and lobules. High-grade lesions may completely obliterate normal breast architecture. In areas, spindle cells may merge with areas that have a more epithelioid appearance. In mixed lesions, areas of invasive breast carcinoma not otherwise specified or DCIS can provide evidence of the epithelial nature of the lesion. However, in pure spindle cell tumors, immunohistochemical stains for keratin and other markers may be required for the correct diagnosis. Immunoreactivity for keratins may be only focal and use of a panel of cytokeratin antibodies may be necessary, including broad-spectrum and high-molecular weight/basal cytokeratin antibodies. Spindle cell carcinomas also commonly express markers associated with myoepithelial cells, including p63 and actins.

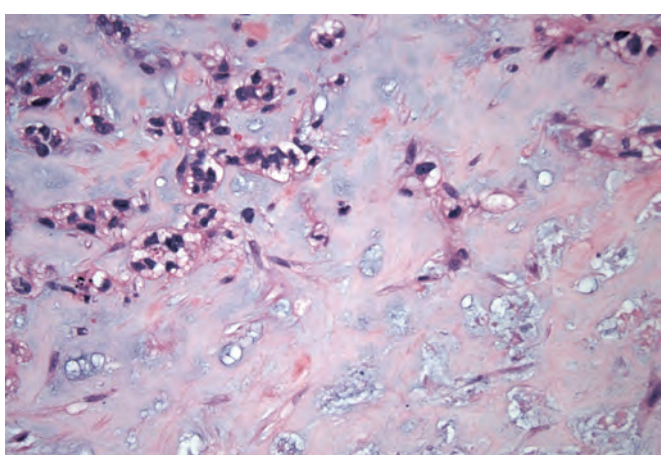


FIGURE 25-13 **Metaplastic carcinoma with chondroid metaplasia.** A small area of conventional invasive ductal carcinoma is present at the left side of this photomicrograph. The major portion of this tumor, however, is composed of neoplastic cells in a chondroid matrix.

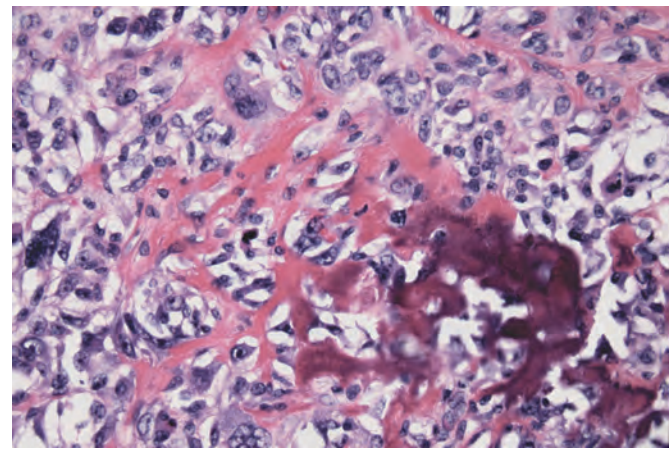


FIGURE 25-14 **Metaplastic carcinoma with osseous metaplasia.** Although some of this neoplasm shows features of invasive ductal carcinoma (left), foci of osteoid formation are evident.

Pure *squamous cell carcinoma* of the breast is rare; however, foci of squamous differentiation may be seen in invasive carcinomas of no special type and are commonly seen in carcinomas with medullary features. Pure squamous cell carcinoma of the breast often shows prominent cystic degeneration and may range from well to poorly differentiated. In well-differentiated cases, parts of the tumor may be composed of squamous epithelial-lined cysts resembling benign epidermal inclusion cysts. Spindle cell differentiation is commonly seen in association with squamous differentiation. In pure squamous cell lesions, the differential diagnosis should include spread from a squamous cell carcinoma at another site.

Low-grade adenosquamous carcinoma is an unusual subtype of metaplastic carcinoma that appears to represent a distinct clinicopathologic entity (86,87) (Fig. 25-16). These tumors may sometimes arise in association with a preexisting benign sclerosing process, such as a complex sclerosing lesion, sclerosing papilloma or adenomyoepithelioma (87). Low-grade adenosquamous carcinomas are typically smaller than other metaplastic carcinomas, with a median size between 2.0 and 2.8 cm (range 0.5 to 8.6 cm) (86,87). They exhibit a firm, yellow cut surface with irregular borders. Histologically, these tumors are well differentiated, show epidermoid differentiation, and often have a peculiar collagenized, lamellated stroma. Areas of squamous differentiation are present in most tumors, and are admixed with areas of glandular differentiation (Fig. 25-16). The glands often show elongated, compressed lumens, which may suggest syringomatous differentiation. Microcysts filled with

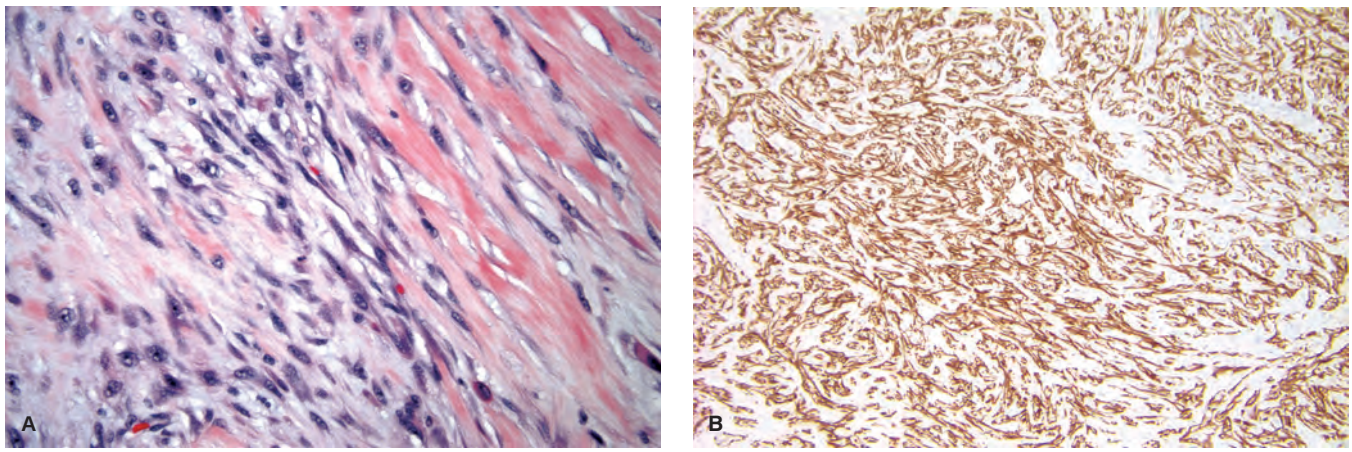


FIGURE 25-15 **Metaplastic carcinoma, spindle cell type. (A)** Hematoxylin and eosin-stained sections reveal interlacing fascicles of spindle cells without evidence of epithelial differentiation. **(B)** Immunoperoxidase stain for keratin reveals that most of the tumor cells show immunoreactivity for this protein, characteristic of cells with an epithelial phenotype.

keratinaceous material may be present. DCIS is usually not seen. Clusters of stromal lymphocytes may be present at the periphery of the lesion.

The differential diagnosis of low-grade adenosquamous carcinoma includes syringomatous adenoma of the nipple, reactive squamous metaplasia, and tubular carcinoma. These lesions may be locally aggressive, but have a relatively good prognosis when compared with other metaplastic carcinomas (86,87).

Fibromatosis-like metaplastic carcinoma is a low-grade metaplastic breast tumor composed of bland spindle cells that resemble those seen in fibromatosis (88). Unlike fibromatosis, the spindle cells in this lesion show expression of cytokeratin at least focally. Small foci of squamous differentiation or epithelioid cell clusters may also be present. These tumors may sometimes arise in association with a preexisting benign sclerosing process (87). This rare tumor is associated with a high rate of local recurrence (80). Regional and distant metastases have also been reported (88).

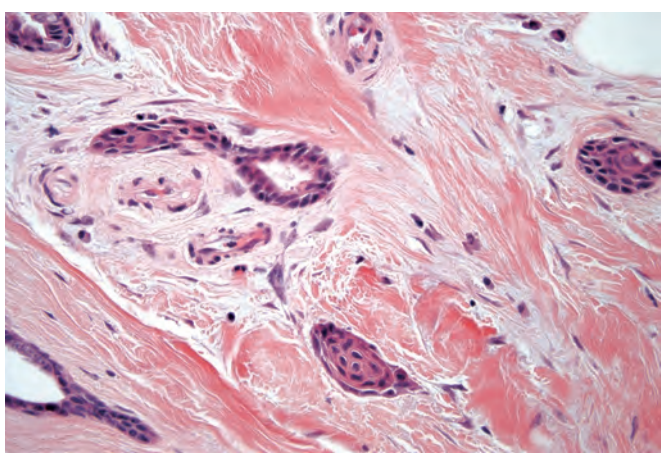


FIGURE 25-16 **Low-grade adenosquamous carcinoma.** The tumor shows foci of glandular and squamous differentiation. The neoplastic cells have low-grade nuclear features.

Biomarkers

Metaplastic carcinomas are typically negative for estrogen receptor, progesterone receptor, and HER2, regardless of the histologic subtype examined. Many show at least focal expression of basal cytokeratins (CK5/6, 14, and 17), EGFR, and p63. Some metaplastic carcinomas express myoepithelial markers, blurring the distinction between metaplastic carcinomas and myoepithelial carcinomas (see below). In gene expression studies, some metaplastic carcinomas cluster in the basal-like group and others in the claudin-low group (24).

Clonality in metaplastic carcinomas has been assessed using microdissection techniques and evaluation of loss of heterozygosity at multiple chromosomal loci (85). In one study, all six cases of metaplastic carcinoma demonstrated identical clonality of the epithelial and mesenchymal components, and the same clone was also identified in nearby DCIS in one case. The authors concluded that the mesenchymal component of these lesions arose from mutation of the epithelial component (85).

Clinical Course and Prognosis

The reported frequency of axillary lymph node metastases in patients with metaplastic carcinoma is lower than for patients with invasive carcinomas of no special type of equivalent size and grade (1). As with other triple-negative breast cancers, distant metastases, especially to lung and brain, may be seen even in the absence of axillary lymph node metastases. Metastatic lesions may either demonstrate an epithelial phenotype, the metaplastic phenotype, or both.

Survival data reported in various studies are difficult to compare due to the relatively small numbers of patients included in the studies, differences in tumor types, differences in treatment and follow-up intervals and the paucity of studies that stratify patients by stage. However, as a group, patients with metaplastic carcinomas appear to have a lower rate of response to chemotherapy and a poorer outcome than patients with other triple-negative breast carcinomas (89). At the present time, it is difficult to determine the prognostic significance of the presence or absence of specific metaplastic components. However, low-grade

adenosquamous carcinoma and low-grade fibromatosis-like metaplastic carcinoma both appear to have a relatively favorable prognosis (87,90).

CARCINOMAS WITH NEUROENDOCRINE FEATURES

Some invasive breast cancers show evidence of neuroendocrine differentiation at the morphologic level, histochemical level, immunohistochemical level, or some combination of these. In addition, in rare instances, breast carcinomas can secrete hormonal products that cause clinical symptoms.

Clinical Presentation

With the exception of the very rare functioning neuroendocrine tumor which results in clinical manifestations due to hormone production and secretion, carcinomas with neuroendocrine differentiation do not demonstrate unique clinical manifestations. In most studies, the median age of patients and the location in which these tumors arise in the breast are similar to those seen in invasive cancers of no special type. Distinctive mammographic or ultrasound characteristics of invasive carcinomas with neuroendocrine differentiation have not been reported.

Gross Pathology

Invasive carcinomas with neuroendocrine differentiation are not associated with distinctive gross characteristics and the reported mean size in most studies is similar to invasive cancers of no special type.

Histopathology

Carcinomas with neuroendocrine differentiation represent a heterogeneous group of neoplasms. This is related to the fact that "neuroendocrine differentiation" is defined differently in various studies. Many invasive carcinomas of no special type and some mucinous and solid papillary tumors show neuroendocrine differentiation by histochemical or immunohistochemical studies. Most reports refer to "argyrophilic" carcinomas, lesions that demonstrate distinctive granular material in the cytoplasm of tumor cells (argyrophilic granules) when stained with histochemical stains such as the Grimelius stain. Argyrophilic granules have been reported in up to half of all breast carcinomas, depending on methodology, interpretation and, possibly differences in patient selection (91). Argyrophilic carcinomas can be associated with a variety of histologic appearances, including tumors with no overt morphologic evidence of endocrine differentiation. Tumors with typical endocrine morphology may fail to demonstrate histochemical evidence of argyrophilia. Most tumors with morphologic evidence of neuroendocrine differentiation also demonstrate immunoreactivity for one or more specific neuroendocrine markers such as chromogranin or synaptophysin; however, many "argyrophilic" tumors are negative for these markers by immunohistochemistry (92). Therefore, argyrophilic carcinomas clearly represent a heterogeneous group of tumors, only some of which should be considered as showing true neuroendocrine differentiation.

In a study of neuroendocrine differentiation in a series of breast carcinomas using immunohistochemistry for neuron-specific enolase, chromogranin A and synaptophysin 11% of cases were positive for more than one endocrine marker (94). However, none of the tumors showed more than 50% tumor cells positive for the neuroendocrine markers and many cases had fewer than 5% of tumor cells positive. There was no significant association between neuroendocrine differentiation and tumor size, grade, or stage. In addition, overall or disease-free survival did not differ among patients with tumors with or without neuroendocrine differentiation (94).

Of tumors showing morphologic evidence of neuroendocrine differentiation by routine light microscopy, distinct morphologic subtypes have been recognized. Primary tumors that are morphologically indistinguishable from carcinoid tumors occurring elsewhere in the body comprise less than 1% of all breast cancers (Fig. 25-17) and are classified as neuroendocrine carcinoma, well differentiated, in the most recent WHO classification (1). These tumors must be distinguished from metastatic carcinoids, which occasionally involve the breast and may even initially present as breast masses (95). In some cases, the presence of DCIS in the region of the tumor can assist with this differential diagnosis. In equivocal cases, a clinical evaluation to rule out an alternate primary site may be required.

At the other end of the neuroendocrine spectrum are primary breast carcinomas which are indistinguishable from small-cell (oat-cell) carcinomas (neuroendocrine carcinoma, poorly differentiated/small-cell carcinoma in the most recent WHO classification 1) or large-cell neuroendocrine carcinomas in other sites (96). Again, these tumors must be distinguished from metastatic small cell or large cell neuroendocrine carcinoma involving the breast, and a clinical evaluation to rule out an alternate primary site, such as the lung, may be required (97).

Biomarkers

There is only limited information regarding the expression of biomarkers in invasive carcinomas with neuroendocrine differentiation. Small studies suggest that most tumors are positive for estrogen receptor and progesterone receptor (96) and negative for HER2 amplification or membrane overexpression (96). In gene expression profiling studies, ER-positive carcinomas with neuroendocrine differentiation cluster together with mucinous carcinomas in the luminal subtype (24).

Clinical Course and Prognosis

There appears to be no significant difference in the incidence of axillary lymph node metastases in patients with invasive carcinoma with neuroendocrine differentiation compared

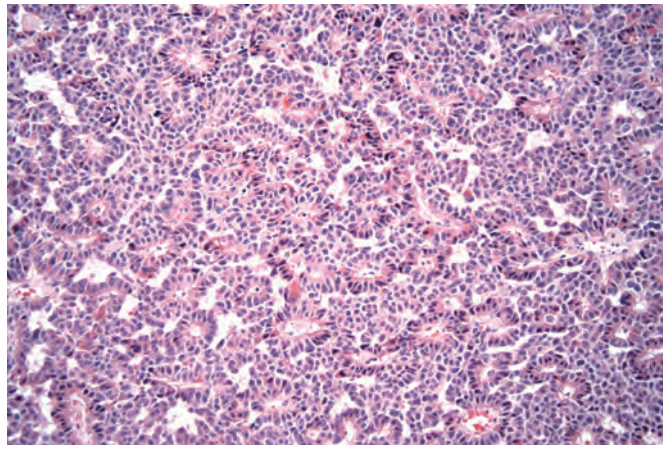


FIGURE 25-17 **Carcinoid tumor.** This tumor is composed of nests of cells that focally form acinar structures. The nuclei are small and uniform, and the cytoplasm is eosinophilic and granular. This histologic appearance is identical to that seen in carcinoid tumors in other sites.

with patients with invasive carcinoma of no special type. With regard to survival data, some of the retrospective reports provide limited follow-up data, but it is difficult to reach firm conclusions regarding the prognostic implications of endocrine differentiation in invasive breast cancer due to the relatively small numbers of patients included in the studies, differences in inclusion criteria, differences in treatment and follow-up intervals, the lack of appropriately matched control groups, and the lack of studies which stratify patients by stage. Nevertheless, with regard to patients with argyrophilic tumors and carcinoid tumors, the available data do not point to any difference in prognosis from that of patients with invasive cancers of no special type. On the other hand, as may be expected based on the behavior of small-cell carcinoma arising from other sites, most but not all reports indicate an aggressive clinical course in patients with primary small-cell carcinoma of the breast (95,96).

Small studies have examined the use of breast-conserving treatment for patients with neuroendocrine carcinomas. Three patients with node-negative carcinoid tumors were treated by excision alone and followed for 15 months to 7 years (93), and no recurrences were observed. In a recent study of 9 patients with small-cell carcinoma, 3 underwent mastectomy and 6 had breast-conserving therapy (lumpectomy) (96). Two of 9 patients developed metastases; all patients were alive at 3 to 35 months of follow-up. Firm conclusions cannot be drawn from these anecdotal data. Patients with invasive breast cancers with neuroendocrine differentiation should be treated in a manner appropriate to the size and stage of the lesion.

ADENOID CYSTIC CARCINOMA

Adenoid cystic carcinoma is a rare and morphologically distinct form of invasive carcinoma. These tumors comprise less than 0.1% of all breast cancers (1) and are associated with an excellent prognosis.

Clinical Presentation

The median age of patients with adenoid cystic carcinoma varies among studies, but is usually in the sixth or early seventh decade, with a wide age range reported. These tumors present as a palpable mass with the majority of lesions discovered in the subareolar or central region of the breast (98,99). These lesions are rarely multicentric and the incidence of contralateral breast cancers does not appear increased. Rarely, this tumor has been reported in males (99).

Mammographically, these tumors can appear as well-defined lobulated masses, ill-defined masses, or spiculated lesions (60). Some adenoid cystic carcinomas present with mammographic microcalcifications, whereas others are mammographically occult.

Gross Pathology

The reported size range of adenoid cystic carcinomas is broad. Grossly, these tumors are usually circumscribed and nodular; however, the microscopic extent of the lesion may be appreciably greater than the grossly evident lesion in 50% to 65% of cases (99).

Histopathology

Histologically, these tumors are similar to adenoid cystic carcinomas that arise in the salivary glands and are composed of epithelial cells with variable degrees of glandular, squamous, and sebaceous differentiation, myoepithelial/basaloid cells, and characteristic collections of acellular basement membrane material (Fig. 25-18). The epithelial component can assume variable architectural patterns including solid, cribriform, tubular, and trabecular configurations. A solid variant of adenoid cystic carcinoma in which the cells display prominent basaloid features has been described (100). Some of these patterns may raise the differential diagnosis of *in situ* or invasive cribriform carcinoma, or benign conditions such as collagenous spherulosis. Immunohistochemical studies have documented the presence of two cell populations. Cytokeratin 7-positive epithelial cells line true lumens with intact polarity in the glandular component. In addition, pseudolumens, containing myxoid or eosinophilic basement membrane material, are surrounded by cells positive for myoepithelial markers, such as p63, smooth muscle myosin heavy chain, calponin, and basal cytokeratins. Associated DCIS is seen in a minority of cases. Perineural invasion is also seen in some cases and may be prominent. Lymphatic vessel invasion is only rarely identified.

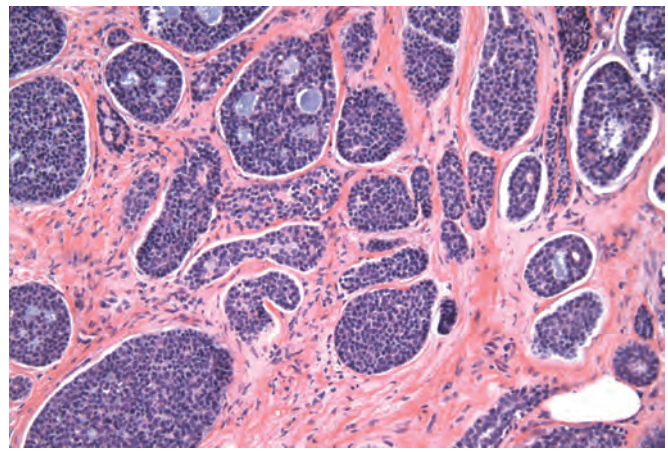


FIGURE 25-18 **Adenoid cystic carcinoma.** In this specimen, the invasive tumor cells grow in a cribriform pattern. Intraluminal aggregates of basement membrane material are present.

Biomarkers

Adenoid cystic carcinomas are usually estrogen and progesterone receptor negative and lack HER2 overexpression/amplification. Expression of KIT protein is characteristic, but not specific for, adenoid cystic carcinomas. Similar to salivary gland adenoid cystic carcinomas, these tumors are also characterized by a recurrent t(6;9) translocation (q22-23; p23-24) that results in the MYB-NFIB fusion transcript (101). These cancers cluster in the basal-like group on gene expression profiling studies (24).

Clinical Course and Prognosis

Patients with adenoid cystic carcinoma have an excellent prognosis. Only rare instances of axillary lymph node metastases have been reported (98). Based on a small number of cases, there is some evidence to suggest that the solid variant of adenoid cystic carcinoma with basaloid features may have a greater incidence of lymph node metastases (100). Distant metastases are also infrequent (98,100), and death due to adenoid cystic carcinoma is exceedingly rare (98). Some investigators have proposed using the histologic grading system employed for adenoid cystic carcinomas of salivary glands and have reported that the grading

system provided prognostically useful information (98). The prognostic utility of this grading system, however, has been disputed (99).

There are only sporadic reports of breast-conserving treatment for patients with adenoid cystic carcinoma. While local recurrences following excision alone have been described (98,99), details regarding microscopic margin status are rarely provided. At the present time treatment of patients with adenoid cystic carcinoma should follow the same guidelines as those of other invasive breast cancers.

CARCINOMAS WITH APOCRINE DIFFERENTIATION

Although many invasive breast cancers of various types show some evidence of apocrine differentiation, extensive apocrine differentiation throughout the tumor is less frequent, reported in up to 4% of invasive breast carcinomas (1). While the morphologic features of these tumors are distinctive, available evidence suggests that patients with these tumors have the same prognosis as patients with invasive breast cancers of no special type.

Clinical Presentation

Patients with apocrine carcinomas are similar in age and mode of presentation to patients with invasive carcinoma of no special type, with the exception of one report in which 7 of 34 patients (21%) demonstrated skin involvement by tumor (102). Only rare examples of apocrine carcinoma have been reported in males. There is a low reported incidence of multifocal lesions and contralateral tumors.

The mammographic characteristics of apocrine carcinomas are not distinctive (60). Most tumors present as masses with ill-defined margins, and microcalcifications are infrequent. In addition, the ultrasound findings associated with these tumors are nonspecific (60).

Gross Pathology

No distinctive gross findings are associated with apocrine carcinoma, and the size distribution is similar to invasive carcinomas of no special type.

Histopathology

In contrast, the histologic features of apocrine carcinoma are highly distinctive. The invasive patterns are usually those seen in invasive ductal carcinoma, but in some cases, lesions with apocrine cytology can exhibit a pattern of invasion more characteristic of invasive lobular carcinomas. One variant with a distinctive discohesive and diffusely infiltrative pattern has been designated as having "myoblastoid" or "histiocytoid" features (20), and in some cases this lesion may mimic a granular cell tumor. Cytologically, the tumor cells have cytoplasm that is abundant and eosinophilic, with obvious granularity in some cases. The nuclei vary in grade, but typically show prominent nucleoli (Fig. 25-19). There is frequently associated DCIS that may have apocrine features.

Biomarkers

Apocrine carcinomas are typically estrogen receptor negative and progesterone receptor negative. They characteristically show immunoreactivity for gross cystic disease fluid protein 15 (22) and androgen receptor (103). HER2 overexpression and amplification are also commonly seen. In one recent study, 88% of HER2-positive tumors showed apocrine features (104). In gene expression profiling studies, about half of these cancers show a "molecular apocrine" signature, with the remainder of cases clustering with the luminal or HER2 subtypes (24). These data support the notion that carcinomas with apocrine differentiation do not represent a distinct entity (1).

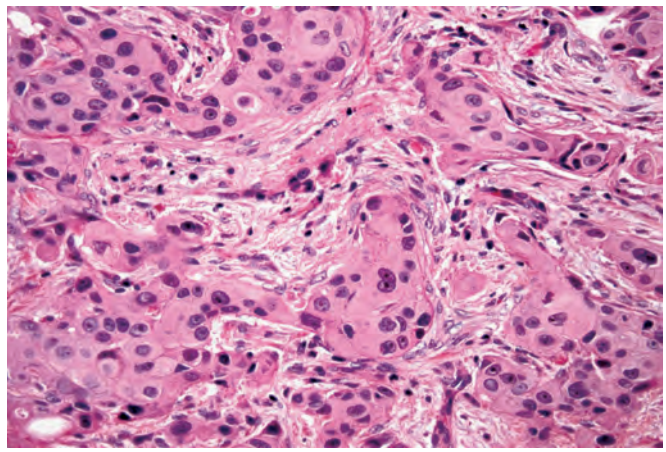


FIGURE 25-19 **Apocrine carcinoma.** The tumor cells show abundant eosinophilic granular cytoplasm.

Clinical Course and Prognosis

Patients with apocrine carcinoma do not appear to have a significantly different incidence of axillary lymph node involvement at presentation compared with patients with invasive carcinoma of no special type. Furthermore, a number of studies have compared patients with apocrine carcinoma with control patients with invasive carcinomas of no special type, matched for stage, and no appreciable differences in disease-free or overall survival have been observed (102). These observations have led some to conclude that apocrine carcinomas are more a morphologic curiosity than a distinct clinicopathologic entity. On the other hand, the presence of androgen receptor in many of these cases suggests an alternate therapeutic strategy for at least some of these cancers (103).

SECRETORY CARCINOMA

Secretory carcinoma is a rare low-grade invasive breast carcinoma that accounts for less than 0.1% of all breast cancers (1). Although secretory carcinomas occur over a wide age range, they account for a substantial number of primary breast cancers diagnosed in childhood, and thus have also been referred to as "juvenile breast carcinoma." In most cases, secretory carcinomas are associated with an indolent clinical course.

Clinical Presentation

Secretory carcinomas present over a wide age range (3 to 73 years) with a median age in the third decade (1). The majority of reported cases have been in females, but rare cases have occurred in males including several examples in association with gynecomastia. Most lesions are detected as palpable masses. These can arise anywhere in the breast but are most commonly subareolar. No association has been documented with underlying medical conditions or hormonal abnormalities. In addition, no increased incidence of a positive family history of breast cancer has been reported

in patients with secretory carcinoma. Only rare cases have been reported to be multicentric, and there does not appear to be an increased incidence of contralateral breast cancer in these patients.

Mammographic abnormalities associated with secretory carcinoma in adults have not been described in detail. On ultrasound examination, these lesions sometimes appear as hypoechoic lesions with heterogeneous internal echo texture and posterior acoustic enhancement, similar to a fibroadenoma (60).

Gross Pathology

Secretory carcinomas are typically grossly well circumscribed. A broad size range has been reported, with a median size of 3 cm noted in one relatively large series (105).

Histopathology

Histologically, these lesions are characterized by a proliferation of relatively low-grade tumor cells that form glandular structures and microcystic spaces filled with a vacuolated, lightly eosinophilic secretion that is periodic acid Schiff-positive, diastase-resistant (Fig. 25-20). The tumor cells have abundant eosinophilic or clear cytoplasm. Nuclei typically show little pleomorphism and few mitoses. DCIS is frequently present in association with the invasive component, and can be of the solid, cribriform, or papillary patterns, most often with low-grade nuclear features. The tumor border is typically well circumscribed, but may be infiltrative.

Biomarkers

Of the small number of cases that have been evaluated, most appear to be estrogen receptor, progesterone receptor, and HER2 negative (106). Secretory carcinomas are characterized by a balanced translocation t(12;15), creating a *ETV6-NTRK3* gene fusion encoding a chimeric tyrosine kinase (107). In gene profiling studies, secretory carcinomas cluster with the basal-like subtype (24).

Clinical Course and Prognosis

The majority of patients with secretory carcinoma have stage I disease and an indolent clinical course. Nevertheless, approximately one-quarter to one-third of the reported cases of secretory carcinomas have been associated with axillary lymph node metastases, and this ratio holds true in both younger and older age groups (105). The vast majority of axillary metastases involve three lymph nodes or fewer.

Limited clinical follow-up data are available, but the prognosis for secretory carcinomas appears favorable, particularly in children and young adults (1). However, late recurrences in the breast (105) and chest wall (108) have been reported in older patients.

Distant metastases are rare, but do occur in patients with secretory carcinoma and have resulted in patient deaths in rare instances (105). Neither the efficacy of conservative surgery and radiation therapy nor the role of adjuvant chemotherapy in patients with secretory carcinoma has been defined.

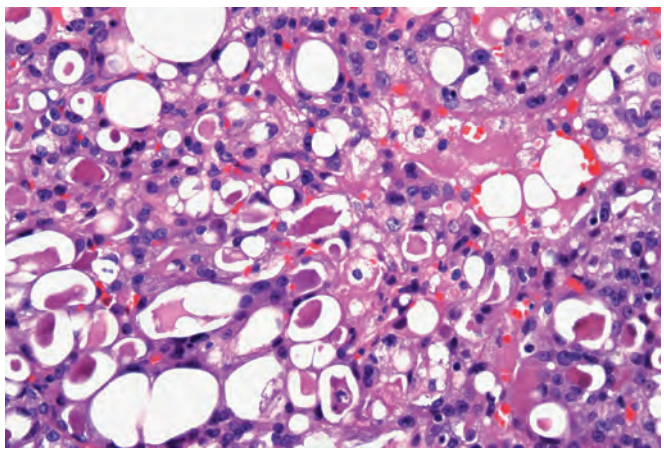


FIGURE 25-20 **Secretory carcinoma.** The tumor cells form glandular spaces, many of which contain eosinophilic secretions.

MISCELLANEOUS RARE INVASIVE BREAST CANCERS

Invasive Carcinoma with Osteoclast-Like Giant Cells

Invasive carcinoma with osteoclast-like giant cells is characterized by an invasive epithelial component with admixed giant cells that morphologically resemble osteoclasts and have the phenotypic features of histiocytes on immunohistochemical and ultrastructural analysis. The clinical features of patients with these tumors and their location within the breast are similar to patients with invasive carcinomas of no special type. Invasive carcinoma with osteoclast-like giant cells is associated with a benign appearance both mammographically (109) and grossly, due to the presence of circumscribed borders. On macroscopic examination, these lesions are typically circumscribed, fleshy, and brown in color due to recent and remote hemorrhage and benign vascular proliferation. Hemorrhage and hemosiderin deposition are characteristic features. The epithelial component of the tumor is usually moderately to poorly differentiated invasive ductal carcinoma (Fig. 25-21), but osteoclast-like giant cells have also been reported in invasive lobular carcinomas and most other special type cancers (110). The giant-cell component can be, but is not invariably present in metastatic lesions (110). Although the prognostic significance of the giant-cell component is not know with certainty, available evidence

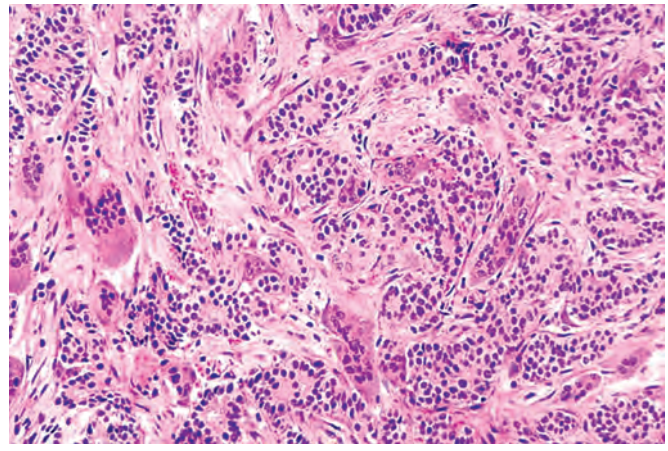


FIGURE 25-21 **Invasive carcinoma with osteoclast-like giant cells.** The epithelial component of this tumor forms solid nests and glands and has low-grade nuclear features. Numerous multinucleated giant cells resembling osteoclasts are admixed with the neoplastic epithelial cells.

suggests that these tumors do not appear to be any more or less aggressive than breast cancers of no special type and that the prognosis is related to the characteristics of the associated carcinoma.

Invasive Carcinoma with Choriocarcinomatous Features

Invasive carcinoma with choriocarcinomatous features is an exceedingly rare form of breast cancer. Only two reports have described the presence of choriocarcinomatous elements (i.e., trophoblastic differentiation) admixed with conventional breast carcinomas (111,112). The choriocarcinomatous component was associated with invasive ductal carcinoma in one case (111) and metastatic mucinous carcinoma in the second (112). The choriocarcinomatous elements in these tumors produce human chorionic gonadotropin (111). If choriocarcinomatous features are encountered in a breast tumor, the differential diagnosis should include choriocarcinoma metastatic to the breast, as several such cases have been reported.

Lipid-Rich and Glycogen-Rich Carcinomas

Variable amounts of lipid and/or glycogen are commonly present in the cytoplasm of breast cancer cells. However, a small proportion of breast carcinomas are characterized by tumor cells that contain abundant lipid or abundant glycogen within their cytoplasm. These lesions have been termed *lipid-rich carcinomas* and *glycogen-rich carcinomas*, respectively. On routine light microscopy the tumor cells comprising these lesions show vacuolated, clear cell cytoplasmic features, due to the fact that the lipid and glycogen are dissolved during tissue processing. However, neither lipid-rich nor glycogen-rich carcinomas appear to be distinct clinicopathologic entities and the importance of recognizing these lesions lies in the fact that they may mimic other forms of malignancy, particularly metastatic renal-cell carcinoma (1).

Mucinous Cystadenocarcinoma

Mucinous cystadenocarcinoma is a rare variant of invasive breast carcinoma that is morphologically indistinguishable from mucinous cystadenocarcinoma of the ovary or pancreas (113). Although these tumors may be associated with the extravasation of mucin, they are otherwise morphologically distinct from conventional mucinous carcinoma of the breast. The importance of recognizing these tumors is that they must be distinguished from metastatic lesions in the breast, particularly those of ovarian origin. The prognostic significance of primary mucinous cystadenocarcinoma of the breast is currently unknown.

Carcinoma of the Male Breast

Carcinoma of the breast in men arises at a later age than in women and is approximately 100 times less frequent than carcinoma of the female breast. It is more common in certain parts of the world such as Egypt, where it is related to chronic liver disease secondary to schistosomiasis. Hormonal factors play a less important role than in breast cancer in women, with radiation exposure and genetic factors being more important (114). An association has also been noted with Klinefelter syndrome (118) and prostate cancer. The association with prostate cancer is difficult to evaluate because of both the use of estrogens to treat prostate cancer (119) and the likelihood of prostate cancer to metastasize to the breast, where it may be confused with primary breast cancer (120).

A significant proportion of men with breast cancer have a positive family history, many being associated with germline mutations in *BRCA2* and a smaller number with germline mutations in *BRCA1* (115). In a recent study of 382 male breast cancers using immunohistochemical profiles four molecular subtypes were represented, luminal A being the most common (68%), luminal B (27%), triple negative (4%), and HER2-positive (2%) (116).

Breast cancer in men tends to present at higher stage than in women. Ulceration of the overlying skin is common. Infiltrating ductal carcinoma is the most common histologic type followed by papillary carcinoma; however, all histologic types of carcinoma have been reported. Although the prognosis of male breast cancer is reported to be poorer than that of breast cancer in females, this appears largely related to more advanced disease stage at presentation. When adjusted for tumor grade and stage, prognosis appears to be similar for males and females (117). Male breast cancers are usually estrogen and progesterone receptor positive and most are also positive for androgen receptor. HER2-positive cancers have been reported in men, but appear to be less common than in women. Treatment in most reported series has been radical mastectomy with adjuvant radiotherapy and chemotherapy.

EXTRAMAMMARY MALIGNANCIES METASTATIC TO THE BREAST

There are numerous reports of metastatic tumors involving the breast. Secondary tumor deposits in the breast may emanate from the contralateral breast or from virtually any nonmammary site. In one series, metastases to the breast from nonmammary malignancies comprised 1.2% of all malignancies diagnosed in the breast (97). Because many nonmammary malignancies can mimic the features of usual or unusual types of primary breast tumors, it can be very difficult to distinguish between the two in a subset of cases, particularly when there is no history of a prior nonmammary malignancy. Nevertheless, this distinction is critical for appropriate patient management.

Metastatic lesions involving the breast almost never occur in the absence of metastases to other sites, even when the breast metastasis is the first clinically detected site. When metastases are detected in the breast, a solitary unilateral lesion is present in 85% of cases; multiple lesions are present in 10% of cases, and diffuse involvement of the breast occurs in 5% of cases (121). The presence of tumor in ipsilateral axillary lymph nodes does not necessarily imply that the malignancy is a primary breast tumor, as metastatic deposits simultaneously involving the breast and axillary lymph nodes are not infrequent (121).

Although metastatic lesions in the breast can mimic the mammographic appearance of primary breast cancers, they are more likely to be multiple, bilateral, and exhibit well-defined margins without evidence of spiculation (60,121). Mammographic microcalcifications associated with metastatic lesions are rare, but have been reported in association with metastatic ovarian tumors. On ultrasound examination, metastatic tumors involving the breast are usually round or ovoid masses with some degree of lobulation, and variable internal echoes (60).

Metastatic tumors to the breast have a variable gross appearance, depending on the type of metastasis. In general, however, these lesions may be single or multiple, and are generally well demarcated from the surrounding breast parenchyma. The histologic and cytologic appearance of these neoplasms is related to the site of origin of the primary

tumor. Metastatic lesions most frequently described in the breast include malignant melanoma (97,121), lung carcinoma (97,121), carcinoid tumors from a variety of primary sites (95), and prostate carcinoma in men (120). Less frequent metastases to the breast include ovarian carcinoma, gastric carcinoma, renal cell carcinoma, thyroid carcinoma, various malignant tumors from the head and neck, various types of sarcoma, colorectal carcinoma, medulloblastoma, neuroblastoma, malignant mesothelioma, carcinoma of the urinary bladder, endometrial carcinoma, cervical carcinoma, chloroma, and choriocarcinoma (1).

To a variable degree, the histologic features of many of the aforementioned tumors may mimic a primary breast carcinoma. Therefore it is important that the pathologist consider the possibility of metastasis in cases with unusual clinical, mammographic, or pathologic features. It is also imperative that any relevant information (such as a history of prior malignancy or simultaneous unexplained masses occurring elsewhere) is conveyed to the pathologist. If a tumor displays unusual histologic findings that raise the possibility of a metastasis, the pathologist may opt to additionally sample the tumor to look for areas more typical of primary breast carcinoma and for foci of associated DCIS. In addition, immunohistochemical stains for a variety of markers may be helpful in defining a tumor as being of mammary or nonmammary origin. The markers chosen will depend on the differential diagnosis in any given case. Expression of estrogen receptor, CK7, GCDFP15, and/or mammaglobin may support a primary carcinoma of breast in an appropriate clinical setting.

MOLECULAR TUMOR CLASSIFICATION

Gene expression profiling studies have identified at least four major breast cancer subtypes: luminal A, luminal B, HER2, and basal-like (122). These subtypes differ with regard to their patterns of gene expression, clinical features, response to treatment, and outcome. Luminal A and luminal B cancers in general have a good prognosis and show high expression of hormone receptors and associated genes. Together these two subtypes account for approximately 70% of all breast cancers. The luminal B cancers tend to be higher grade than the luminal A cancers and some may overexpress HER2. Both luminal A and luminal B cancers tend to respond to endocrine therapy, with luminal A cancers showing the best response. Response of the luminal cancers to chemotherapy is variable, with the luminal B cancers generally showing better response.

The HER2 cancers show high expression of HER2 and low expression of estrogen receptor and associated genes. They account for approximately 15% of all breast cancers and are generally ER/PR negative. HER2 cancers are more likely to be high grade and lymph node positive. These cancers show the best response to trastuzumab and to anthracycline-based chemotherapy, but overall have a poor prognosis.

One of the most interesting findings of these studies is the elucidation of basal-like breast cancers that are associated with a particularly poor prognosis. The basal-like breast cancers show high expression of basal epithelial genes and basal cytokeratins, low expression of estrogen receptor and ER-associated genes, as well as low expression of HER2. They constitute approximately 15% of all breast cancers and are often referred to as "triple-negative" cancers, as they are invariably ER, PR, and HER2 negative. The basal-like tumor phenotype is especially common in African American women and is also the characteristic phenotype of *BRCA1*-associated breast cancers. Basal-like cancers have a poor prognosis and are not amenable to treatment with either endocrine therapy or trastuzumab since they are hormone receptor negative and do not show HER2 overexpression or amplification.

Breast cancers are not routinely classified for clinical purposes using gene expression profiling. However, the molecular subtype of a given tumor may be approximated using immunohistochemistry for ER, PR, HER2, CK5/6, EGFR, and Ki67. In general, luminal A cancers are ER/PR positive, HER2 negative with a low proliferative rate (e.g., Ki-67 less than 14%). Luminal B cancers are ER/PR positive, HER2 negative with a high proliferation rate (e.g., Ki67 over 14%), or HER2 positive. HER2 subtype cancers are ER/PR negative and HER2 positive, and basal-like cancers are ER/PR negative and HER2 negative (so called "triple negative"). It should be noted, however, that while basal-like cancers are triple negative, not all triple-negative cancers are basal-like. The use of additional immunostains (particularly cytokeratin 5/6 and epidermal growth factor receptor) may be used to further refine the categorization of basal-like cancers.

In addition to its important role in the classification of breast cancers, expression profiling has also been used to grade invasive breast cancers ("genomic grade index"). Using the genomic grade index, histologic grade 3 invasive breast cancers and histologic grade 1 invasive breast cancers have distinct gene expression patterns. In contrast, no distinct expression signature is seen for histologic grade 2 tumors. The genomic grade index allows further stratification of patients with histologic grade 2 tumors into good and poor prognosis groups (123).

HISTOPATHOLOGIC FEATURES OF HEREDITARY BREAST CANCER

Up to 10% of breast cancers are associated with mutations in high-penetrance susceptibility genes (reviewed in reference 117). Of these, breast cancers that develop in women with a genetic predisposition as a result of inherited mutations in *BRCA1* and *BRCA2* have been the most extensively characterized. Recognition of histologic features that may indicate a genetic predisposition might be useful for providing insight into the function of these genes and as an aid to identify patients in whom screening for these genetic abnormalities might provide a high yield.

There is general agreement that *BRCA1*-related cancers are more frequently carcinomas with medullary features and other basal-like carcinomas than are cancers in patients without this genetic alteration. Cancers associated with *BRCA1* mutations typically have high histologic grade, high mitotic rate, geographic necrosis, pushing margins, and an associated lymphocytic infiltrate. In addition, *BRCA1*-related cancers are usually ER, PR, and HER2 negative (triple negative), express basal cytokeratins, and have *TP53* mutations. These cancers cluster with the basal-like group on gene expression profiling studies (24). None of these features, singly or in combination, uniquely identifies a cancer as being related to *BRCA1* mutation. Similar features can be seen in sporadic basal-like breast cancers, many of which show somatic inactivation of *BRCA1*.

The histologic features reported in *BRCA2*-related breast cancers have been less consistent. Some studies have noted a higher proportion of tubular-lobular group cancers (including tubular, lobular, tubulolobular, and pleomorphic lobular) in *BRCA2* mutation carriers than in other patients. However, this has not been confirmed in larger studies. Some investigators have reported that *BRCA2*-related cancers tend to be of high histologic grade, whereas others have not noted a significant difference in histologic grade when

BRCA2-related cancers are compared with controls. In the largest study to date, Bane et al. studied 64 *BRCA2*-associated breast cancers and 185 *BRCA* mutation negative age and ethnicity matched controls (124). In this series, the majority of *BRCA2*-associated cancers were invasive ductal carcinomas, with lobular carcinomas showing similar frequency in the two groups. *BRCA2*-associated tumors were less likely to be grade I/III (6% vs. 19% in controls) and more likely to be grade III/III (60% vs. 39% in controls) and, in general, showed pushing rather than infiltrative margins. Controlling for tumor grade, *BRCA2*-associated cancers were more often positive for estrogen receptor and less likely to express basal cytokeratins or overexpress HER2. *BRCA2*-associated tumors and controls overall showed no difference in expression of TP53, BCL2, Ki67 or CCND1(cyclin D1) (124).

HISTOPATHOLOGIC PROGNOSTIC FACTORS

There is much interest in identifying biological, molecular and genetic markers that may be useful to help assess the prognosis of patients with invasive breast cancer. This is discussed in other chapters. However, a considerable amount of useful prognostic information can still be obtained from routine histopathologic examination of specimens with breast cancer. Clinical follow-up studies have repeatedly demonstrated that features such as axillary lymph node status, tumor size, histologic type, histologic grade, and lymphatic vessel invasion represent powerful and independent prognostic indicators. In fact, these traditional prognostic factors should be considered the standard against which any new prognostic factors are measured.

Axillary Lymph Node Status

There is uniform agreement that the status of the axillary lymph nodes is the single most important prognostic factor for patients with breast cancer and that disease-free and overall survival decrease as the number of positive lymph nodes increases. Current AJCC staging classifies lymph node metastases as macrometastases (over 2 mm), micrometastases (over 0.2 mm up to 2 mm) or isolated tumor cells (ITCs) (up to 0.2 mm or less than 200 cells) (125). Although the adverse clinical impact of axillary macrometastases on outcome is well established, the significance of axillary micrometastases and ITCs has been controversial, particularly those identified exclusively by the use of immunohistochemistry. Two recent clinical trials have looked specifically at this question. In the NSABP B32 trial, 5-year survival was 95.8% for patients without occult metastases and 94.6% for those with occult metastases (126). The authors concluded that although the difference (1.2%) was statistically significant, it was not clinically important. The ACOSOG Z0010 trial showed a 5-year survival of 95.7% for patients without occult metastases and 95.1% for those with occult metastases (not statistically significant) (127). These data do not support the routine use of immunohistochemistry in the evaluation of axillary lymph nodes for the purpose of identifying occult micrometastases or ITCs.

Tumor Size

Numerous studies have demonstrated that the size of an invasive breast cancer is one of the most powerful prognostic factors for both axillary lymph node involvement and clinical outcome. In a study of almost 25,000 breast cancer cases, Carter et al. demonstrated a linear relationship between tumor size and axillary nodal involvement as well as between tumor size and survival (129). The prognostic significance of tumor size is independent of axillary lymph node status and is a particularly valuable prognostic indicator in women with node-negative disease (Tables 25-4 and 25-5). A number of studies have suggested that even among patients with breast cancers 2 cm and smaller (T1), assessment of tumor size permits further stratification of patients with regard to the likelihood of axillary lymph node involvement and outcome. In a study of 644 patients with T1 breast cancer from Memorial Sloan-Kettering Cancer Center, the likelihood of axillary nodal involvement was 11% for tumors 0.1 to 0.5 cm, 15% for lesions 0.6 to 1.0 cm, 25% for tumors 1.1 to 1.3 cm, 34% for tumors 1.4 to 1.6 cm, and 43% for cancers that were 1.7 to 2.0 cm (130). Furthermore, among node-negative patients treated by mastectomy without adjuvant systemic therapy, those with cancers 1cm or smaller had a 20-year recurrence-free survival rate of 88%, significantly higher than the 72% recurrence-free survival rate observed for patients with tumors 1.1 to 2.0 cm in size (41). However, there is substantial variation in the reported rates of axillary node involvement and clinical outcome for patients with small tumors, particularly tumors that are 1 cm and smaller and not all investigators have observed that patients with tumors 1cm and smaller have significantly lower rates of axillary node involvement and disease recurrence than those with tumors between 1 and 2 cm. Nonetheless, most studies have reported a very favorable clinical outcome for node-negative patients with tumors 1 cm and smaller, with 5- to 10-year disease-free survival rates of 90% or greater.

TABLE 25-4

Five-Year Survival Rates (in Percentage) according to Tumor Size and Axillary Lymph Node Status

	Lymph Node Status		
Tumor Size (cm)	*Negative*	*1–3 Positive*	*≥4 Positive*
<2	96.3	87.4	66.0
2–5	89.4	79.9	58.7
>5	82.2	73.0	45.5

Adapted from Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status and survival in 24,740 breast cancer cases. *Cancer* 1989;63(1):181–187.

TABLE 25-5

Five-Year Survival Rates according to Tumor Size in Patients with Axillary Node–Negative Breast Cancer

Tumor Size (cm)	*No. Patients*	*5-Year Survival (%)*
<0.5	269	99.2
0.5–0.9	791	98.3
1.0–1.9	4,668	92.3
2.0–2.9	4,010	90.6
3.0–3.9	2,072	86.2
4.0–4.9	845	84.6
>5.0	809	82.2

Adapted from Carter CL, Allen C, Henson DE. Relation of tumor size, lymph node status and survival in 24,740 breast cancer cases. *Cancer* 1989;63(1):181–187.

Several studies have suggested that the prognostic significance of size may be related to the method of detection of the cancer. For example, Silverstein et al. (133) reported that for every substage among the T1 tumors and among T2 tumors, nonpalpable lesions were less likely to have axillary node involvement than palpable lesions. In that study, positive axillary lymph nodes were seen in 2 of 51 (4%) nonpalpable T1a lesions (≤0.5 cm) and in 3 of 50 (6%) palpable T1a tumors. Among T1b lesions (0.51 to 1.0cm), the frequency of positive nodes was 7% among the 92 nonpalpable lesions compared with 23% among the 143 palpable cancers. In patients with T1c lesions (1.1 to 2.0 cm) the frequency of positive lymph nodes was 16% for nonpalpable lesions compared with 31% for palpable tumors. Among patients with T2 tumors (2.1 to 5.0 cm), axillary nodes were involved in 23% of patients with nonpalpable lesions and in 48% of those with palpable tumors. Arnesson et al. also reported that mode of detection had an impact on axillary lymph node involvement in breast cancers 1 cm or smaller (134). In that series, lymph nodes were involved in 9% of the 221 T1a and T1b tumors detected by mammographic screening compared with 20% of the 89 clinically detected lesions ($p < .03$). Patients with screen-detected invasive cancers also have more favorable long-term survival. In a recent study of almost 2,000 cases in Finland, 22% of cancers were screen-detected and 88% were detected by other means. In this study, 15-year survival was 86% for patients with screen-detected cancers and 66% for patients with cancers detected by other methods (128).

Accurate measurement of breast cancer size is essential to provide the most clinically meaningful information. However, studies of the significance of tumor size in breast cancer have used various methods to determine size including clinical measurement, mammographic assessment, gross measurement, microscopic measurement of the entire lesion, and microscopic measurement of only the invasive component. In some studies, the method used to measure the tumor is not stated. This may at least partially explain differences in rates of axillary node involvement and clinical outcome in various studies. The most clinically significant measure of tumor size is the size of the invasive component of the lesion as determined from microscopic evaluation. The AJCC Cancer Staging Manual notes that the pT stage should be based on the measurement of the invasive component only (125). This approach appears to be justified since several studies have indicated that in many cases there are substantial differences in the size of the lesion as determined from gross pathologic examination and the size determined from microscopic measurement of the invasive component, particularly for small lesions. For example, in one series of 118 patients in whom the gross tumor size was measured as 2 cm or smaller, the gross tumor size was smaller than the microscopic size in 31% of cases, larger in 46%, and the same in only 22% (131). In 35% of these cases, the gross and microscopic tumor sizes differed by more than 3 mm. Similar discrepancies between gross and microscopic size were seen when the analysis was limited to those lesions in which the gross tumor size was measured as smaller than 1 cm. Of greatest importance, however, is the observation that the microscopic size of the invasive component of the tumor is the one that is most closely correlated with prognosis (131).

One important, but unresolved, issue for both pathologists and clinicians is how to assess and report the tumor size in lesions that have more than one focus of invasive cancer, since it is not known if the prognosis is related to the largest single focus or to the cumulative volume of invasive cancer. There is some evidence to suggest that invasive carcinomas with multiple foci of invasion have higher rates of axillary lymph node involvement than those lesions characterized by a single focus of invasion (135). Additional studies are needed to determine with certainty if the number of lymph node metastases might be predicted best by the aggregate size of the invasive foci. For staging purposes, the size of the largest single focus of invasion is used; however, it seems most prudent for the pathologist to measure microscopically the size of each focus of invasive cancer and report the individual sizes in the pathology report.

Histologic Type

Some histologic types of breast cancer are associated with a particularly favorable clinical outcome (6,41). Special type tumors that have consistently been shown to have an excellent prognosis include tubular, invasive cribriform, mucinous, and adenoid cystic carcinomas. Some authors also place tubulolobular carcinomas and papillary carcinomas in this group. Moreover, Rosen et al. have shown that the 20-year recurrence-free survival of special type tumors 1.1 to 3.0 cm in size is similar to that of invasive ductal carcinomas 1 cm and smaller (87% and 86%, respectively) (41). However, strict diagnostic criteria must be employed in order to observe the favorable outcome reported for these lesions.

Histologic Grade

The importance of tumor grading as a prognostic factor in patients with breast cancer has been clearly demonstrated in numerous clinical outcome studies. In fact, tumor grading has been shown to be of prognostic value even in patients with breast cancers 1cm and smaller. Although a variety of methods of nuclear and histologic grading have been used in these studies, the grading method in most widespread clinical use at the present time is the Nottingham combined histologic grading system of Elston and Ellis (137). These authors advocate the use of histologic grading for all types of invasive breast cancer, acknowledging, however, that histologic grade partially defines some of these histologic types (for example, tubular carcinomas are by definition grade 1 and medullary-type carcinomas are grade 3 lesions). In the Nottingham grading system, 1 to 3 points are assigned for each of three features: tubule formation, nuclear grade, and mitotic rate. The scores are then added, with a total score of 3 to 5 categorized as grade 1 (well differentiated), 6 and 7 as grade 2 (moderately differentiated), and 8 and 9 as grade 3 (poorly differentiated). Long-term follow-up studies have repeatedly shown higher rates of distant metastasis and poorer survival in patients with higher-grade tumors, independent of lymph node status and tumor size.

The results of a study of 1,081 invasive breast cancers from patients treated with conservative surgery and radiation therapy at the Joint Center for Radiation Therapy in Boston illustrate the value of this histologic grading system and also illustrate some important caveats in the interpretation of grading data. In that study, time to distant recurrence was greatest for grade 1 cancers and least for grade 3 tumors (Fig. 25-22). Furthermore, in a polychotomous logistic regression analysis, increasing tumor grade was associated with a significantly increased risk of distant metastasis at 10 years (138). However, the hazard ratios for distant failure among the three grades were not constant over time. In particular, the risk of distant metastasis was highest for grade 3 tumors only within the first 3 years of follow-up. Beyond that time, the risk of metastasis associated with grade 2 tumors was actually greater than the risk associated with grade 3 cancers (Fig. 25-23). These observations emphasize that in interpreting data relating histologic grade

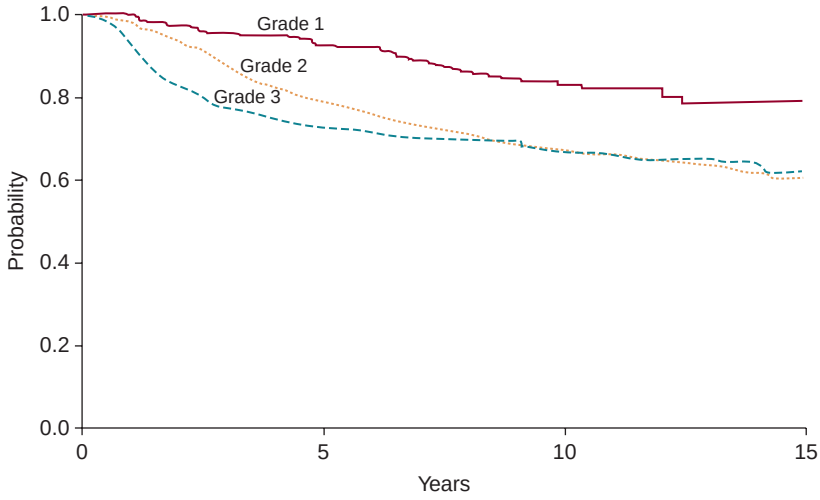


FIGURE 25-22 Kaplan-Meier curves indicating time to distant failure for 1,081 patients with invasive breast cancer according to histologic grade.

to clinical outcome, the length of follow-up must be taken into consideration. They further suggest that grade may be best viewed as an indicator of time to recurrence rather than absolute rate of recurrence.

Histologic grade also provides useful information with regard to response to chemotherapy and is, therefore, a predictive factor as well as a prognostic indicator. The results of several studies have suggested that the presence of high histologic grade is associated with a better response to chemotherapy than low histologic grade (139). For example, although basal-like carcinomas are associated with shorter relapse-free and overall survival, they are also associated with high response rates to neoadjuvant chemotherapy (140).

A frequent criticism of the use of histologic grading is that this assessment is subjective and, as a consequence, prone to considerable interobserver variability. Most of the studies that have suggested this have used grading systems that lack precisely defined criteria and/or did not attempt to educate the participating pathologists in the use of the system evaluated. Recent studies have indicated that the use of strict criteria and guidelines for histologic grading can result in acceptable levels of interobserver agreement and also identify areas that might benefit from refinement. In one of these studies, six pathologists each graded 75 invasive ductal carcinomas using the Elston and Ellis grading system (141). Moderate to substantial agreement was found for the overall histologic grade. There was substantial agreement with regard to tubule formation, moderate agreement for mitotic count, and near moderate agreement for nuclear pleomorphism as determined by generalized kappa statistics. These authors concluded that this grading system is suitable for use in clinical practice and suggested that efforts to improve agreement on nuclear grading would be of value in further fostering agreement in histologic grading.

Lymphovascular Invasion

The presence of tumor emboli in lymphovascular spaces has been shown in numerous studies to be an important and independent prognostic factor (Fig. 25-24). Its major clinical value is in identifying node-negative patients at increased risk for axillary lymph node involvement and adverse outcome. The identification of lymphatic vessel invasion may be of particular importance in patients with T1, node-negative breast cancers, since this finding may permit the identification of a subset of patients at increased risk for axillary lymph node involvement and distant metastasis in

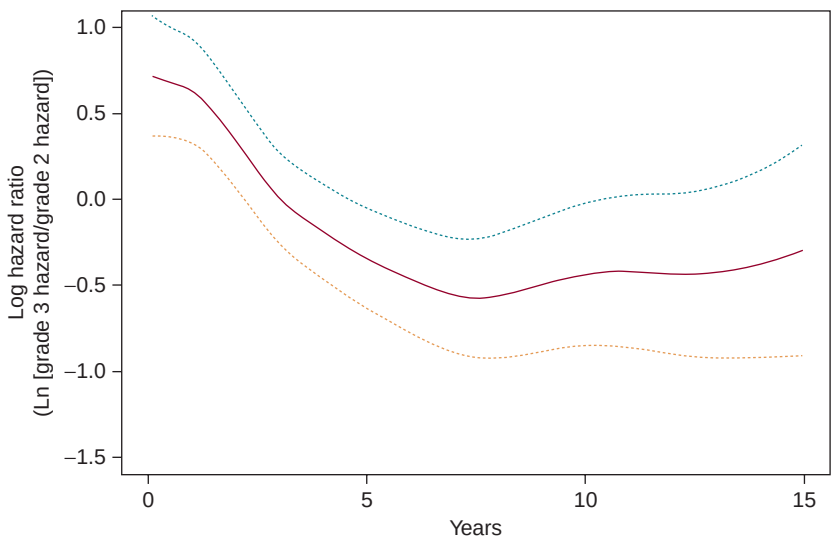


FIGURE 25-23 **Hazard ratio for distant recurrence for patients with histologic grade 3 tumors compared with those with grade 2 tumors.** Distant recurrence is greater for patients with grade 3 tumors than for those with grade 2 tumors when the curve is above zero, and less for those with grade 3 than for those with grade 2 when the curve is below zero (*dotted lines* represent 95% confidence limits).

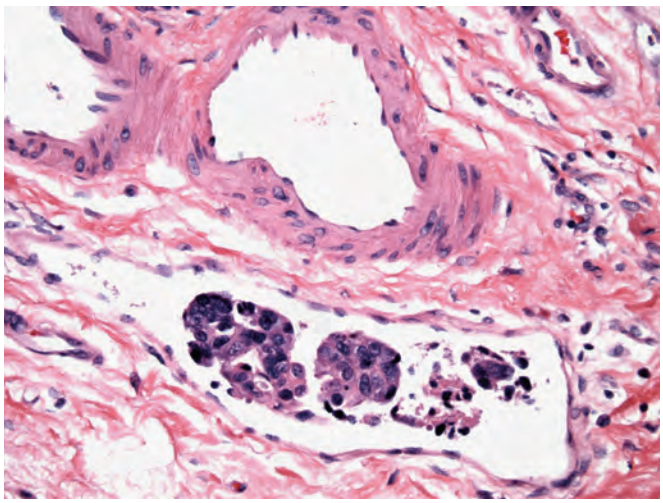


FIGURE 25-24 **Lymphatic vessel invasion.** A tumor embolus is present in a thin-walled, endothelial-lined space.

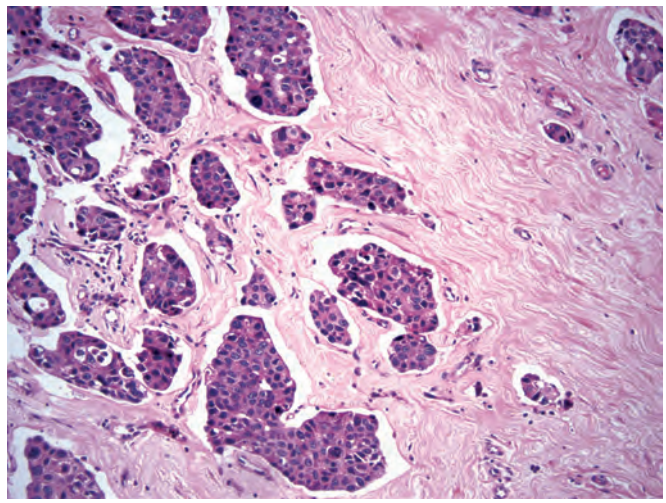


FIGURE 25-25 **Retraction artifact.** Tumor cells are present in artifactual tissue spaces, created by retraction of the surrounding stroma. These spaces lack an endothelial lining.

this otherwise favorable group. For example, in one recent study, lymphatic vessel invasion was the only clinical or pathologic factor associated with lymph node metastasis in patients with tumors 1 cm and smaller. In that study, lymph node involvement was present in four of seven patients whose tumors showed lymphatic vessel invasion (57%) compared with only 1 of 100 patients without lymphatic vessel invasion (132). In another study of 461 patients with T1, node-negative breast cancer, patients with tumors lacking lymphatic vessel invasion had a 20-year survival rate of 81% compared with 64% for those whose tumors exhibited lymphatic vessel invasion (41). Similar findings have been reported by others, even when the analysis is restricted to the subset of T1 breast cancers that are 1 cm and smaller.

As with histologic grade, the ability of pathologists to reproducibly identify lymphatic vessel invasion has been challenged. The use of strict criteria for the identification of lymphatic vessel invasion is, therefore, imperative. In particular, retraction of the stroma is not uncommonly seen around nests of invasive cancer cells, and care should be taken not to interpret this erroneously as lymphatic vessel invasion (Fig. 25-25). For this reason, assessment for lymphovascular invasion is best performed outside the area of the invasive carcinoma.

A number of investigators have evaluated the use of immunohistochemical stains for endothelial cells (including stains for factor VIII–related antigen, CD34, Ulex europaeus agglutinin I, and blood group isoantigens) and basement membrane components as an aid in the identification of lymphatic vessel invasion. However, these stains have been of limited value due both to staining of other elements in the tissue as well as false negative staining. The monoclonal antibody D2-40 recognizes lymphatic endothelium and appears to be the most useful for the detection of lymphatic vessel invasion in routinely processed tissue sections. Otherwise, lymphatic vessel invasion is best assessed on routine hematoxylin and eosin-stained sections using strict diagnostic criteria.

Other Factors

A number of other histologic factors have been reported to have prognostic value in patients with invasive breast cancer. The presence of *blood vessel invasion* (i.e., invasion of veins and arteries) has been reported to have an adverse effect on clinical outcome. In the long-term follow-up study from Memorial Sloan-Kettering Cancer Center, blood vessel invasion was identified in 14% of patients with T1N0 cancers and in 22% with T1N1 lesions using elastic tissue stains (136). A significantly worse outcome was seen for patients with than those without blood vessel invasion in both groups in that study. However, there is a broad range in the reported incidence of blood vessel invasion, ranging from under 5% to almost 50% (1). This is due to a variety of factors including the nature of the patient population, the criteria and methodology used to determine the presence of blood vessel invasion, and the occasional difficulty in distinguishing blood vessels from mammary ducts. Some studies use the term *blood vessel invasion* to denote those vascular structures that possess a muscular or elastic tissue component in their wall, whereas others include in addition thin-walled vessels of capillary caliber, many of which probably represent lymphatic spaces. Furthermore, some studies have based the evaluation for blood vessel invasion on examination of hematoxylin and eosin stained sections whereas others have employed elastic tissue stains. In our experience, invasion of arterial and venous caliber vascular structures is uncommon.

The relationship between clinical outcome and the extent of *mononuclear inflammatory cell infiltrate* in association with invasive breast cancers has also been investigated. The presence of a prominent mononuclear cell infiltrate has been correlated in some studies with high histologic grade (138). However, the prognostic significance of this finding is controversial with some studies noting an adverse effect of a prominent mononuclear cell infiltrate on clinical outcome and others observing either no significant effect or a beneficial effect (142).

The presence of *perineural invasion* is sometimes observed in invasive breast cancers. This phenomenon is often seen in association with lymphatic vessel invasion but it has not been shown to be an independent prognostic factor.

The *extent of ductal carcinoma in situ* associated with invasive cancers has also been studied as a potential prognostic factor. Numerous investigators have shown that the presence of an extensive intraductal component is

a prognostic factor for local recurrence in the breast in patients treated with conservative surgery and radiation therapy when the status of the excision margins is unknown. However, this factor is not an independent predictor of local recurrence following conservative surgery and radiation therapy when the microscopic margin status is taken into consideration (reviewed in reference 29). Silverberg and Chitale reported an inverse relationship between the amount of ductal carcinoma *in situ* and both the risk of axillary lymph node metastasis and the 5-year survival rate in a series of patients with invasive ductal carcinoma treated by mastectomy (143). However, in another series of 573 patients with invasive ductal carcinoma treated by mastectomy, there was no significant relationship between the extent of intraductal involvement and either recurrence or survival (144). Similarly, among 533 patients with invasive carcinoma treated with conservative surgery and radiation therapy, the presence of an extensive intraductal component was not associated with the risk of distant metastasis in a multiple logistic regression analysis (145). Therefore, while the extent of associated ductal carcinoma *in situ* is a consideration in the local management of patients treated with breast-conserving therapy, it does not appear to be a significant prognostic factor with regard to distant metastasis or survival.

Combining Prognostic Factors

Although a variety of prognostic factors have been reported for patients with invasive breast cancer, how best to integrate these factors to assess patient outcome and formulate therapeutic decisions is an ongoing challenge. Several authors have developed prognostic indices for this purpose, which take into account various combinations of factors. The Nottingham Prognostic Index, for instance, takes into consideration tumor size, lymph node status and histologic grade. This index has been used to stratify patients with breast cancer into good, moderate and poor prognostic groups with annual mortality rates of 3%, 7%, and 30%, respectively (146). Another group of investigators has proposed a prognostic index which combines tumor size, lymph node status and mitotic index (morphometric prognostic index) (147). This index has been shown to be a useful prognostic discriminator for premenopausal patients with both node-negative and node-positive disease. Although prognostic indices such as these have not yet been widely accepted into clinical practice, they represent important attempts to refine prognostication in patients with invasive breast cancer.

CONTENTS OF THE FINAL SURGICAL PATHOLOGY REPORT

The final surgical pathology report for specimens containing invasive breast cancer should include, in addition to the diagnosis, information needed for staging and therapeutic decision making. The information used by clinicians in determining treatment options varies among different institutions. However, at a minimum, every surgical pathology report for specimens containing an invasive breast cancer should include the type of specimen submitted, laterality, specimen size, tumor size, histologic type, histologic grade, presence or absence of lymphatic vessel invasion, presence and extent of DCIS, the status of the microscopic margins, and lymph node status (if applicable) (148). In addition, for specimens removed because of the presence of mammographically detected microcalcifications, it is important to note the location of the calcifications (i.e., in association with invasive cancer, carcinoma *in situ*, benign breast ducts and lobules, stroma or blood vessels). If ancillary studies are in progress (e.g., hormone receptor assays, HER2, other prognostic markers, etc.), this should also be documented in the final report. The use of standardized, synoptic-type reports, either in addition to or in place of a narrative report, is encouraged. A protocol and checklist for the reporting of invasive breast cancer is available from the College of American Pathologists (www.cap.org).

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CHAPTER 26

Estrogen and Progesterone Receptor Testing for Prognosis and Prediction

Mitchell Dowsett and William Miller

CHAPTER CONTENTS

BACKGROUND

The major actions of steroid hormones are mediated through specific receptors that bind hormones with high affinity and thereby generate effective signaling. Some but not all breast cancers retain the hormonal sensitivity of the target organ in which they have developed such that their growth and development appear to depend on estrogen and, possibly, progesterone. As a consequence, treatments targeted at hormones and their signaling pathways have been used both to prevent and treat breast cancer. The hormonal sensitivity and therapeutic effects appear to be mediated through estrogen receptors (ERs) and progesterone receptors (PgRs). Consequently, measurement of these steroid receptors in breast cancers is used for estimating patient prognosis, particularly the likelihood of tumor response to and patient benefit from endocrine therapy.

Thus, the objectives of this chapter are to describe (a) the different forms of ER and PgR and their biology; (b) the methodology used to measure steroid receptors; (c) the utility of ER and PgR in determining clinical outcome of patients with breast cancer; and (d) the current status of the receptors in predicting the likelihood of response to treatment and therefore the selection of specific therapies in individual patients.

BIOLOGY OF ESTROGEN RECEPTORS (ERs) AND PROGESTERONE RECEPTORS (PgRs)

Structure and Function

ER and PgR belong to a family of nuclear hormone receptors that function as transcription factors when bound to their respective ligands.

Two separate ER isoforms have substantial homology, ERα and ERβ, and are encoded by two separate genes, ESR1 and ESR2, respectively (Fig. 26-1). The precise cell-specific physiologic and pathophysiologic roles of ERβ in breast cancer are currently unclear. Also few definitive data support any clinical role for ERβ at present, and routine evaluation of ERβ is rarely performed. Therefore, in the absence of qualification, the term ER refers to the product of ESR1 (ERα) throughout this review. PgR also exists in two separate but highly homologous isoforms (PgR A and B), which have been shown to have different regulatory effects but so far have not been shown to have significantly different predictive value.

Human ERα, ERβ, and PgR share common structural and functional organization with a central DNA binding domain (DBD) and a carboxyl-terminal hormone binding domain

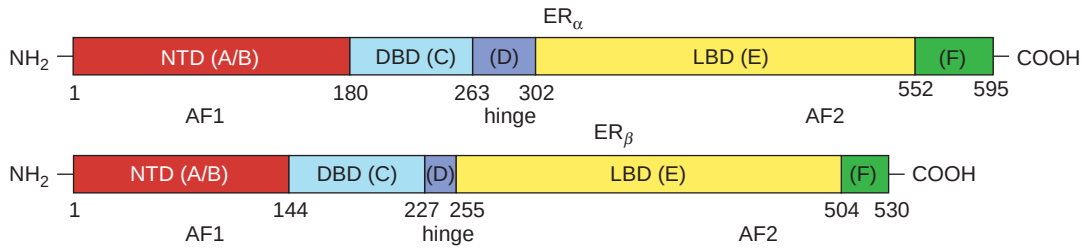

FIGURE 26-1 Linear organizational structure of ERα and ERβ. NTD: amino terminal domain; DBD: DNA binding domain; LBD: ligand binding domain; amino acid numbering for the extent of each domain is shown below the structure. (From Kumar R, Zakharov MN, Khan SH, et al. The dynamic structure of the estrogen receptor. *J Amino Acids* 2011;2011: 812540. Published online July 26, 2011.)

(HBD) (Fig. 26-1). Binding the hormone to its specific receptors activates the receptors and facilitates binding to response elements present in the promoter of responsive genes. Coregulatory proteins coordinately act to influence transcription of responsive genes and influence the nature of response.

Regulation

Mechanisms regulating ERα and β function include differential usage of upstream untranslated exons, the splicing of their messenger RNA (mRNA), and post-translational modifications (1). At least seven different promoters have been identified for ER (1). Alternative RNA splicing is relatively common in breast cancers, but there is little evidence that these result in equivalent protein variants that are detectable in clinical specimens, and none are recommended for use as prognostic or predictive tumor markers.

Post-Translational Modifications

Numerous post-translational modifications of ER and PgR have been reported, most notably through phosphorylation, ubiquination, and acetylation.

Phosphorylation of receptor protein is particularly influential. Several kinases can phosphorylate ERα, including p38 mitogen-activated protein kinase (*MAPK*), cyclin A-CDK2, CDK7, c-Src, and $pp90^{rsk1}$ (2). Other important signaling molecules, such as AKT, and extracellular regulated kinase (ERK1/2) MAPK can also differentially phosphorylate ERα. Phosphorylation of ERα can occur at several sites and may alter response to ligands (2); for example, phosphorylation of ERα serine (S) 167 by AKT and S118 by ERK1/2 can produce ligand-independent activation of ERα (and thereby confer apparent hormone resistance) (3). ERα phosphorylation can also occur at S118, producing complex effects, and be decreased by endocrine therapy. Phosphorylation events are complex and interdependent and, for example, phosphorylation at ERα S305 can regulate the subsequent phosphorylation of S118 (4). Receptor phosphorylation also affects events such as receptor turnover, cellular localization, and transcriptional activity; however, the clinical utility of measuring ERα phosphorylation has not yet been demonstrated. Both PgR-A and B isoforms are phosphorylated at multiple serine residues (5), but how PgR serine phosphorylation regulates its function is not well defined.

Ubiquitination can regulate ERα protein levels and response to estrogen (6) by mediating proteasomal degradation (6) or influencing transcriptional activity. Acetylation can occur on several lysine residues within the ER protein and thereby change DNA binding and ligand-dependent activation.

Estrogen Receptor Gene Alterations

Only a few mutations have been reported in the ERα gene. The (K303R *ERα*) mutation that causes a single amino acid change in the ERα hinge domain leads to hypersensitivity to the growth effects of estrogen. One group has reported this to be present in about one-third of premalignant lesions and in one-half of invasive breast tumors (7). However, the literature is not consistent, and other studies employing different methodologies have failed to detect the mutation in invasive cancers (8), reported it in only 6% of breast cancers (9), or associated the mutation to a family history of breast cancer (10). Clearly, more definitive research needs to be performed.

Whether the ER gene locus (*ESR1*) is a target for increased gene copy number (amplification) is controversial and not as frequent as originally thought. However, amplifications between primary and metastatic tumors appear to be concordant, and tumors with *ESR1* gene amplification also express higher levels of ERα by immunohistochemistry (11). Although some preliminary results suggest that *ESR1* amplification may predict resistance to adjuvant tamoxifen in postmenopausal women with ER positive breast cancer (12), findings currently are not sufficiently robust to be used to define a subtype of primary breast cancers optimally suited for hormonal therapy on the basis of amplification. Further independent analyses of large series of breast cancers are warranted to determine the definite prevalence of *ESR1* amplifications and its potential clinical significance.

Mechanism of Action: Genomic

ER and PgR function as tissue-specific and ligand-dependent transcription factors. Binding hormone to its receptor leads to a conformational change in the receptor and induces dimerization. The ligand/receptor complex then binds directly or indirectly to response elements in the promoter regions of responsive genes, enhancing transcription. The precise cellular response depends on tissue-specific nuclear coregulatory proteins, designated coactivators, and corepressors. More than 170 coregulatory proteins have been identified.

In the absence of hormone, histone deacetylase (HDAC) and receptor corepressors (such as N-CoR and SMRT) are bound to the receptor. Histone deacetylation silences or inhibits transcription by causing DNA to wrap more tightly around the core histone proteins. Once hormone binds to receptor, the activated complex displaces the repressor proteins, and acetyltransferases are recruited along with coactivator proteins (such as p160 coactivator, steroid receptor coactivator [SRC1], transcriptional inhibitory factor [TIF2], amplified in breast 1 [AIB1]) complex). The coactivators appear to cycle on and off the promoter during hormone treatment (13). There is therefore a dynamic and complex

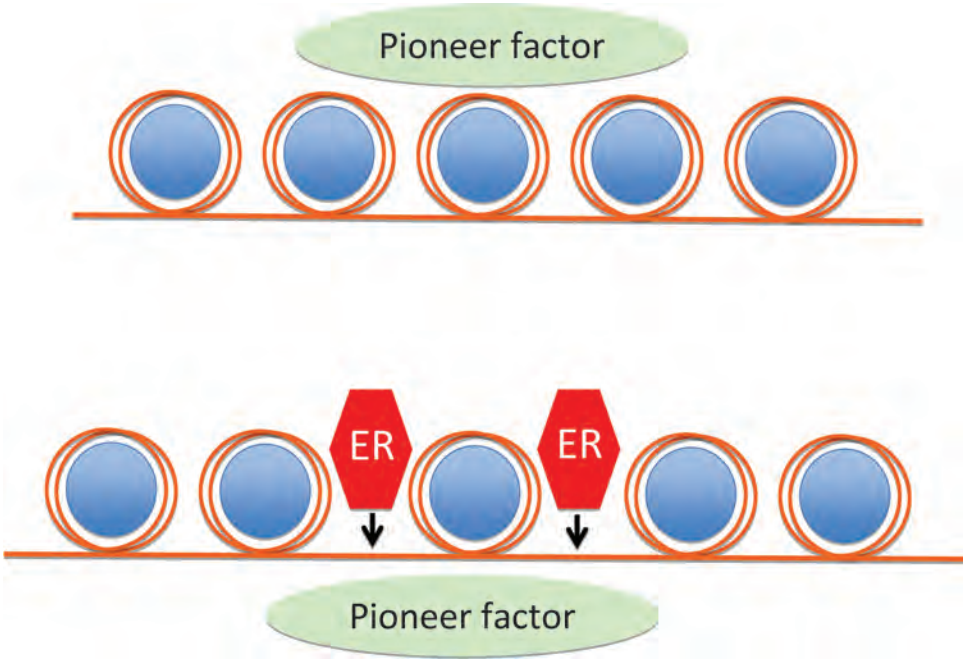

FIGURE 26-2 Mode of putative ER pioneer function. Upper panel: pioneer factor associates directly with compacted chromatin and provides accessibility to transcription factors such as ER to bind to DNA largely at oestrogen response elements. (Adapted from Jozwik KM, Carroll JS. Pioneer factors in hormone-dependent cancers. *Nature Reviews Cancer* 2012;12:381–385.)

array of proteins present on estrogen regulated promoters, many of which coordinately contribute to the hormonal regulation of gene expression.

Recent data indicate that the so-called pioneer factor FOXA1 cooperates with ER also to bind at large numbers of nonpromoter sites across the genomes (Fig. 26-2). The points through the genome that bind FOXA1 or ER vary among breast tumors and are affected by external influences such as growth factors (14).

Phosphorylation of ER coregulators is important in the transduction of signaling by the ER pathway. It can augment ER dependent transcription, even in the absence of ligand or in the presence of antiestrogens, by increasing subcellular nuclear localization and recruitment of other transcriptional coregulators to the receptor–promoter complex. Some coactivators, for example AIB1, are often gene-amplified or overexpressed in breast tumor cells. This may have clinical significance, and AIB overexpression has been associated with tamoxifen resistance, poor disease-free survival being observed after adjuvant tamoxifen therapy in patients whose tumors express high levels of both the ERBB2 oncogene, and the ER coactivator AIB1 (15). It may be the relative balance of bound coregulators that determines response to therapy.

Mechanism of Action: Nongenomic Activities

In addition to ER genomic activity in the nucleus, rapid effects of estrogens and plasma membrane estrogen binding sites have been described. It is possible that ER, PgR, and other steroid receptors can therefore mediate signaling cascades originating from the membrane or the cytoplasm through direct activation of signal transduction mediators. This nongenomic ER action occurs within seconds or minutes and is independent of gene transcription. Accruing evidence also suggests that such signaling may be associated with the growth and survival of breast cancer cells (16).

The identity of nongenomic receptors, their subcellular localization, and precise mechanism of action are still controversial and the topics of active research. However, immunohistochemical, biochemical, and genetic studies suggest that a subpopulation of the classic ERα and β subtypes located outside the nucleus and closely related nonclassic short forms of ERα may act as transducers of rapid estrogen signaling (17). These membrane and cytoplasmic ERs appear to transmit signals through kinase cascades, including growth factor receptors, cellular tyrosine kinases, and through calcium, cyclic adenosine monophosphate (cAMP), and other second messengers ultimately to regulate transcription in the nucleus (18). Membrane-initiated ER activity via growth factor signaling cascades can, in turn, modulate the activity of nuclear ER and its sensitivity to endocrine therapy (19).

In addition, nongenomic activity is also influenced by other cellular ER coregulatory proteins and by other pathways functioning in a given tumor. Increased expression of tyrosine kinase receptors (TKRs), such as in tumors amplified for HER2, can significantly augment ER nongenomic activity in response to both estrogen and tamoxifen (19).

Growth Factor and Estrogen Receptor Crosstalk–Implications for Hormone Resistance

Molecular bidirectional crosstalk occurs between growth factors, other signaling pathways, and the ER pathway. This crosstalk may be important in modulating ER activity and tumor response to endocrine therapies (20). For example, the bidirectional interaction between ER and the TKR pathway EGFR/HER2 can activate growth factor pathways by increasing the expression of ligands (i.e., transforming growth factor [TGF] α, amphiregulin), receptors (i.e., IGF-1), or other signaling intermediate molecules (e.g., insulin receptor substrate-1 [IRS-1]). Signaling through the HER pathway can also activate the transcriptional function of ER in the nucleus by phosphorylating coactivators and corepressors as well as ER itself (19).

There are also data that suggest that breast tumors with increased expression of growth factor signaling components, particularly of the EGFR/HER2 pathway, are associated with a poor response to tamoxifen (15,21). Additionally, neoadjuvant trials observed higher response rates to aromatase inhibitors in HER2-overexpressing tumors as compared with those to tamoxifen (22,23).

Although ER and HER receptors can amplify each other's signals, inhibitory actions have also been observed. Activation of ER can down-regulate the expression of the HER receptor family, including EGFR1 and HER2, and HER signaling can down-regulate the expression of ER and PgR (24). It seems likely that the interaction between FOXA1 and ER in eliciting estrogen-dependent transcription is affected by phosphorylation of FOXA1, but the details of this remain to be elucidated.

Crosstalk raises the possibility that in some breast cancers, a simultaneous blockade of both ER and HER signaling pathways may be required to bypass resistance mechanisms and achieve optimal treatment benefit. Two recently reported randomized phase II trials comparing tamoxifen with or without gefitinib and anastrozole with or without gefitinib support this idea (25,26).

OVERALL IMPORTANCE OF RECEPTORS IN CLINICAL BREAST CANCER

Approximately 30% to 40% of patients with ER positive metastatic disease responds to first-line hormonal therapies, and another 20% experience disease stabilization (27). Adjuvant hormonal therapy approximately halves the recurrence rate of patients with ER positive breast cancer. Hormonal therapy is also relatively nontoxic and therefore is a first-line option for virtually all patients with ER positive disease in both early and advanced disease. It is clear, particularly in the adjuvant setting (28) that patients with ER negative tumors do not derive benefit from endocrine treatment. Thus, ER acts as both a target and a biomarker for endocrine treatment.

The ER pathway can be targeted either by strategies that act on the receptor itself (i.e., selective ER modulators, such as tamoxifen, or potent pure antagonists that can degrade the receptor, such as fulvestrant) and by approaches that deprive the receptor of estrogen (i.e., aromatase inhibition and ovarian ablation). PgR is generally measured as a marker of an intact oestrogen-responsive pathway, and in the metastatic setting, it can aid in predicting a greater or lesser chance of response. However, in early breast cancer, PgR is helpful as a prognostic but not predictive marker of endocrine treatment benefit.

Before considering the importance of ER and PgR in breast cancer in more detail, it is instructive to understand the methodologies for their measurement in tissues.

METHODS FOR MEASURING ESTROGEN AND PROGESTERONE RECEPTORS

Assessment of ER status should be undertaken in all invasive breast cancers. Measurement of PgR is less important for selecting patients for endocrine therapy given that benefit is similar in ER+ PgR– and ER+ PgR+ cases. However, it is helpful in identifying the small population of ER– PgR+ tumors that merit endocrine therapy, and the identification can act as a quality control for ER measurement. Although ER status provides prognostic information, this is secondary to its value to assess the likelihood that a patient will respond to hormonal therapies.

Early studies relied on radiolabeled ligand-binding assays, such as the dextran-coated charcoal (DCC) method, which was rigorously validated and standardized in the United States. These methods were replaced in the 1990s with immunohistochemical (IHC) assays, which until recently have been subject to lower levels of QA.

Dextran-Coated Charcoal Ligand-Binding Assay (DCC-LBA)

The first assays of ER in breast cancer were introduced in the mid-1970s and were performed on crude tumor cytosols derived by centrifugation after homogenization. Tumor cytosols were incubated with high specific-activity radiolabeled steroid (estrogen or progestin), and the results reported as femtomoles (fmol) of receptor protein per milligram (mg) of total cytosol protein having been calculated from Scatchard plots in most instances (29). Although not used today, an understanding of the DCC assay is important because the data relating clinical benefit from endocrine therapy have been derived almost exclusively using this assay. The most widely used definition of positivity was at least 10 fmol/mg protein, but some described levels of more than 3 to 9 as borderline positive and negative as less than 3. Several disadvantages of the DCC assay existed, including variable tumor cellularity and heterogeneity as well as the requirement for fresh or snap-frozen tissue. These assays provide an overall score for the entire fragment of the tumor including neoplastic and non-neoplastic cells and may give false results, depending on the relative proportion of cancer versus other cell types within the tumor. Breast cancers display a broad dynamic range in ER and PgR expression using these assays. Overview analysis of 10,000s of patients treated with adjuvant tamoxifen showed little or no benefit for tumors with less than 10 fmol ER/mg protein, yet recurrence was reduced by about one-third in patients with tumors with 10 to 19 fmol/mg and by about one-half in those ≥200 fmol/mg. Mammographic screening dramatically reduced the average size of breast cancer below that required for the DCC assay. This and the availability of specific antibodies to ER and PgR led to the DCC no longer being performed for clinical management.

Immunohistochemical Assays

The development of specific, reliable, and commercially available ER and PgR antibodies (30) allowed the development of robust IHC technologies, and these are now virtually the only assays used to measure receptor levels. IHC allows for the determination of receptor status at the individual cell level, accommodating the problem of tissue heterogeneity within the tumor. IHC assays are less labor intensive and less expensive than extraction assays. They are also amenable to small tumors, and importantly, they can be performed on formalin-fixed, paraffin-embedded tissue, including archival tissues. IHC is also not affected by bound ligand (an issue with the DCC assay in pre-or perimenopausal patients).

IHC is performed on thin sections of formalin-fixed tissue that are subject to one of a number of antigen retrieval methods. This is followed by incubation of the section with a primary antibody directed against ER or PgR. Then a number of secondary detection systems, such as the use of secondary antibodies that have been conjugated to an enzyme such as horseradish peroxidase, are applied. The sections can finally be counterstained and viewed microscopically. For both ER and PgR, the staining produces a predominantly nuclear stain. The analytical systems have become increasingly sensitive and have resulted in most tumors being either completely negative or high positives (31,32). Several scoring systems have been developed and implemented. Examples of ER and PgR staining are shown in Figure 26-3.

Comparison of Assay Methods and Standardization

There have been very few assessments of the relationship between IHC staining levels and benefit from endocrine

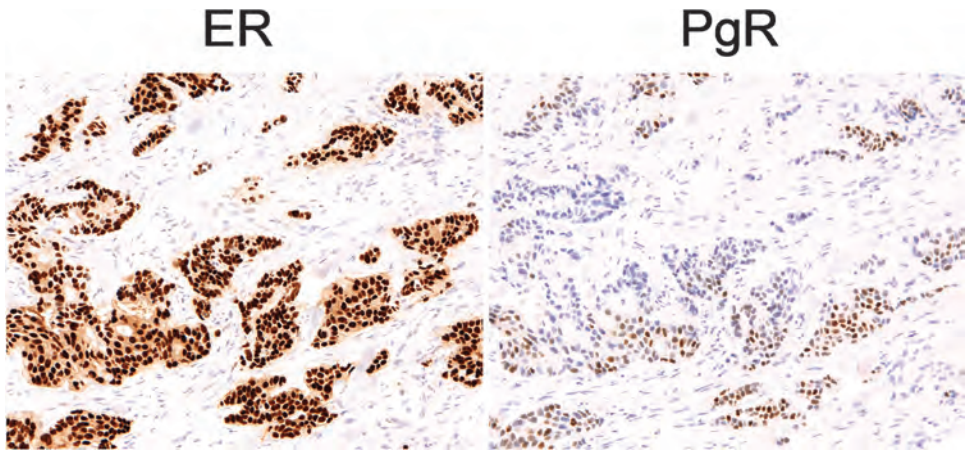

FIGURE 26-3 Examples of strong ER and weak PgR positive immunohistochemical staining in the same tumor. Brown nuclei are positively stained.

therapy, but those that exist and others that assessed prognosis either in untreated or hormonally treated tumors show good, although not perfect, concordance. When hormone receptor status of tumors determined by IHC assay has been compared with that determined by extraction assays, discordances between 10% and 30% have been reported for both ER and PgR status (33,34). In some cases, IHCs have been found to have superior ability to predict hormone response in patients (35). Regan et al. (36) reported that, for ER status, concordance between IHC and DCC assays was higher among postmenopausal women (88%) than among those who are premenopausal (81%), possibly because of the interference that can occur in the DCC with high premenopausal estrogen levels. In contrast, concordance for PgR status was marginally lower in postmenopausal patients (76% vs. 80% premenopausal).

Like other IHCs, IHC staining for ER and PgR can be significantly affected by a variety of pre-analytic factors, including the efficiency of antigen retrieval and the time of tissue fixation (37). Hormone receptors degrade in unfixed tissue; thus, avoidance of unfixed tissue sitting at room temperature is important. Given that it may take many hours for formalin to fully penetrate to the center of a large excised tumor or mastectomy specimen tissue, slicing to improve penetration is needed to avoid artifacts such as that revealed in the higher levels of ER observed in core-cuts versus excision biopsies of the same tumor. Numerous other pre-analytical and analytical factors can affect ER IHC results. In the absence of good-quality control and external quality assurance programs, these can lead to serious errors in ER measurement and inappropriate treatment decisions.

In recognition of this, the American Society of Clinical Oncology and College of American Pathologists (ASCO/CAP) jointly convened an expert panel in 2008 to develop evidence-based guidelines that were published in 2010 and have subsequently been widely adopted (38). A key recommendation was that ER and PgR be measured on all invasive breast cancers but with no agreement about the value of this in DCIS because the evidence is equivocal regarding the efficacy of tamoxifen in preventing progression of or recurrence from this disease being restricted to ER negative disease.

Other key recommendations included ER or PgR having the same cutoff of ≥1% cells being accepted as positive. Negativity should be ascribed if <1% nuclei are positive in samples where some nontumor nuclei exhibit staining and act as an internal positive control. The data directly supporting this are not as strong as one might wish as they are derived predominantly from a paper by Harvey and colleagues (35) that demonstrated prognostic but not necessarily predictive significance of such low percentages of cells staining. A low cutoff is, however, supported in general by the significant benefit from tamoxifen noted above in tumors with only 10 to 19 fmol/mg protein and should minimize the risk of false negativity (39). The Harvey paper describes the use of what became known as the Allred score (Allred being the senior author) that is created by the addition of separate scores based on the percentage of cells stained and the intensity of staining to give a score of 0 or between 2 and 8 in which values of at least three were positive. ASCO/CAP recommended that the percentage of cells and intensity of staining should be noted because these can provide ongoing data on assay quality and may be helpful as contributors to prognostic evaluation (38). The derivation of the Allred score is shown in Figure 26-4 and together with that of a Quickscore (40) and the H-score (41) in Table 26-1. The latter has advantages over the Allred score for those interested in deriving

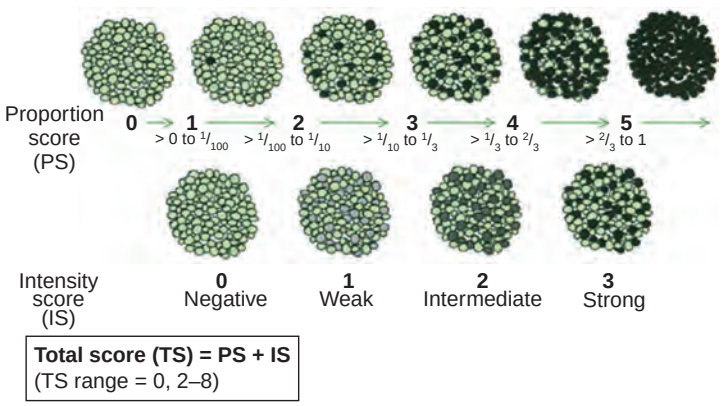

FIGURE 26-4 Derivation of the widely used Allred score. (Harvey JM, Clark GM, Osborne CK, et al. Estrogen receptor status by immunohistochemistry is superior to the ligand-binding assay for predicting response to adjuvant endocrine therapy in breast cancer. *J Clin Oncol* 1999;17:1474–1481.)

TABLE 26-1

Derivative Scores Commonly Used for Semiquantitation of ER and PgR Immunohistochemical Staining

	Categories		
Name	*Percent*	*Intensity*	*Calculation to Give Score*
Allred (35)	0 None 1 <1 2 1–10 3 10–33 4 33–66 5 66–100	0 None 1 Weak 2 Intermediate 3 Strong	Intensity category + Percentage category
Quickscore (40)	1 0–4 2 5–19 3 20–39 4 40–59 5 60–79 6 80–100	0 None 1 Weak 2 Intermediate 3 Strong	Intensity category × Percentage category
H-score (41)	Continuous	0 None 1 Weak 2 Intermediate 3 Strong	Percentage staining intensity 1 + 2 × Percentage staining intensity 2 + 3 × Percentage staining category 2

a quantitative score for ER or PgR because the Allred score markedly compresses higher values into a small number of categories, but it is far more laborious and is unnecessary for describing positive or negative status.

Using both the Allred Score (AS) and a manual estimate of the percentage of ER positive tumor cells in a series of 800 breast cancers, it has been reported that ER staining using different methodology has a near bimodal frequency distribution (Fig. 26-5) (31). Most breast cancers were either entirely ERα negative or unambiguously ERα positive; weak ERα positivity was rare. These results are similar to those reported by others using percentage positivity scoring in a series of more than 5,900 breast cancers (32). These data may be on the extreme side but in general reflect the experience of most pathologists using modern methods that relatively few tumors express low levels of positive staining. This distribution, which differs from that reported by Harvey et al., is likely to result from the increasing sensitivity of modern IHCs that also reduces the likelihood of false negativity.

Where quantitation of ER IHC is desired, there can be some value in using an image analysis system. Of note, the frequency distribution from these automated systems is continuous, similar to that obtained with DCC assay and with RNA analyses. The linearity of the image analysis systems is accomplished by their reliance on fluorescent labeling that provides a linear quantitative signal. The need to identify the receptor staining as being in malignant epithelial cells still requires visual assessment, but this can be aided by dual staining systems, such as with the AQUA, and pattern recognition systems for identifying malignant cells are in development.

RNA-Based Assays

Accurate quantitation of ER expression may also be achieved by RNA-based assays, such as quantitative reverse transcription-polymerase chain reaction (qRT-PCR). The development of the 21-gene Onco*type* DX qRT/PCR assay using fixed tissue

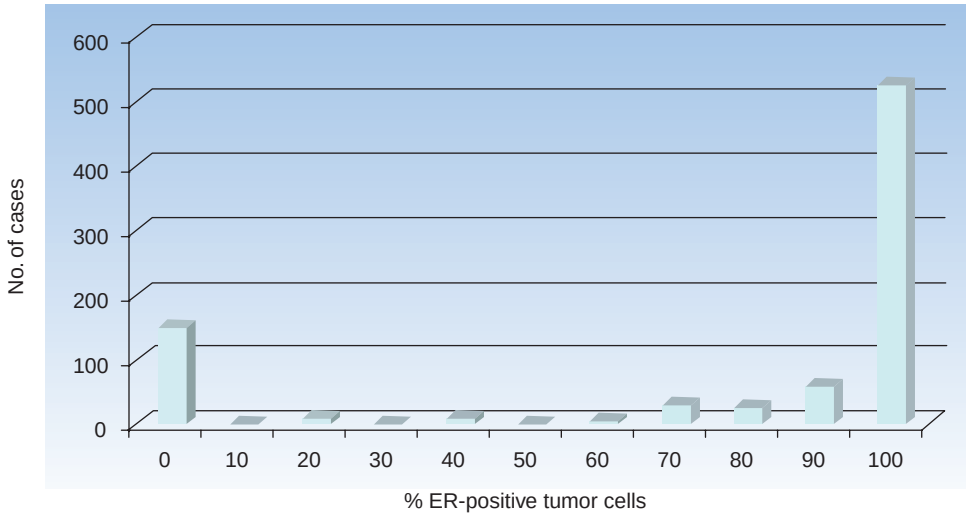

FIGURE 26-5 A frequency distribution of the percentage of cells showing nuclear staining for estrogen receptor among 825 primary breast cancers (31).

material showed that it is possible to measure ERα and PgR RNA levels reliably from archived tissues (42). Oncotype DX RT-PCR assay exhibited a continuous distribution of expression over a 3,000-fold and 1,000-fold range, respectively, for ER and PgR (43). Although qRT-PCR has emerged as an alternative method for determining hormone receptor status, the development of robust cutoffs for hormone sensitivity remain a challenge. A number of studies have showed a high degree of concordance between the two analytical approaches, particularly for ERα (43). In ECOG 2197 samples, measuring ERα by qRT-PCR was statistically superior to IHC in predicting relapse in tamoxifen-treated, ERα positive patients (43), but IHC for PgR outperformed RNA-based assays.

One strategy under investigation to augment the predictive value of hormone receptors is the evaluation of estrogen-regulated genes determined by RNA microarray analysis (44,45). Profiling with expression arrays allows for the simultaneous assessment of thousands of mRNA species in tumor samples, but smaller numbers may be useful, such as with the sensitivity to endocrine therapy (SET) score (46), or the eight-gene (and housekeeper genes) EndoPredict (47). These indices show an association with outcome on endocrine therapy but have not established their validity for selecting whether or not to use endocrine therapy.

A strategy has been developed to explore ER positive patients to endocrine therapy for the short period between diagnosis and excision (48). The assessment of changes in markers of proliferation such as Ki-67 or estrogen responsive genes may indicate an estrogen-dependent tumor. Change in Ki-67 is now widely accepted as an intermediate endpoint for assessing the comparative effectiveness of endocrine therapies.

RECEPTORS FOR THE CLINICAL MANAGEMENT OF BREAST CANCER

The place of ER and, to a lesser extent, PgR in selecting patients for tamoxifen therapy is well established (27). There are, however, several other potential roles in clinical management, including (a) predicting response to newer endocrine modalities such as AIs and fulvestrant in advanced disease; (b) predicting clinical benefit from adjuvant therapy with endocrine agents and chemotherapeutic drugs; (c) managing non-invasive disease; (d) using ER and PgR as prognostic factors; and (e) including ER and PgR as factors within predictive/prognostic panels such as IHC4 and as RNA in Oncotype DX.

Estrogen and Progesterone Receptors as Predictive Factors for Hormonal Therapy in Advanced Disease

Groundbreaking studies carried out in the early 1970s demonstrated that ER status might be used as a predictor of response to endocrine therapy in advanced breast cancer. ER positive disease had substantially higher response rates to a variety of hormonal therapies with only very rare responses in ER negative tumors (27). Subsequently, studies performed over the next 30 years confirmed these original observations and demonstrated that approximately 50% to 60% of all ER positive patients showed an objective response to first-line hormonal therapy; in contrast, only 5% to 10% of ER negative tumors responded (these responses may represent false negative assay results). Patients relapsing after successful endocrine treatment often benefit from a new second-line endocrine therapy that lacks cross resistance with the primary agent. ER status is also important in predicting benefit from such second-line and subsequent hormonal treatments.

Third-generation aromatase inhibitors (AIs) and "pure" antioestrogens were approved as first-line treatment for postmenopausal patients with MBC about 15 years ago. To address the relationship between hormone receptor status and outcome to AIs in MBC patients, Buzdar et al. (49) reviewed data on AIs from phase III trials. Positive hormone receptor status (ER, PgR, or both) was important in determining an improved time to progression (TTP) with the use of first-line treatment with these AIs. More recently, the AIs were approved for use in adjuvant treatment. The restriction of recruitment within these trials to ER positive patients and the absence of a nontreatment arm for comparison do not allow the direct assertion of no benefit in ER negative tumors, but a wealth of indirect clinical and laboratory evidence suggests this position. In advanced disease, a 7% objective response rate was observed to third generation AIs in 29 ER negative cases (50).

Multiple clinical trials have also shown that increasing levels of ER and PgR are also associated with better response, longer time to treatment failure, and longer survival (38). Although ER and PgR are correlated, PgR appears to provide information independent of ER with response rate higher by one-third in patients with ER positive/PgR positive tumors in comparison with patients with ER positive/PgR negative tumors. Higher PgR and Ki-67 levels are significantly associated with increased and decreased TTF, respectively, in ER positive patients receiving AI treatment of advanced disease. However, the higher proliferation seen in PgR negative tumors does not explain the poorer clinical responsiveness of this subgroup (50).

Hormone receptor status of metastases does not always correlate with that of the primary tumor with approximately 20% to 30% conversion rate from ER positive to ER negative and much less frequently from ER negative to ER positive at relapse (51). The receptor status of the metastasis may be more predictive of response. Thus, one study showed that, although 74% of patients with ER positive primary tumors whose recurrent tumors retained ER expression responded to endocrine therapy, only 12% of patients with ER positive primaries and ER negative metastases likewise responded (51). Similar discordances between hormone receptor content of primary breast cancer versus MBC have also been documented, and loss of ER may be associated with a significantly shorter median survival. The metastatic tumor ER status was shown to be a better predictor of survival than the primary tumor ER status (51). In biopsies from patients who developed resistance to tamoxifen, changes in hormone receptor status, as well as in other signaling pathway molecules, such as ERBB2, have also recently been documented (52). Similarly, a proportion of PgR positive tumors also lose PgR expression in their metastasis, and loss of PgR in sequential biopsies, particularly with intervening endocrine therapy, is associated with poorer survival as compared with tumors retaining PgR (53). A recent study compared ER, PgR, and HER2 expression in a large number of paired primary breast carcinomas and lymph nodes (54). Overall, 46.9% cases had disparate breast cancer/node receptor status of at least one receptor. Many of the differences in expression between primary tumor and node were large magnitude (greater than fivefold) changes. Triple-negative phenotype changed in 23.1% of cases. Different explanations have been suggested for this discordance, including (a) intratumor heterogeneity of breast cancer, which can lead to clonal selection of different clones with distinct hormone receptor properties that can change over time; (b) changes within single cells themselves as an adaptive mechanism for treatment; (c) tumor

dedifferentiation with the development of metastasis; or (d) technical laboratory difficulties in hormone receptor assessment of small biopsy specimens. Regardless of the cause, the high level of discordance between primary and metastatic disease has increased the frequency of biopsy at progression. Most oncologists nonetheless take the view that a trial of endocrine therapy is appropriate even when ER negativity has emerged in a metastasis. The less common conversion from ER negativity to positivity can, therefore, be of more clinical relevance because treatment with an endocrine agent would then be instigated.

Approximately 5% of breast cancers have an ER negative, PR positive phenotype (55). Although the phenotype may be real, it also may be artifactual, resulting from false negative ER assays. These tumors still benefit from endocrine therapy, although some data suggest a worse clinical outcome than ER positive tumors (55).

Adjuvant Therapy

As noted above, the EBCTCG overview analyses have provided conclusive evidence that overall ER negative tumors gain no significant benefit from tamoxifen therapy, but there is substantial benefit in tumors that have even very low levels (Figs. 26-6 and 26-7) (39). There is a small group of ER negative PgR positive tumors, and a small amount of

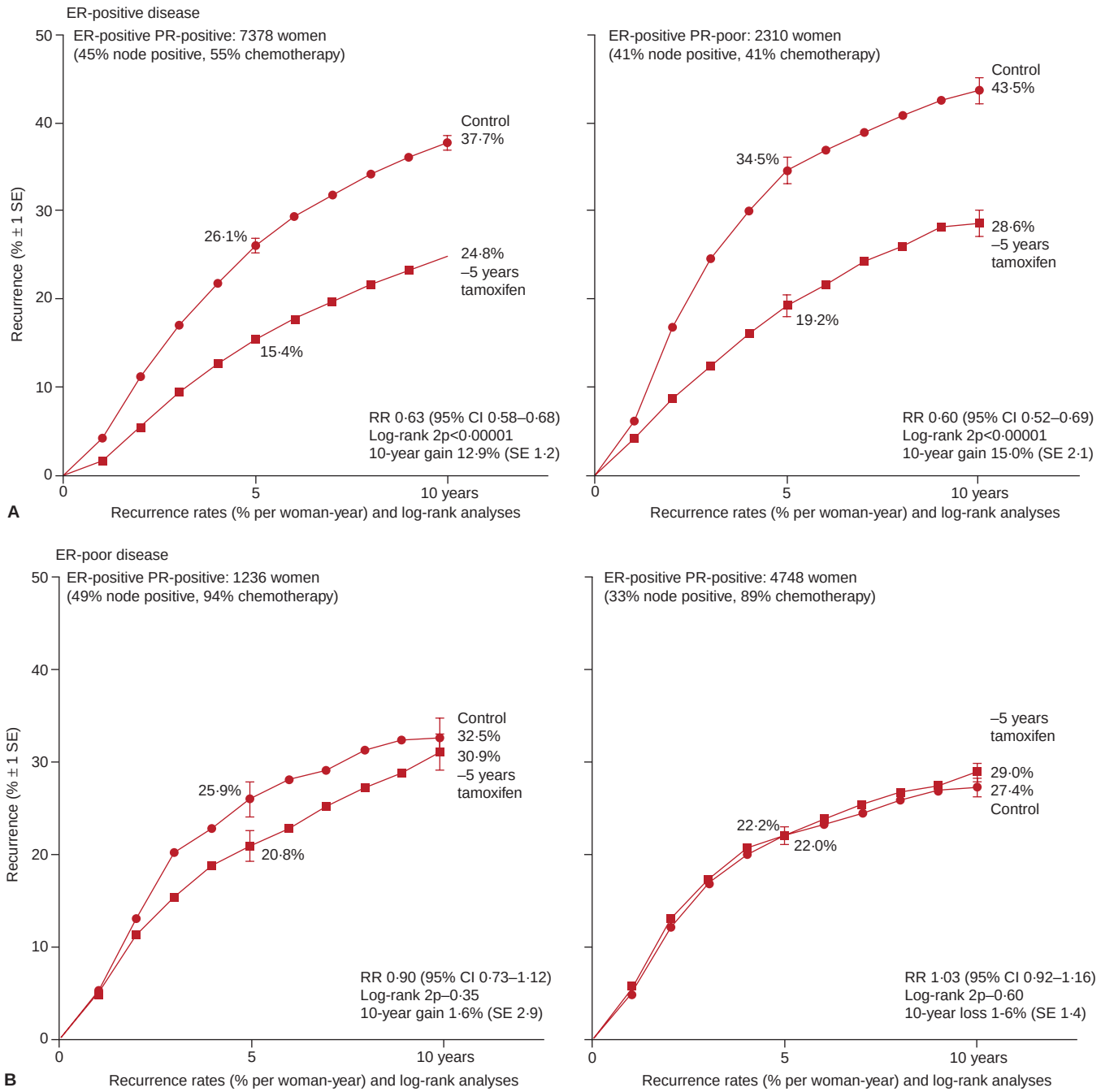

FIGURE 26-6 Impact of **(A)** ER and **(B)** PR status on risk of recurrence from about 5 years of tamoxifen versus no tamoxifen (70). ER and PR were measured using the ligand binding assay.

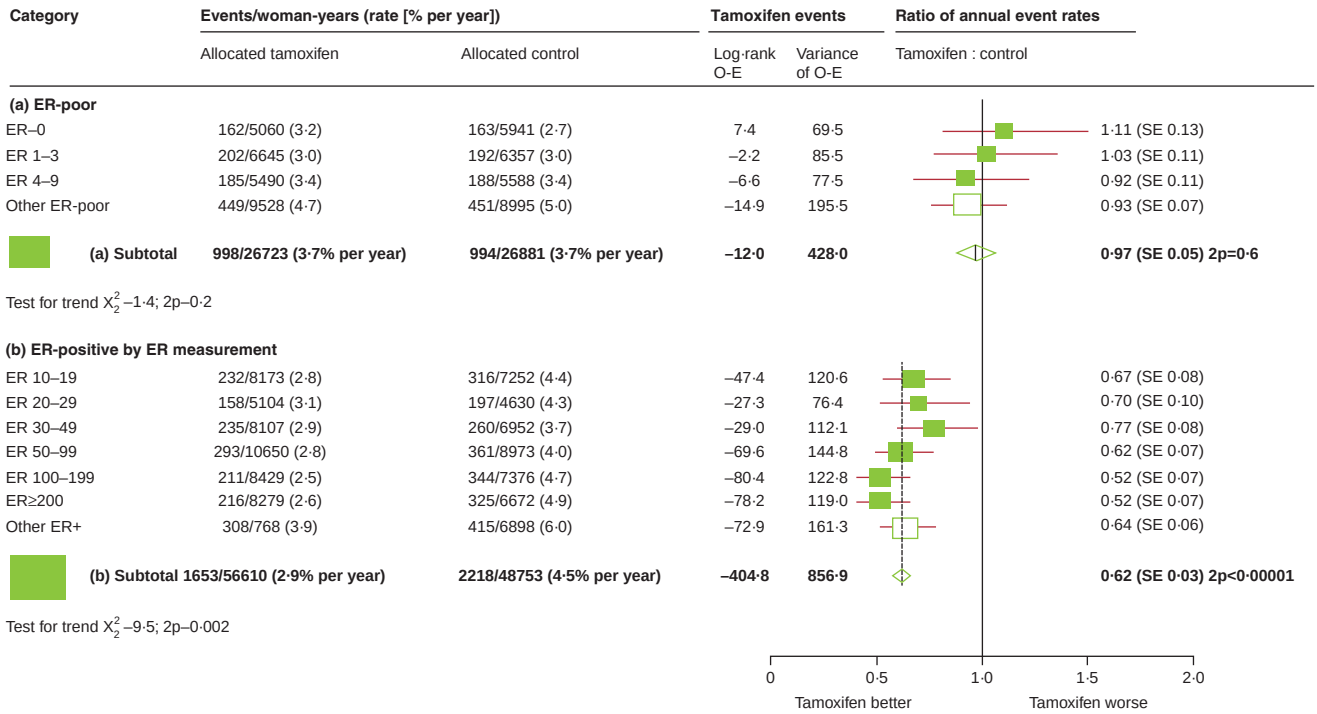

FIGURE 26-7 Degree of benefit from about 5 years of adjuvant tamoxifen according to levels of ER as measured using the ligand binding assay. (From Early Breast Trials Collaborative Group (EBCTCG), Davies C, Godwin J, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011; 378:771–784.)

benefit may occur in these, but the small number of cases makes this uncertain. The percentage of such tumors in most recent series is only around 1% to 2%, and this may be in part because of tissue heterogeneity, false negative ER assays, or false-positive PgR assays.

Given that few ER negative tumors were included in adjuvant trials of aromatase inhibitors of GnRH agonists, there is no direct evidence that they are refractory to such treatments, but a wealth of circumstantial evidence supports this such that these modern therapies are applied to only ER positive cases.

For many years, PgR-positivity has been regarded as an indicator of an intact ER signaling axis and led to a view that ER positive PgR positive cases should gain more benefit from tamoxifen or other endocrine therapy than ER positive PgR negative cases. Some large nonrandomized studies have indicated that PgR is an independent predictive factor for benefit from adjuvant endocrine therapy (56), but evidence from the overview analyses of randomized studies indicates that this is not the case and that relative benefit is very similar between positive and negative cases (39): Indeed, the absolute degree of benefit in PgR negative cases is greater than that in PgR positive ones because of their poorer prognosis (Fig. 26-6).

There have been numerous publications on the possible differential benefit from aromatase inhibitors versus tamoxifen in large adjuvant trials. An initial hypothesis-generating study from the ATAC trial of anastrozole versus tamoxifen reported that PgR negativity as measured by locally performed assays was associated with a markedly greater relative benefit from the aromatase inhibitor. However, a validation study performed on centrally determined PgR status failed to support this (57). An overview analysis that also incorporated data from the BIG1-98 study of letrozole versus tamoxifen found no significant interaction between treatment and PgR status as was the case in trials that switched from tamoxifen to an aromatase inhibitor after 2 to 3 years (58).

Although the status and expression levels of ER or PgR do not provide guidance to the relative benefit from these endocrine therapies, data from the same trials provide strong evidence for levels of expression of both receptors being associated with residual risk (57). The integration of these into single scores such as with the IHC4 (59), which also incorporates Ki-67 and HER2, has been found to predict long-term outcome after 5 years of adjuvant endocrine therapy at least as well as Oncotype DX. For widespread application of these as tests for patient management, greater consistency in measurement of the receptors by IHC will be needed, but the potential for affecting choice of whether or not to treat additionally with adjuvant chemotherapy was shown in a study of 101 patients with recommendations on the treatment of about one-third of patients being affected (60).

Estrogen Receptor in Noninvasive Breast Cancer

ER occurs in approximately 50% to 60% of DCIS tumors in which it is a good prognostic indicator with expression being inversely related to nuclear grade. ER negative tumors are more likely to recur than are ER positive tumors (61).

Although tamoxifen after local excision for DCIS (with or without adjuvant radiotherapy) reduces the risk of recurrent DCIS (in the ipsi and contralateral breast), there is still clinical uncertainty as to whether postoperative hormonal

treatment after surgery confers benefit in overall survival and incidence of recurrent carcinoma. However, in one influential study (NSABP B-24) that randomized 1,804 patients with DCIS undergoing excision and radiation for 5 years of adjuvant tamoxifen versus placebo, the tamoxifen arm was associated with about 40% reduction in all breast cancer events, which were largely confined to those patients whose original DCIS expressed ER (62). Because the results were intuitive and consistent with previous studies of invasive/metastatic breast cancer, the ASCO/CAP Breast Tumor Markers Guideline Panel indicated value in assessing ER in patients with DCIS (38). However, the panel recommended leaving it to patients and their physicians to decide on testing rather than making a formal recommendation. PgR status has been investigated in two large observational studies totalling 182 women with DCIS. The risk of ipsilateral breast tumor recurrence was lower in PgR positive tumors in both studies. However, on pooling data in a meta-analysis, the overall 44% decreased risk for recurrence failed to reach significance. PgR is not routinely measured in DCIS.

Estrogen and Progesterone Receptors as Prognostic Factors

Although ER is routinely used as a predictive factor, it can also be employed prognostically. In historic studies, women with ER positive tumors not receiving systemic therapy after surgery have rates of recurrence at 5 years, which are 5% to 10% lower than in those with ER negative tumors. However, ER may be a time-dependent variable, and studies with longer follow-up suggest that, with time, different rates of relapse and death significantly diminish and eventually disappear (63). It is possible therefore that ER status is associated with indolent, slow-growing tumors and less with metastatic potential. ER positive tumors are more frequently found in older patients; are more likely to have a well-differentiated histology, lower fraction of dividing cells; are diploid; are less likely to exhibit a mutation, loss, high expression, or amplification of breast cancer related genes such as TP53, *ERBB2*, or EGFR and have a luminal subtype of breast cancers by molecular gene expression profiling.

The utility of PgR as a prognostic factor in the absence of endocrine therapy is still an area of debate; some studies are supportive, but other data are not. Among ER positive tumors, PgR positive tumors are likely to be smaller in size, to have a lower S-phase fraction, and to be diploid. ER positive/PR negative tumors, in comparison to ER positive/PgR positive tumors, have twice as many DNA copy number changes, including specific regions of gain or loss (64). PgR loss correlates with the aggressive luminal B breast cancer subtype with EGFR and ERBB2 expression and with a gene signature of the PI3K/Akt/mTOR oncogenic pathway (64).

Multi-Parameter Testing in ER/PgR Positive Tumors

ER's being a pure prognostic factor is moot because virtually all ER positive patients will receive endocrine therapy, and its value as a biomarker of long-term outcome needs to be interpreted in that setting. Over recent years, a series of prognostic indices and molecular signatures have been developed to combine a variety of markers with ER and PgR for the evaluation of residual risk of recurrence in ER positive patients. These indices and molecular/genetic signatures include the sensitivity to endocrine therapy (SET) index (46) (derived from genes correlated with ER) and Adjuvant online! (65), genomic grading Index (66), IHC4 (59), Mamma-Print (67), and Oncotype DX (42) (which have been derived more empirically).

The SET index is based on the principle that expression of genes correlated with ER might predict response to endocrine treatment more accurately than ER expression alone. Microarray gene expression profiling of a discovery set of ER positive tumors resulted in the identification of 165 genes coregulated with ER. This 165-gene signature has been applied to independent data sets composed of microarray samples from patients with ER positive cancers receiving either adjuvant tamoxifen for 5 years, neoadjuvant chemotherapy followed by endocrine therapy (tamoxifen or aromatase inhibition), or no adjuvant systemic treatment. SET was associated with the outcome of patients receiving any type of endocrine treatment (tamoxifen or chemo endocrine treatment) but had no prognostic value in untreated patients (46). This signature has the potential to add additional predictive information to existing clinical-pathological models to determine which patients should receive endocrine therapy.

Several gene signatures illustrate that the molecular profiles of ER positive and ER negative tumors are different, providing convincing evidence that ER positive and ER negative breast cancers are distinct diseases. Thus, the seminal class-discovery studies undertaken by Perou and colleagues (44) and Sorlie and co-workers (68) revealed that ER positive and ER negative breast cancers are fundamentally distinct diseases in molecular terms and revealed the existence of at least four molecular subtypes of breast cancer: namely, luminal (now subdivided into A and B), HER2-enriched, basal-like, and normal breast-like. At the RNA level, the identification of these subtypes was shown to be mainly driven by the expression of ER and ER related genes, proliferation-related genes, and, to a lesser extent, HER2 and genes mapping to the region of the HER2 amplicon (44,68).

Signatures such as MammaPrint, Recurrence Score, and Genomic Grade Index can subdivide ER positive breast cancers (in some cases within others without endocrine therapy) into good and poor prognosis patients. Thus, recent studies have demonstrated that the signatures identify an overlapping group of highly proliferative ER positive tumors that have poor prognosis (69). Although the overlap between the genes that compose each of these signatures is limited, their prognostic impact is largely derived from the quantification of two biological processes: proliferation and ER signaling. This explains why virtually all ER negative cancers and almost all high-grade ER positive cancers are classified as high risk by these methods. The most important practical contribution of genomics to breast cancer management is that the signatures can distinguish low and high risk prognostic groups among ER positive, early stage breast cancers. Thus, these patients are at such low risk of recurrence that gains from chemotherapy are likely to be minimal and the patients may be spared its toxicity. In the past, selection of adjuvant chemotherapy for ER positive cancers was based on tumor size, nodal status, histologic grade, patient preference, and comorbid illnesses. However, none of these variables, with the exception of grade, have a consistent association with sensitivity to chemotherapy.

It is important that the prognostic information from these new molecular indices be integrated with that from classical clinicopathological index for optimal prognostic assessment.

However, the prognostic information provided by signatures may not be above and beyond that offered by semiquantitative assessment of ER, PgR, HER2, and Ki-67; and multi-IHC tests including these markers may accomplish similar risk stratification. For example, the IHC4 test was shown to be just as effective at predicting high and low

risk women as the expensive American Oncotype DX® (59). Oncotype DX® is a valuable method of identifying patients whose breast cancer could recur, but many healthcare systems do not have the money available to use it. IHC4 could make this information available to them without adding significantly to costs and could help reduce spending by cutting unnecessary chemotherapy treatment.

Concluding Remarks

ER and, to a lesser extent, PgR have long been accepted as playing a central role in the pathobiology and treatment of breast cancer; standard practice requires assessment of hormone receptors to select appropriate treatment. Furthermore, genomic analyses reveal a close association between the presence or absence of ER and substantive biological groupings. There is still much to learn about the control of transcription by the receptors, the interaction of treatments with those controls, and how this affects clinical outcome. Better understanding of these may provide new concepts for influencing the receptors' function and improved targeting of therapeutic interventions.

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CHAPTER 27

HER2/ERBB2 Testing: Assessment of Status for Targeted Therapies

Michael F. Press and Yanling Ma

CHAPTER CONTENTS

Amplification of the human epidermal growth factor receptor type 2 (HER2 or ERBB2) gene in human breast cancers is an example of an acquired molecular alteration on which human breast cancer cells with this alteration depend for maintenance of a fully malignant phenotype and which has come to represent a molecular subtype of the disease. HER2/ERBB2 (also known as *neu* oncogene) amplification with resultant HER2/ERBB2 protein overexpression has been shown to play a role in sustaining multiple cancer pathways, including self-sufficiency in growth signals, sustained angiogenesis, increased cell division, and enhanced invasion (1,2). Inhibition of HER2/ERBB2 membrane signaling in these cancer cells through administration of humanized anti-HER2/ERBB2 antibodies (trastuzumab [Herceptin], pertuzumab [perjeta], Trastuzumab emtansine) or administration of small molecule inhibitors of HER2/ERBB2 tyrosine kinase activity (lapatinib [Tykerb]) is associated with improved patient outcomes for women with both primary and metastatic disease (3–7). Because improvements in outcome are only documented in women whose breast cancers have alterations in the HER2/ERBB2 gene or protein product, accurate clinical testing for HER2/ERBB2 amplification or overexpression has become an important clinical consideration. The importance of this issue is reflected by the fact that the American Society of Clinical Oncology (ASCO) recommends routine testing of only three predictive markers: estrogen receptor (ER), progesterone receptor (PR), and HER2/ERBB2 in women diagnosed with primary, invasive breast carcinomas.

ASSOCIATION OF HER2/ERBB2 AMPLIFICATION WITH HER2/ERBB2 OVEREXPRESSION

The HER2/ERBB2 gene encodes a 185 kDa monomeric protein also known as phosphoprotein 185 ($p185^{HER2/ERBB2}$). The HER2/ERBB2 protein is a receptor tyrosine kinase that is classified as a member of the epidermal growth factor receptor (EGFR) family of tyrosine kinases based on significant homology to EGFR (8,9). HER2/ERBB2 is a membrane protein expressed at low levels in all epithelial cells in normal fetal and adult tissues (10).

The HER2/ERBB2 gene is amplified, or increased in copy number, in approximately 25% of human breast cancers (11,12) as well as a variable percentage of ovarian (12), bladder (13), endometrial (14), salivary gland (15), esophageal, and gastric cancers (16). HER2/ERBB2 gene amplification has been associated with pathologically increased levels of expression of HER2/ERBB2 messenger RNA (mRNA) and $p185^{HER2/ERBB2}$ protein product (12). Although HER2/ERBB2 gene amplification status and expression level were originally found to be closely associated in 90% of frozen breast cancer specimens (12), subsequent work by the same investigators has demonstrated a near complete concordance between the HER2/ERBB2 amplification status and expression status in the same tissue samples (17,18). The 10% of breast cancers that were originally discordant cases were predominantly stromal-rich breast cancers that were classified as

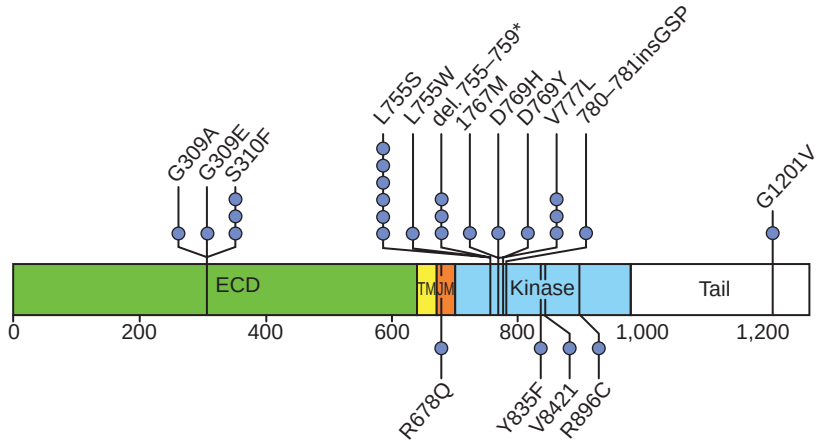

FIGURE 27-1 Schematic illustration of the locations of activating mutations identified in the HER2/ERBB2 gene through genome-wide DNA sequence analyses. The HER2/ERBB2 somatic mutations observed in 25 patients are illustrated with blue circles representing each case with the indicated mutation out of 1,499 with complete genome-wide DNA sequence analysis information available. Two patients had two HER2 somatic mutations each, resulting in a total of 27 mutations in 25 patients. del.755–759* indicates that two patients had del.755–759 and one patient had del.755–759 with a S760A change. ECD, extracellular domain; JM, juxtamembrane region; SNP, single-nucleotide polypeptide; TM, transmembrane region; WT, wild type. (From Bose R, Kavuri SM, Searleman AC, et al. Activating HER2 mutations in HER2 gene amplification negative breast cancer. *Cancer Discov* 2013;3(2);224–237.)

nonamplified, overexpression breast cancers. HER2/ERBB2 gene amplification status had been originally determined by Southern hybridization in these stromal-rich breast cancers and dilution of tumor DNA by more abundant normal DNA resulted in Southern blots that failed to show HER2/ERBB2 gene amplification, owing to the dilution of tumor DNA by the more abundant normal DNA. Reanalysis of these same cases by fluorescence *in situ* hybridization (FISH) permitted a nucleus-by-nucleus evaluation of the HER2/ERBB2 gene copy number and demonstrated HER2/ERBB2 gene amplification in the tumor cell nuclei of these cases that were previously considered not to be amplified (by Southern blot), but had overexpression by Northern hybridization, Western Immunoblot, and frozen section immunohistochemical assay (12). Therefore, one can conclude, when working with frozen tissue specimens, there is a close association between HER2/ERBB2 gene amplification status and overexpression status. That is, when the HER2/ERBB2 gene is not amplified, then the products of the gene are not increased and overexpression is not observed. Similarly, when HER2/ERBB2 gene is amplified, overexpression is consistently observed. Although this close association can be demonstrated in frozen tissue samples, tissue fixation and paraffin embedding of these same specimens lead to difficulties in analysis of protein expression, especially by immunohistochemistry (12,19–21). This problem is addressed subsequently in this chapter when we discuss clinical assay methods for assessment of HER2/ERBB2 status.

IDENTIFICATION OF FUNCTIONALLY ACTIVE MUTATIONS IN HER2/ERBB2

Genome-wide DNA sequence data from eight different studies encompassing 1,499 subjects demonstrated 25 breast cancers with mutations in the HER2/ERBB2 gene, seven of which are activating mutations (22). These seven activating mutations (G309A, D769H, D769Y, V777L, P780ins, V842I, and R896C; Fig. 27-1) represent an alternative mechanism for activation of HER2/ERRB2 in addition to gene amplification. Only one of the mutations (V777L) has been identified in breast cancers with HER2/ERBB2 gene amplification. A HER2/ERBB2 in-frame deletion 755–759, which is homologous to EGF receptor (EGFR) exon 19 in-frame deletions, had a neomorphic phenotype with increased phosphorylation of EGFR or HER3. These HER2/ERBB2 somatic mutations are estimated to be present in approximately 1.6% of breast cancers. While some of these mutations are resistant to lapatinib, all were sensitive to the irreversible HER2/ERBB2 tyrosine kinase inhibitor, neratinib. A clinical trial is in progress to evaluate this approach as a treatment strategy in women whose breast cancers lack HER2/ERBB2 gene amplification.

CLINICAL IMPORTANCE OF HER2/ERBB2 GENE AMPLIFICATION AND OVEREXPRESSION STATUS

HER2/ERBB2 gene amplification or overexpression is a prognostic marker of poor outcome in the absence of adjuvant treatment and an important predictive marker of responsiveness to certain treatments. The HER2/ERBB2 alteration has been associated with an increased rate of metastasis, decreased time to recurrence, and decreased overall survival (11,12,23). HER2/ERBB2 gene amplification is significantly associated with shorter disease-free survival and shorter overall survival in primary, invasive, node-negative breast cancer patients treated with surgery alone, without chemotherapy, without hormone therapy, and without radiation therapy in the adjuvant setting (24). HER2/ERBB2 is a prognostic marker independent of nodal status, tumor size, grade, and hormone receptor status (24).

As a predictive marker, HER2/ERBB2 amplification or overexpression has been correlated with responsiveness to

anthracycline-based chemotherapy (25,26), paclitaxel-containing chemotherapy (27), and, most importantly, trastuzumab (Herceptin) and lapatinib (Tykerb) anti-HER2 targeted therapies. Currently, patients with HER2/ERBB2-positive tumors are treated with therapy directed against the HER2/ERBB2 protein. Humanized antibodies directed against the extracellular domain of the HER2/ERBB2 membrane protein (trastuzumab [Herceptin], pertuzumab [Perjeta], and trastuzumab emtansine [T-DM1]), and a dual tyrosine kinase inhibitor of EGFR and HER2/ERBB2 (lapatinib [Tykerb]), are currently approved by the U.S. Food and Drug Administration (FDA) for use in the treatment of HER2/ERBB2-positive invasive breast cancers. Trastuzumab is approved for use in the treatment of both metastatic and primary, invasive HER2/ERBB2-positive breast cancer. Pertuzumab and lapatinib are approved for the treatment of HER2/ERBB2-positive metastatic breast cancer (28). Clinical trials are in progress to evaluate utility in primary breast cancer with HER2-targeted agents such as lapatinib, pertuzumab, and T-DM1, and newer drugs such as neratinib are being actively tested in the metastatic setting. Several other biological agents directed at HER2/ERBB2 or the pathway are in development. Each of these therapeutic agents requires the use of a companion diagnostic test to select the most appropriate patients for treatment (Table 27-1).

Inaccurate assessment of HER2/ERBB2 status can lead to the inappropriate treatment of breast cancer patients in both the adjuvant and metastatic settings and subject patients to unnecessary risk. With current practice guidelines, false-negative HER2/ERBB2 status is a serious concern because these patients are denied the substantial benefit of HER2/ERBB2 targeted therapies. On the other hand, false-positive HER2/ERBB2 status is also important because cardiac toxicity is a significant risk for patients who are treated with combinations of trastuzumab and anthracycline-containing chemotherapy. For these reasons, accurate determination of HER2/ERBB2 alterations in breast carcinomas, if present, are of critical importance.

DETECTION OF HER2/ERBB2 AMPLIFICATION AND OVEREXPRESSION IN CLINICAL PRACTICE

In 1998, the humanized mouse 4D5 monoclonal antibody trastuzumab (Herceptin), directed against the human epidermal growth factor receptor type-2 (HER2/ERBB2) (7,29), was approved for the treatment of HER2/ERBB2-positive metastatic breast cancer. These patients had been selected for entry to the registration clinical trials of trastuzumab with an immunohistochemistry assay method, known as the *Clinical Trials Assay* (CTA) (7,30–32). The CTA used two different antibodies: 4D5 (the mouse monoclonal antibody used to produce humanized trastuzumab) and CB11 (a mouse monoclonal antibody). Antigen retrieval techniques were used for both antibodies in the CTA. However, because the CTA was not considered appropriate for commercialization, a second immunohistochemistry (IHC) assay method, the Dako HercepTest, was developed for commercial testing of HER2/ERBB2 status to select women for treatment with trastuzumab. This companion IHC assay method to assess HER2/ERBB2 membrane staining was approved by the FDA based on a 79% concordance rate (95% confidence interval [CI], 76%, 82%) between the immunostaining results of the CTA and the immunostaining results of the HercepTest for 548 breast cancer specimens from the National Cancer Institute Cooperative Breast Cancer Tissue Resource, a group of tumors that lacked clinical outcome information. Subsequently, a fluorescence *in situ* hybridization assay method was also approved by the FDA to identify women whose breast cancers had HER2/ERBB2 gene amplification for selection to trastuzumab therapy. This approval was based on a blinded, retrospective analysis of archival tissue sections from the breast cancers of women entered in the H0648g and H0650g registration trials (33). This analysis demonstrated that women entered in the H0648g trial

TABLE 27-1

Clinical Laboratory Assays for HER2/ERBB2 Testing Approved by the U.S. Food and Drug Administration

Year	*Assay Name*	*Method*	*Indication*	*Company*
1997	INFORM HER2[a]	FISH	High-risk for recurrence or disease-related death	Oncor, Inc. (Ventana Medical Systems, Inc.)
1998 2012	HercepTest	IHC	Trastuzumab Pertuzumab	Dako, Inc.
2000	Pathway anti-HER2/neu (CB11[b])	IHC	Trastuzumab	Ventana Medical Systems, Inc. / Roche, Inc.
2002	PathVysion	FISH	Trastuzumab	Vysis, Inc. (Abbott-Molecular)
2004	InSite HER2/neu (CB11) kit[c]	IHC	Trastuzumab	Biogenex Laboratories, Inc.
2005	HER2 FISH pharmDX Kit	FISH	Trastuzumab Pertuzumab	Dako, Inc.
2008	SPOT-Light HER2 CISH kit	CISH	Trastuzumab	Invitrogen, now Life Technologies, Inc.
2011	INFORM HER2	Dual ISH	Trastuzumab	Ventana Medical Systems, Inc. / Roche, Inc.
2011	HER2 CISH pharmDx Kit	Dual ISH	Trastuzumab	Dako, Inc.
2012	Bond Oracle HER2 IHC	IHC	Trastuzumab	Leica Biosystems

[a]INFORM HER-2/neu FISH assay originally approved in 1997 by Oncor, Inc. and subsequently in 2000 by Ventana Medical Systems, Inc. was withdrawn from the market in October 2007. The currently approved "INFORM HER2" has been revised as a SISH assay using a different HER2 DNA probe.
[b]Although originally approved with CB11 mouse monoclonal antibody, this assay currently uses the 4B5 rabbit monoclonal antibody.
[c]The INSITE HER2/neu (CB11) kit was withdrawn from the market in 2006.

of trastuzumab for metastatic disease whose breast cancers were IHC 2+ or 3+ but lacked HER2/ERBB2 gene amplification by FISH did not show any incremental benefit from the addition of trastuzumab to the chemotherapy regimen (33). Those women whose breast cancers were HER2/ERBB2 amplified by FISH and received trastuzumab with chemotherapy had a significantly improved overall survival compared with women whose breast cancers were HER2/ERBB2 amplified and were treated with chemotherapy alone. The separation of the outcomes was greater in this comparison than in the original efficacy population (p = .009) (33).

Three FISH assays, two of which are commercially available (PathVysion by Vysis, Inc., now Abbott-Molecular, Inc., and pharmDx by Dako, Inc.), four IHC assay methods (HercepTest by Dako, Pathway by Ventana Medical Systems/Roche, InSite by Biogenex, and Oracle by Leica), and three chromogenic, silver, or dual (bright field microscopic) *in situ* hybridization (INFORM-HER, originally a FISH assay by Oncor, Inc., is now a bright-field ISH owned by Ventana Medical Systems, Inc.; pharmDx kit by Dako, Inc.; and SPOT-Light by Life Technologies, Inc.) assay methods are approved by the FDA to select women for trastuzumab therapy (Table 27-1).

Because HER2/ERBB2 gene amplification is directly correlated with HER2/ERBB2 expression levels at the mRNA and protein levels, determination of HER2/ERBB2 status could potentially be made at any of these levels and should correspond to the HER2/ERBB2 status determined with any of the other measures. Although this is approximated when frozen tissues are used, the use of formalin-fixed, paraffin-embedded tissues for these determinations introduces practical problems that result in some errors in HER2/ERBB2 characterization, especially when IHC is used to assess HER2/ERBB2 status in formalin-fixed paraffin-embedded tissues. We briefly review the various methods used to assess HER2/ERBB2 in breast cancer specimens, and then compare and contrast the results obtained with different methods of analysis, especially between IHC and FISH. A summary of these techniques is provided in Table 27-2.

CLINICAL ASSAYS FOR ASSESSMENT OF HER2/ERBB2 STATUS

Although HER2/ERBB2 status has been highly concordant among assays of DNA, mRNA and protein in frozen tissues, the current clinical use of paraffin-embedded tissue limits the type of HER2/ERBB2 analyses that can be performed. The types of assay choices for formalin-fixed, paraffin-embedded tissues include FISH, CISH, and SISH to determine gene amplification status; quantitative real-time reverse transcriptase-polymerase chain reaction (RQ-PCR) analysis and microarray-based RNA expression profiles (RNA-EP) to determine HER2/ERBB2 mRNA expression status (34,35); and IHC to determine HER2/ERBB2 protein overexpression status. The most popular of these methods is IHC, with approximately 85% or more (36) primary HER2/ERBB2 assessments being performed with this method. The second most popular method for assessment is FISH, with 6% to 15% of assays performed with this assay method, predominantly for "reflex" FISH testing after primary IHC testing yields an immunostaining score of IHC 2+ (36). The Genomic Health proprietary Oncotype DX 21-gene assay measures messenger RNA for a series of markers including ER, PR, and HER2/ERBB2 and proliferation markers in the clinical setting with ER, PR, and HER2/ERBB2 results now reported separately. A new biotechnology method, nanostring, also measures mRNA from formalin-fixed paraffin-embedded tissues (37). These assay methods are briefly reviewed below.

IMMUNOHISTOCHEMISTRY

Immunohistochemistry uses antibodies that recognize antigenic determinants of the full-length HER2/ERBB2 protein to assess indirectly and qualitatively the overall level of HER2/ERBB2 protein expression in paraffin-embedded tumor samples (Figs. 27-2 and 27-3). Overexpression of the HER2/ERBB2 protein by IHC is associated with a poor patient prognosis because of increased metastatic potential, and it is an independent predictor of disease-free and overall survival in patients with breast cancer containing this alteration (12,38–42).

The Clinical Trials Assay (CTA) (31) is the first clinical assay developed to select women for entry into the clinical trials investigating trastuzumab therapy in metastatic breast cancer patients (7,30,32). The HercepTest (Dako, Carpenteria, California) and the CB11 IHC assays (Pathway, Ventana Medical Systems, Tucson, Arizona), two of the IHC assays currently approved by the FDA for determination of HER2/ERBB2 status, were modeled on the CTA and were approved by the FDA through concordance studies. The HercepTest was approved based on a direct comparison of the agreement rate, or concordance, with the CTA. As summarized above, the agreement rate between these assay methods was 79%. The Ventana Pathway assay used one of the two antibodies from the original CTA, the CB11 anti-ERBB2 antibody, as the detection antibody in the initial formulation of this assay method; however, the 4B5 monoclonal anti-HER2 antibody is used in the current kit. The Pathway IHC method was originally approved by the FDA based on a 92.4% concordance (95% CI, 89.6%–94.7%) with the HercepTest.

The HercepTest utilizes a rabbit anti-human HER2/ERBB2 polyclonal antibody to detect the HER2/ERBB2 protein, whereas the Pathway anti-HER2 (4B5) assay uses a rabbit antihuman monoclonal antibody. The scoring of immunostaining intensity for both of these assay methods is modeled after scoring in the original CTA. The microscopic appearance of the immunostained tumor cell membranes is subjectively graded by a pathologist on a scale of 0 to 3+, with 0 and 1+ considered low expression, 2+ considered indeterminate, and 3+ considered overexpression. To reduce the subjective variation in scoring by different pathologists, a series of cell line controls are used in parallel to provide a comparison with a negative control (0) (MDA-MB-231 cells), a slightly positive control (1+) (MDA-MB-175 cells), and a strongly positive control (3+) sample (SKBR3 cells) for Dako reagents. Alternately, a different set of cell lines is available for Ventana reagents, including a negative control (0) (MCF7 cells), a slightly positive control (1+) (T47D cells), a moderately positive control (2+) (MDA-MB-453), and a strongly positive control (3+) (BT474 cells). Previously in the CTA, IHC2+ immunostaining was considered to be overexpression, but these cases were found to have a highly variable proportion with HER2/ERBB2 gene amplification and it was decided by the College of American Pathologists (CAP) and, more recently, by a joint guideline from the ASCO and the CAP that these cases should be considered *indeterminate* and *reflexed* to FISH for evaluation of HER2/ERBB2 gene amplification to determine the status of the case (43,44). The original CTA and HercepTest scoring system approved by the U.S. Food and Drug Administration (FDA) required a minimum of 10% of tumor cells to be immunostained with a particular intensity for scoring at a particular level; however, initial ASCO-CAP guidelines required the use of 30% as the proportion of tumor cells stained to achieve a particular staining level (43,44) but has been reversed to the FDA-approved 10% proportional requirement in the current

TABLE 27-2

Summary of Assays Used to Determine HER2/ERBB2 Status in Tissue Specimens

Parameter		*HER2/ERBB2 Protein Immunohistochemistry*			*HER2/ERBB2 Gene*			
						FISH	*CISH*	*SISH*
Assay Manufacturer	CTA Home-brew Assay	HercepTest Dako	Pathway Ventana	Oracle Leica	PathVysion Abbott	PharmDx Dako (now Agilent)	SPoT-Light Invitrogen/Zymed (now Life Technologies)	INFORM HER2 Ventana (now Roche)
Methodology	CB11 and 4D5 Monoclonal Antibodies	A0485 Polyclonal antibody	4B5 Monoclonal antibody	CB11 Monoclonal antibody	Directly labeled fluorescent ERBB2 and chromosome 17 centromere probes	Indirectly labeled fluorescence probes for ERBB2 chromosome 17 centromere	Digoxigenin labeled ERBB2 DNA probe and detection via anti-digoxigenin antibody followed by antimouse peroxidase	Dinitro-Phenol ERBB2 probe with detection by enzyme metallography and dig-labeled CEP17 probe
Status	Research Assay used in trastuzumab clinical trials	FDA-approved	FDA-approved	FDA-approved	FDA-approved	FDA-approved	FDA-approved	FDA-approved

Information modified from Wolff AC, Hammond ME, Schwartz JN, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. *J Clin Oncol* 2007;25(1):118–145, with permission.

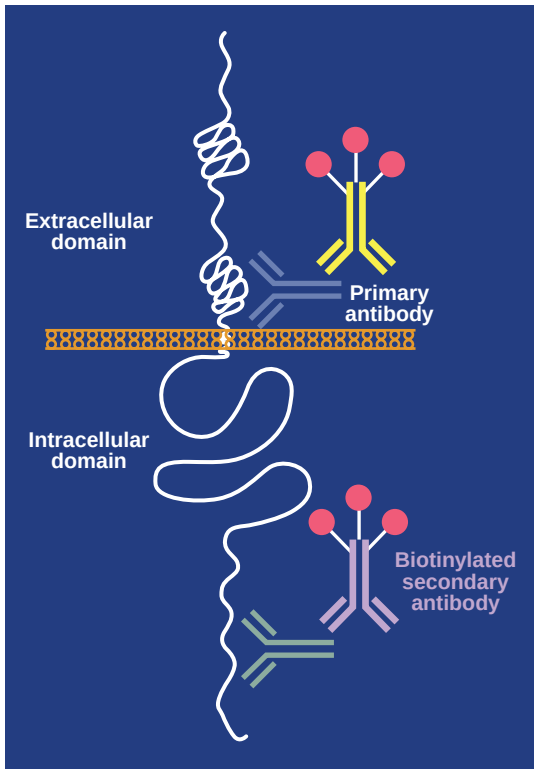

FIGURE 27-2 **Schematic illustration of the Clinical Trials Assay (CTA) to assess HER2/ERBB2 expression by immunohistochemistry.** In the CTA two different primary anti-ERBB2 monoclonal antibodies are used on sequential sections, not on the same section as illustrated in this schematic drawing. One of the primary anti-HER2/ERBB2 antibodies, 4D5, is the mouse monoclonal antibody that was humanized to synthesize trastuzumab. This antibody (*blue*) recognizes an extracellular domain of the HER2/ERBB2 protein. The other antibody, CB11 (*green*), recognizes an intracellular domain of the HER2/ERBB2 protein. These antibodies are each identified by biotinylated secondary antimouse IgG antibodies (*yellow* and *purple*) decorated with horseradish peroxidase (*red*). The site of HER2/ERBB2 is recognized by light microscopic identification of a diaminobenzidine reaction product deposited by the action of horseradish peroxidase. (Courtesy of Allison Bruce, Noel Dybdal, and Genentech.)

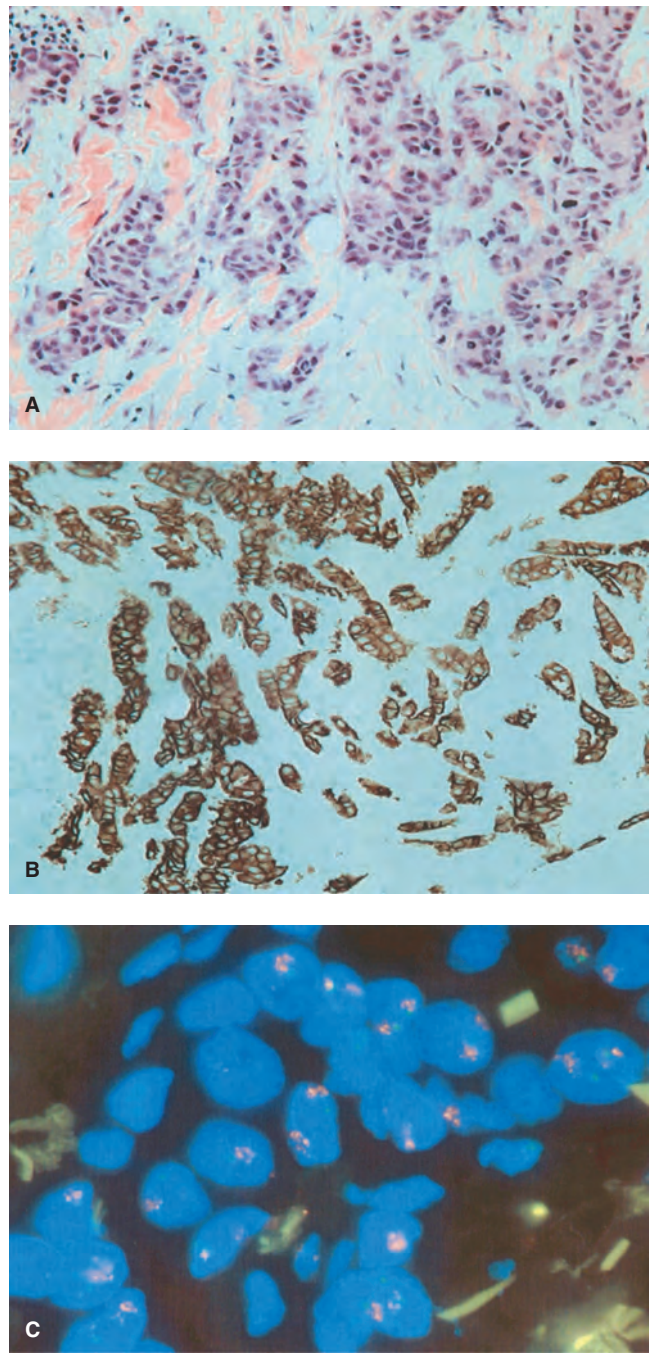

FIGURE 27-3 **Infiltrating ductal carcinoma breast cancer with HER2/ERBB2 gene amplification and overexpression.** A formalin-fixed, paraffin-embedded breast cancer is characterized **(A)** for histopathology by hematoxylin-and-eosin staining, **(B)** for HER2/ERBB2 protein overexpression by immunohistochemistry (IHC 3+), and **(C)** for HER2/ERBB2 gene amplification by FISH.

ASCO-CAP guidelines (45). No objective published data demonstrate the need for 10% as a suitable scoring minimum nor were objective data offered for a change from 10% to 30% as the minimum needed for assessment of a particular score such as IHC 3+. In fact, in frozen tissues nearly all tumor cells in a given breast cancer show the same level of immunostaining, either 1+, 2+, or 3+ (12,18), with substantial variability in staining intensity appreciated almost exclusively in the formalin-fixed, paraffin-embedded tissue samples (12,18,19,40). Nevertheless, both the HercepTest and Pathway anti-HER2 assays are approximately 90% accurate at assigning the known, molecularly determined status of breast cancer specimens (20).

The use of IHC to determine HER2/ERBB2 status is appealing for several reasons. HER2/ERBB2 IHC tests are simple, rapid, inexpensive, and easily accommodated by existing surgical pathology laboratory practices. In addition, pathologists have an established familiarity with the IHC technique and reagents. However, application of IHC to assess HER2/ERBB2 status is problematic for a number of reasons. The clinical assays are performed on fixed, paraffin-embedded (FPE) tissues and HER2/ERBB2 IHC analyses of this type of material are associated with several problems (12,18–20,33,40,46–48). Tissue handling, fixation, and

processing can greatly affect immunoreactivity of tissue antigens (12,18,19,49,50). It has been proposed that loss or significant reduction of HER2/ERBB2 immunostaining may occur in approximately 10% of HER2/ERBB2-positive (amplified) samples, owing to formalin fixation (46,47,49) or storage of unstained sections (18,51) before use for IHC. HER2/ERBB2 positivity by IHC in FFPE tissues is dependent on the HER2/ERBB2 antibody used for the protocol (12,19,20). For example, 95% of the HER2/ERBB2-amplified tumors examined were HER2/ERBB2-positive using the CB11 test, but only 84% of these same tumor samples were HER2/ERBB2-positive using the HercepTest (52).

Interpretation of IHC is inherently subjective and qualitative. This leads to observer variability and affects the accuracy of results using the IHC technique (53), although relatively high concordance rates can be achieved among experienced observers using standardized scoring systems (54). Considerable evidence indicates that IHC performance is poorly controlled "in the real world" (43,44,47,55–57). The initial ASCO-CAP guidelines on HER2/ERBB2 testing draw attention to this with the claim that "20% of HER2/ERBB2 assays performed in the field were incorrect" (43,44). The United Kingdom National External Quality Assurance Scheme (UK-NEQAS; see http://www.ukneqasicc.ucl.ac.uk/neqasicc.shtml) documents performance of diagnostic laboratories within the United Kingdom and across Europe and Asia and includes participants from the United States. Data from this scheme shows a marked difference between the levels of acceptable performance for IHC-based assays. Although computerized image analysis could reduce the subjective nature of the pathologist scoring, it cannot address the preanalytic variability owing to tissue fixation and processing. Despite these issues, IHC remains the favored technique to determine the HER2/ERBB2 status of patients in the majority of laboratories. There are continuing efforts being made to standardize IHC testing (45) and increasing numbers of laboratories are participating in the College of American Pathologists proficiency testing program for HER2/ERBB2 testing by IHC (58). Even though the quality of HER2 testing appears to be improving, there is also concern that significant numbers of breast cancer patients who may be eligible for HER2/ERBB2-targeted therapy are either not being tested or the results of these tests are not being used in treatment decisions (36).

The ASCO and the CAP have updated the 2007 Guideline recommendations. As in the original Guideline (43,44), immunohistochemistry remains acceptable as a primary test for HER2 status provided the clinical laboratory has demonstrated a high level of concordance, previously 95% (43,44) and currently 90% (45), for each immunostaining category that will be used to determine eligibility for HER2-targeted therapies (i.e., IHC 0, 1+, and 3+ categories). All IHC2+ cases will continue to be reflexed to FISH for assessment of HER2 status. A review of the literature on the subject demonstrates that few laboratories (4/33) have attained the required 95% concordance between FISH and IHC for all three IHC categories (0, 1+, and 3+) either before or after the 2007 publication of the ASCO-CAP guidelines (Table 27-3), while the majority of these laboratories (17/33) would now be able to achieve the prescribed concordance for all three IHC categories when the required percentage is lowered to 90% concordance.

IN SITU HYBRIDIZATION

A variety of *in situ* hybridization (ISH) techniques—fluorescence *in situ* hybridization (FISH), chromogenic *in situ* hybridization (CISH), and silver *in situ* hybridization (SISH)—have been used to determine HER2/ERBB2 gene amplification status in paraffin-embedded tissue sections (24,59–61) (Figs. 27-3 through 27-6).

HER2/ERBB2 Gene Amplification by Fluorescence *In Situ* Hybridization

Fluorescence *in situ* hybridization is the second most frequently used technique for determination of the HER2/ERBB2 status in clinical practice. As described above, a strong correlation exists between HER2/ERBB2 protein overexpression and HER2/ERBB2 gene amplification. Similar to HER2/ERBB2 overexpression, amplification of the HER2/ERBB2 gene is associated with unfavorable tumor characteristics, such as high nuclear grade and decreased expression of the estrogen and progesterone receptors, and decreased overall and disease-free survival (11,12,62,63).

Currently two FISH tests are approved by the FDA for selection of patients for treatment with the humanized monoclonal antibody trastuzumab: the PathVysion test (Abbott-Vysis Inc., Des Plaines, Illinois) (20,47) and the PharmDx FISH test (Dako) (64,65). The INFORM test (Ventana Medical Systems) (20,24), the first FDA-approved FISH assay, was withdrawn from the market in 2007 (Table 27-1). The PathVysion and PharmDx tests are dual-probe assays, utilizing both a fluorescent tag-labeled DNA probe specific for the HER2/ERBB2 gene and a fluorescent tag-labeled chromosome 17 centromere-specific enumeration probe (CEP) (20,24,47,64). These probes are hybridized to tissue sections under high stringency conditions (Fig. 27-3) and HER2/ERBB2 gene amplification status is assessed by enumeration of HER2/ERBB2 gene copy signals and chromosome 17 centromere signals. When the ratio of ERBB2 gene copies to chromosome 17 centromere copies is greater than or equal to 2.0, HER2/ERBB2 is considered amplified, whereas those with ratios less than 2 are considered nonamplified (18,20,24,45,47). Although a FISH ratio of 2.0 was recommended by the manufacturers and the FDA as the cutoff value for ERBB2 amplification, the 2007 ASCO-CAP guidelines recommend and CAP requires accredited laboratories to use 2.2 as the cutoff for amplification and consider FISH ratios between 1.8 and 2.2 to be *indeterminate* (43,44). Although the original FISH ratio of 2.0 correlates well with overexpression and has been supported by a number of studies of HER2/ERBB2 gene amplification as a prognostic marker (12,24) and a predictive marker of responsiveness to trastuzumab (32,33,66) and lapatinib (46,67,68), the ASCO-CAP guidelines committee offered no objective data for this change in cutoff ratio (43,44). Fortunately, only approximately 2% of unselected breast cancers have FISH ratios in this indeterminate region (18,47). Limited data currently available suggest that breast cancer patients whose cancers have HER2 FISH ratios between 2.0 and 2.2 do respond to trastuzumab with a similar hazard ratio to patients whose breast cancers have HER2 FISH ratios greater than 2.2 (69). Based on these observations the new ASCO-CAP guidelines (45) has reverted to the FDA-approved and manufacturer-approved cutoff of 2.0 with associated criteria for HER2 gene amplification by FISH.

Evaluation of the INFORM-HER test, originally formulated as a FISH assay with a single DNA probe specific for the HER2/ERBB2 gene, showed that a tumor sample needed more than four signals per nucleus to be HER2/ERBB2-amplified (24). In contrast, the ASCO-CAP guidelines recommend and CAP requires accredited laboratories to use 6.0 HER2/ERBB2 copies per tumor cell nucleus as the minimum copy number required for gene amplification with average HER2/ERBB2 copy numbers of 4.0 to 6.0 per tumor cell nucleus to be considered indeterminate, again without data

TABLE 27-3

Frequency of HER2/ERBB2 Gene Amplification in Each IHC Immunostaining Category (0, 1+, 2+, and 3+) by Study[a]

HER2 Gene Amplification Rate according to IHC Score[b]						
0	*1+*	*2+*	*3+*	*Number in Study*[c]	*IHC Method*	*Study Citation*
0%	0%	17%	89%	100	DAKO HercepTest	Hoang et al. *Am J Clin Pathol* 2000;113(6):852.
1.8%[e]		35.9%	100%	750	DAKO Ab, Unspecified	Ridolfi et al. *Mod Pathol* 2000;13(8):866.
3.5%	66.2%	97.1%	99%	2857	DAKO HercepTest	Simon et al. *J Natl Cancer Inst* 2001;93(15):1141.
0%	2.2%	38.2%	91.4%	189	DAKO A0485 Ab	Wang et al. *Am J Clin Pathol* 2001;116(4):495.
0%	5.7%	18.2%	100%	170	Homebrew Ab	Kobayashi et al. *Hum Pathol* 2002;33(1):21.
3.8%	8.5%	42.2%	100%	198	DAKO HercepTest	McCormick et al. *Am J Clin Pathol* 2002;117(6):935.
3%	7%	24%	89%	1,575	Clinical Trials Assay	Perez et al. *Mayo Clinic Proc* 2002;77(2):148.
0%	0%	0%	89.8%	119	DAKO HercepTest	Roche et al. *J Natl Cancer Inst* 2002;94(11):855.
0.7%[e]		48.1%	94.1%	426	DAKO HercepTest	Dowsett et al. *J Pathol* 2003;199(4):418.
4.2%[e]		6.1%	49%	102	DAKO HercepTest	Hammock et al. *Hum Pathol* 2003;34(10):1043.
1.1%	3.1%	26.5%	89.7%	2,279	DAKO HercepTest	Lal et al. *Am J Clin Pathol* 2004;121(5):631.
0%[e]		20%	90%	360	DAKO HercepTest	Mrozkowiak et al. *Pol J Pathol* 2004;55(4):165.
0%[e]		15%	79%	600	DAKO HercepTest	Varshney et al. *Am J Clin Pathol* 2004;121(1):70.
2.8%[e]		17%	91.6%	2,913	DAKO A0485 Ab	Yaziji et al. *JAMA* 2004;291(16)1972.
3%	7%	24%	89%	529	Clinical Trials Assay	Dybdal et al. *Breast Cancer Res Treat* 2005;93: 3–11.
6.9%[e]		31.8%	90%	114	DAKO HercepTest	Ellis et al. *J Clin Pathol* 2005;58(7):710.
2.4%[e]		72%	100%	215	DAKO HercepTest	Lottner et al. *J Pathol* 2005;205(5):577.
3.6%	6.1%	16.7%	78.1%	2,249	DAKO HercepTest and Ventana Pathway Assay	Press et al. *Clin Cancer Res* 2005;11(18):6598.
12.5%	6.7%	7%	52.4%	108	DAKO HercepTest	Ciampa et al. *Appl Immunohistochem Mol Morphol* 2006;14(2):132.
0%	0%	12.2%	91.6%	289	DAKO HercepTest	Hofmann et al. *J Clin Pathol* 2008;61(1):89.
0%	8.30%	23%	56.3%	661	DAKO HercepTest	Rasmussen et al. *Acta Oncol* 2008;47(4):784.
1.60%[e]		34.9%	86%	697	A0485 antibody (Dako)	Grimm et al. *AJCP* 2010;134(2):284.
12.5%[e]		68.6%	96.3%	171	4B5 antibody	Panjwani et al. *Indian J Med Res* 2010;132:287.
3.3%[e]		57.9%	95.2%	100	DAKO HercepTest	Tsuda et al. *BMC Cancer* 2010;10:534.
0%	3.30%	15.20%	84.1%	200	4B5 antibody	Lambien et al. Acta Oncol 2011;64:200–207.
2.6%	4.80%	28.10%	93.8%	950	A0485 antibody (Dako)	Park et al. *Cancer* 2011;118:914–923.
0%	3.17%	21.51%	90.98%	681	DAKO HercepTest	Jorgenson et al. *AJCP* 2011;136(1):145.
12.8%[e]		43.8%	97.8%	291	DAKO antibody A0485	Bernasconi et al. *Breast Cancer Res Treat* 2011;133(1):161.
0%	10.0%	25.0%	100%	216	CB11 antibody	Martin et al. *Pathol Res Int* 2012, doi: 10.1155/2012/261857.
3.4%	7.1%	49.2%	88.4%	543	CB11 antibody	Lee et al. *Arch Med Res* 2012;43(2):139–144.
2.7%		43.0%	100%	1016	DAKO HercepTest	Vergara-Lluri ME et al. *Modern Pathol* 2012;25;1326–1332.
1.8%		31.9%	93.2%	421	DAKO HercepTest	Vergara-Lluri ME et al. *Modern Pathol* 2012;25:1326–1332.
0%	12.5%	76.5%	97.3%	125	DAKO HercepTest	Kiyose et al. *Pathol Int* 2012;62:728–734.
2.0%	**8.51%**	**40.28%**	**88.35%**		**Average Percentages**[d]	
4.08%[e]				20,777		**Average Percentages**[e]

[a]Inclusion in this tabular summary required a comparison of IHC scores to FISH status in at least 100 cases per study.
[b]The percentage of FISH-positive (ERBB2-gene-amplified) cases within each IHC immunohistochemical category (0, 1+, 2+, 3+) is indicated.
[c]The total number of patients included in each study.
[d]The arithmetic average percentage of patients in the 0/1+, 2+, and 3+ subcolumns.
[e]Some studies reported low expression as pooled 0/1+ rather than separately as 0 and 1+.
Ab, antibody; IHC, immunohistochemistry.

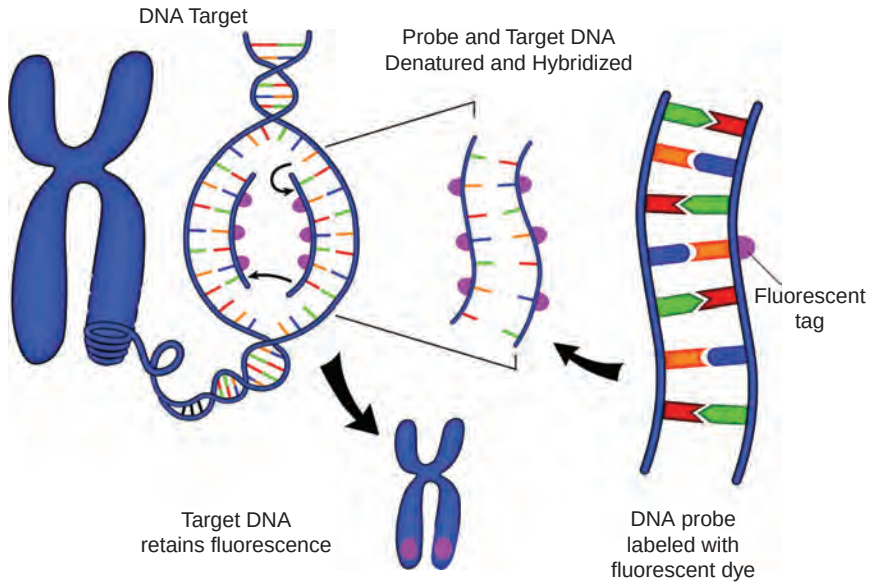

FIGURE 27-4 Schematic illustration of the fluorescence *in situ* hybridization (FISH) technique. Characterization of HER2/ERBB2 gene copy number involves a series of steps. Initially, before probe hybridization DNA-associated proteins are removed with proteinase digestion of all proteins. Subsequently, the double-stranded DNA is denatured by heating to cause separation of the DNA strands. A DNA probe encoding the gene of interest and directly labeled with a fluorescent tag is incubated with the tissue section under high-stringency conditions so the DNA probe binds specifically to the genomic sequence and remains bound to this site following high stringency washes to permit enumeration of the number of gene copies in each nucleus. Although this schematic illustrates hybridization with only one probe, FISH assays for HER2/ERBB2 currently use two different probes, one complementary to the HER2/ERBB2 gene labeled with a red or orange fluorescent tag and a second probe complementary to alpha-satellite DNA of chromosome 17 centromere labeled with a green fluorescent tag for centromere enumeration. (From Wippold FJ II, Perry A. Neuropathology for the neuroradiologist: fluorescence *in situ* hybridization. *AJNR Am J Neuroradiol* 2007;28:406–410.)

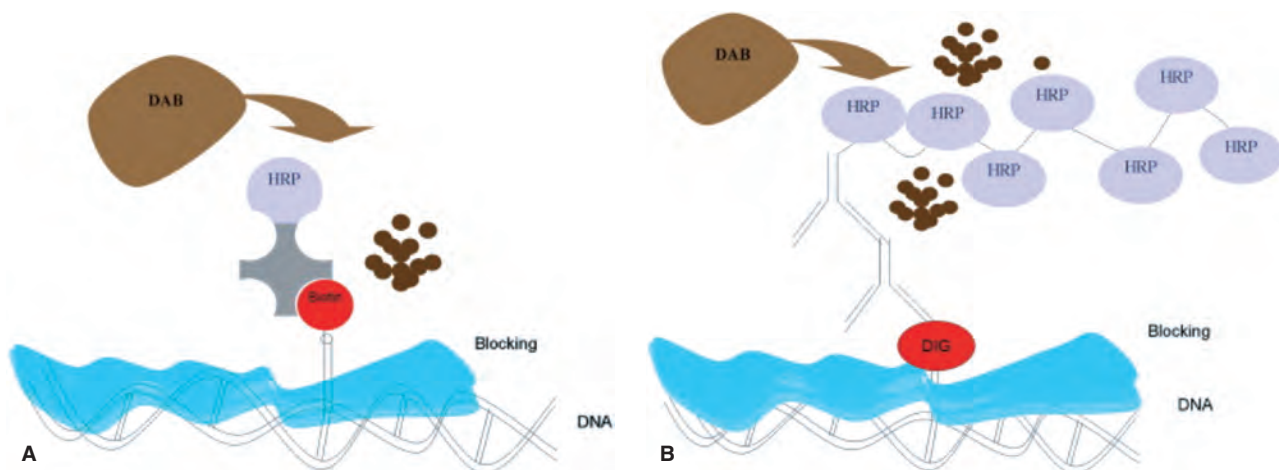

FIGURE 27-5 Schematic illustration of the chromogenic *in situ* hybridization (CISH) technique. (A) Method of localizing HER2/ERBB2 gene in tissue sections involves the use of a biotin-labeled HER2/ERBB2 DNA probe to hybridize specifically with denatured genomic HER2/ERBB2 genetic sequence. The biotin of the hybridized probe is secondarily recognized by horseradish peroxidase (HRP)-labeled avidin. Finally, polymerization of diaminobenzidine (DAB) is catalyzed by HRP to produce a brown precipitate that is microscopically visualized. **(B)** Alternatively, a digoxigen-labeled HER2/ERBB2 DNA probe is hybridized with genomic HER2/ERBB2 sequence. The digoxigen label is bound by an anti-dig mouse monoclonal antibody which is, subsequently, recognized by a secondary anti-mouse IgG rabbit or goat antibody labeled with HRP. The site of this secondary antibody is identified by reaction with DAB to produce a brown precipitate that is identified microscopically. (From Lambros MB, Natrajan R, Reis-Filho JS. Chromogenic and fluorescent in situ hybridization in breast cancer. *Hum Pathol* 2007;38:1105–1122, with permission.)

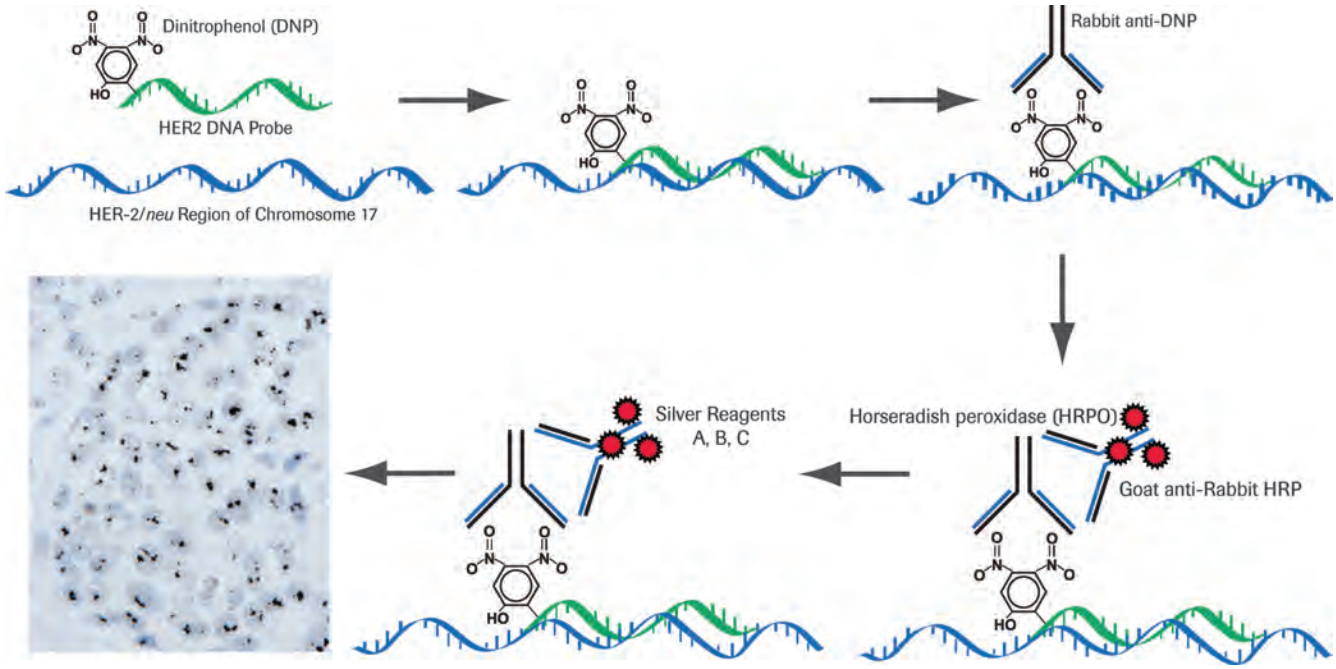

FIGURE 27-6 **Schematic illustration of the silver enhanced *in situ* hybridization (SISH) technique.** SISH is accomplished through horseradish peroxidase catalysis of silver ions to metallic silver leading to the deposition of metal nanoparticles at the site of a target gene hybridized to a DNA probe. SISH detection works as follows: A dinitrophenol (DNP)–labeled probe (upper left), either HER2/ERBB2-specific or chromosome 17 centromere–specific, binds to the genomic DNA target (upper center). A monoclonal rabbit anti-DNP linker antibody binds to the DNP hapten (upper right). The site of this primary antibody is recognized by a second antibody, a goat antirabbit antibody that is labeled with a horseradish peroxidase–labeled (HRP) multimer (lower right). Silver reagents are added to the tissue section, resulting in the deposition of metal nanoparticles at the site of the HRP (lower center), which allow visualization of the *in situ* hybridization signal (lower left). (Reproduced with permission from Ventana Medical Systems, Tucson, Arizona.)

to support a need for this change (43,44). Recent revisions to the ASCO-CAP guidelines have retained 6.0 as the average HER2/ERBB2 gene copy number required for amplification (45). The INFORM-HER FISH assay is no longer commercially available (footnote, Table 27-1). The manufacturer now has a SISH INFORM-HER assay for use with bright field microscopy.

FISH has both disadvantages and advantages. Although a newly marketed HER2 IQFISH pharmDx assay (Dako, Inc.) requires only 1 day for completion, other formulations of the method require 2 days to perform rather than the single day needed for IHC. FISH requires a fluorescence microscope, is interpreted in a darkroom by a pathologist, and the fluorescent signals fade on storage over a period of weeks to months depending on storage conditions. Because of the increased time as well as the use of more expensive reagents, FISH is more expensive than IHC. An additional disadvantage is that some high-volume laboratories use medical technicians, not pathologists, to interpret the signals in tumor cells, leading to some errors in scoring (46) probably related to the technician's inability to distinguish tumor cell nuclei from nuclei of benign reactive cells in some biopsies. An advantage of FISH is that DNA is more stable than protein and, therefore, is relatively insensitive to tissue handling or variations in fixative type or fixation time (70). Indeed, most hybridization failures encountered while performing FISH because of tissue fixation can be remedied by altering the amount of time that samples are exposed to protease digestion solution during the prehybridization phase of the analysis. This relative stability of DNA in FFPE tissues is probably responsible for the increased accuracy of the FISH method relative to IHC (18,47,71). A second advantage of FISH is that results are quantitative and, therefore, interpretation is less subjective. Variability rates between independent observers using FISH is significantly better than IHC (72–75).

HER2/ERBB2 Gene Amplification by Chromogenic *In Situ* Hybridization

A modified *in situ* hybridization technique, chromogenic *in situ* hybridization was developed in 2000 by Tanner et al. (76) and confirmed in multiple laboratories (59,76–80). CISH uses a digoxigenin (DIG)–labeled DNA probe corresponding to the HER2/ERBB2 sequence to localize the HER2/ERBB2 gene in the nuclei of cells (Fig. 27-5). The DIG-CISH probe is hybridized to a tissue section and detected using a fluorescein (FITC)–conjugated anti-DIG antibody followed by a horseradish peroxidase (HRP)–conjugated anti-FITC antibody. The tissue is then treated with diaminobenzidine (DAB), an HRP substrate, staining the region where the probe is bound (80,81). The brown DAB reaction product labels the site of HER2/ERBB2 gene copies that can then be assessed using a standard light microscope. In a second indirect method, the CISH probe is labeled with biotin and hybridized with the tissue section (Fig. 27-5). The tissue is then treated with HRP-conjugated avidin and detected with DAB as in the first method (81). Regardless of which indirect method is utilized, traditional CISH is a single

color assay and an additional slide must be used to determine centromere copy number using a chromosome 17 centromeric probe (81). In addition, CISH does not, in general, permit assessment of the number of HER2/ERBB2 gene copies present in amplified breast cancers because a single large aggregate of reaction product is deposited in the tumor cell nuclei when substantially increased copy numbers are present.

Numerous studies have indicated a good concordance between CISH and FISH with regard to *amplified* versus *not amplified* results in paraffin-embedded breast carcinomas. Hanna and Kwok (82) examined HER2/ERBB2 amplification levels by both FISH and CISH and correlated these results with IHC scores. In IHC-negative patients, the concordance rate between FISH and CISH was 97%. In IHC-positive patients (3+) the concordance rate was 98%. For patients with a 2+ IHC score the concordance rate between FISH and CISH remained high at 93% (82). Similar concordance rates have been reported by other laboratories (76–78,80,81,83–86).

There are several advantages to the CISH technique compared with FISH (Table 27-2). First, CISH probes are generated using subtractive probe technology (80). Using this technology, repetitive DNA sequences that can cause nonspecific hybridization are removed. Therefore, the final probes are very specific and do not require any blocking of nonspecific hybridization with Cot-1 DNA as in traditional FISH assays (80). Second, because the CISH method uses chromogens instead of fluorochromes to label probes, tissue staining is permanent, signals are nonbleaching, and they do not decay over time (81). This allows samples to be archived indefinitely. Third, with the CISH technique gene-copy signals can be assessed using a standard bright-field light microscope, removing the need for a fluorescence microscope, in turn decreasing the cost of the assay (81). Finally, because a light microscope is used to analyze CISH results, CISH permits concurrent analysis of tissue morphology. However, CISH has the disadvantage, described previously, that the number of HER2/ERBB2 gene copies cannot be individually enumerated in breast cancers with HER2/ERBB2 gene amplification because the DAB reaction product results in a large, brown aggregate of reaction product deposited in tumor cell nuclei rather than individual discrete signals that can be counted.

HER2/ERBB2 Gene Amplification by Silver Enhanced *In Situ* Hybridization

Silver enhanced *in situ* hybridization (SISH) is an additional modified *in situ* hybridization technique used to detect gene amplification (Fig 27-6). Instead of being based directly on the traditional FISH technique, SISH is based on an auto-metallographic procedure called gold facilitated auto-metallographic *in situ* hybridization (GOLDFISH), first described by Tubbs et al. in 2002 (61) and Hainfeld et al. in 2000 (87). Briefly, in GOLDFISH a biotin-labeled probe is hybridized to a tissue section. A catalyzed reporter deposition/tyramide signal amplification (CARD/TSA) reaction is then used to amplify the probe signal (88). The sensitivity of the CARD/TSA technique was first demonstrated by Zehbe et al. (88) who utilized the method to detect single copies of the human papillomavirus (HPV) in cell lines. The tissue is finally treated with nanogold particles covalently linked to streptavidin and incubated with GoldEnhance particles that are deposited onto the nanogold particles, making the signal visible by light microscopy (87,89).

Silver enhanced *in situ* hybridization also relies on the action of the peroxidase enzyme linked to a metal to deposit metallic particles at the site of a probe. SISH differs from GOLDFISH in several ways. First, SISH utilizes silver particles instead of gold. Second, the silver particles in SISH are not placed around a metallic core, such as nanogold, but are deposited as a result of direct action of peroxidase on a substrate linked to the metal. Third, SISH does not contain an amplification step in the procedure, such as the CARD/TSA reaction.

Several advantages exist to the SISH technique (Table 27-2). SISH is a sensitive method for detecting gene amplification (60). SISH does not require CARD/TSA amplification. Thus, fewer reagents are required for SISH than for FISH or CISH. Finally, similar to CISH, because no fluorochromes are used to label SISH probes, resulting signals are permanent, not light sensitive, do not decay over time, and may be read using a standard light microscope. The INFORM HER2 Dual ISH assay was approved using a concordance study of 714 breast cancers by comparison with the Abbott-Molecular PathVysion FISH assay. An overall agreement rate of 94% was observed between the two assay methods (Table 27-1).

Enzyme-Linked Immunosorbent Assay for Assessment of HER2/ERBB2 Extracellular Domain in Serum or Plasma

In contrast to IHC, FISH, and alternative FISH techniques, this next technique to determine a patient's HER2/ERBB2 status is not performed directly on the tumor tissue but on the patient's serum or plasma. Since 1991, both manual and automated enzyme-linked immunosorbent assays (ELISA) have been used to measure the amount of soluble HER2/ERBB2 protein extracellular domain (ECD) that is cleaved from cells and shed into patient serum (90) or plasma (91). Because a strong correlation exists between manual and automated results (92–95), both types of assays have been approved by the FDA to manage and monitor women diagnosed with metastatic breast cancer (92).

HER2/ERBB2 ECD can be detected in the plasma of healthy women and ECD levels increase in women diagnosed with both primary and metastatic breast cancer (90,92,96). High concentrations of shed HER2/ERBB2 ECD in serum are reported to correlate with HER2/ERBB2 overexpression (97), increased tumor size (98), higher relapse rates, and poor clinical response to hormone therapy and chemotherapy in patients with metastatic breast cancer (99–101). High HER2/ERBB2 ECD levels are also associated with a shorter progression-free survival (102).

The HER2/ERBB2 ECD test has been suggested as an alternative method to determine a patient's HER2/ERBB2 status. This testing method allows real-time determination of HER2/ERBB2 status and would permit monitoring changes in HER2/ERBB2 levels after surgery (92). However, ERBB2 HER2/ECD tests have not been established as useful in the diagnosis of HER2/ERBB2-positive breast cancer nor in predicting responsiveness to therapies and disease outcome. The results of this test are quantitative and, because the FDA established a cutoff of 15 μ g/L, are not open to subjective interpretation (92). Unlike IHC and FISH, it is impossible to determine the source of the HER2/ERBB2 protein fragment when utilizing this method. Thus, high baseline levels of HER2/ERBB2 ECD may not be caused by direct shedding of the HER2/ERBB2 ECD by tumor, but may be attributed to individual variations in receptor density, tumor burden, the rate of ECD cleavage and release into circulation, and the subsequent degradation of the protein fragment (52,100). In addition, only moderate concordance (87.1%) is found between serum HER2/ERBB2 ECD levels and tissue HER2/ERBB2 levels as measured by IHC and FISH (102,103). Fornier et al. (52) not only observed elevated HER2/ERBB2 ECD levels in breast cancer patients with HER2/ERBB2-positive disease but also among patients with tumors that did not show HER2/ERBB2 overexpression or gene amplification. The HER2/ERBB2 ECD ELISA assay is useful for monitoring recurrent disease among women with established HER2/ERBB2-positive breast cancers.

COMPARISON OF TESTS FOR ASSESSMENT OF HER2/ERBB2 STATUS

Accurate determination of HER2/ERBB2 status is critical in the selection of adjuvant and neoadjuvant therapy for women diagnosed with invasive breast carcinoma as well as women with metastatic disease. Only patients with tumors that overexpress HER2/ERBB2 or exhibit gene amplification are candidates for treatment with targeted therapies directed against the HER2/ERBB2 protein. In patients diagnosed with metastatic breast cancer, clinical benefit from trastuzumab is restricted to HER2/ERBB2-positive tumors as demonstrated by FISH (33). Patients whose breast cancers have gene amplification by FISH but lack overexpression by IHC (IHC ≤2+), the IHC false-negative breast cancer cases, show a clinical benefit from the addition of HER2/ERBB2-targeted therapies to chemotherapy (46). In contrast, those patients with breast cancers lacking HER2/ERBB2 gene amplification by FISH but having IHC 3+ immunostaining, the IHC false-positive cases, show no significant incremental benefit of HER2/ERBB2-targeted therapies beyond that of chemotherapy alone (33). Therefore, differences in the laboratory methods used to assess HER2/ERBB2 status are potentially important. These differences and similarities in HER2/ERBB2 status by FISH and IHC, the concordance rate, for determination of HER2/ERBB2 status are discussed in this section.

As stated previously, assessment of frozen tissue samples shows a direct relationship between HER2/ERBB2 gene amplification and HER2/ERBB2 protein overexpression. When the HER2/ERBB2 gene is amplified, there is consistent concordant overexpression of the receptor. In contrast, when the HER2/ERBB2 gene is not amplified, no increase in receptor expression is observed in frozen tissue samples or in breast cancer cell lines. The association between HER2/ERBB2 gene amplification and protein overexpression has been clearly demonstrated in frozen tissue samples using both IHC and FISH assays. In fixed paraffin-embedded tissue samples, however, equivalent results are more consistently observed when utilizing FISH. Indeed, the fixation and embedding processes not infrequently lead to difficulties and inconsistencies in determining HER2/ERBB2 status when utilizing IHC (12,19–21). This preanalytical variability owing to tissue fixation and processing in addition to the observer variability and subjective interpretation of IHC leads to discordance between IHC and FISH (43,44,48). Because most tissue used to determine HER2/ERBB2 status has been fixed and embedded, this discordance impacts the selection of patients for targeted therapy. To determine if a patient is a candidate for treatment with these HER2/ERBB2 targeting drugs, it is critical to determine a patient's HER2/ERBB2 status accurately. Thus, the method utilized to determine HER2/ERBB2 status is important.

The discordance between the results of IHC and FISH assays for HER2/ERBB2 has been demonstrated in numerous published studies (Table 27-3). In these studies, patients with an IHC score of 0 or 1+ are considered to be HER2/ERBB2-negative, whereas those with a score of 3+ are interpreted as HER2/ERBB2-positive. Patients with an IHC score of 2+ are considered inconclusive or equivocal and are *reflexed* to FISH for assessment of gene amplification (43–45). The greatest discordance between IHC and FISH is observed in patients whose breast cancers are considered equivocal (Table 27-3). Large variations in HER2/ERBB2 amplification rates have been reported for patients in this group (Table 27-3). Indeed, HER2/ERBB2 gene amplification rates in the IHC 2+ group vary from 0% to 97%, although most report amplification rates between 15% and 50% (Table 27-3) (43–45,47,57,104). Because of the large variation in HER2/ERBB2 amplification rates reported for patients with inconclusive IHC results, the ASCO and CAP currently recommend that all patients with inconclusive HER2/ERBB2 IHC results (IHC 2+) undergo reflex reevaluation with FISH for final determination of HER2/ERBB2 status before adjuvant therapy (43–45). The discordance in HER2/ERBB2 status as determined by FISH and IHC is not limited to the IHC 2+ group, although discordance in the 0, 1+, and 3+ IHC categories is more limited.

Although the ASCO-CAP guidelines recommend that the IHC 2+ cases be reflexed to FISH for definitive assessment, the guidelines also accept primary IHC testing as determinative for the IHC 0, 1+, and 3+ categories. They do recommend that any laboratory performing such primary IHC testing to determine HER2/ERBB2 status be able to demonstrate a high level of concordance (>95%) between each IHC category (0, 1+, and 3+) and independently assessed HER2/ERBB2 status by FISH. Unfortunately, the published literature demonstrates that this high level of concordance for all three IHC 0, 1+, and 3+ categories is only seldom achieved (Table 27-3). The percentages in the 0 and 1+ IHC categories shown in Table 27-3 represent the proportion of patients that is HER2/ERBB2-negative by IHC but HER2/ERBB2-amplified by FISH. Although an average of fewer than 10% of patients in the IHC 0 and 1+ categories exhibit amplification of the HER2/ERBB2 gene, because of the large number of breast cancers in this category (approximately 75% of breast cancers) this represents a significant proportion of patients with the HER2/ERBB2 alteration of gene amplification. Indeed, because the HER2/ERBB2 gene is amplified and overexpressed in only approximately 20% to 25% of human breast carcinomas, the 0 and 1+ IHC categories (HER2/ERBB2-negative) contain the most patients. Having as few as 4% of IHC 0/1+ patients with ERBB2 amplification still represents approximately 1 of every 10 women whose breast cancers have this alteration. The percentage of HER2/ERBB2-amplified breast cancers that has IHC 0 or 1+ immunostaining in FFPE samples ranges from approximately 3% to approximately 21%, depending on the study.

Those patients with HER2/ERBB2-negative breast carcinomas by IHC, but with HER2/ERBB2 amplification as determined by FISH, have tumors with biological phenotypes similar to other patients with HER2/ERBB2-amplified breast tumors. All women whose breast cancers have HER2/ERBB2 gene amplification, without exception in frozen tissue, have HER2/ERBB2 overexpression and this overexpression can be obscured by tissue fixation and processing as assessed by IHC staining in a variable proportion of these breast cancers (12). These false-negative IHC assessments, therefore, represent significant diagnostic problems, especially because these women respond to HER2/ERBB2-targeted therapies (46). In these cases, the discordance between HER2/ERBB2 amplification and HER2/ERBB2 overexpression, as determined by FISH and IHC, respectively, results in denial of targeted therapy for patients with HER2/ERBB2-positive tumors that have been shown to respond to treatment (46).

In contrast, the percentage of HER2/ERBB2 not amplified or FISH-negative cases in the IHC 3+ category (Table 27-3) represents patients with strong immunostaining (IHC 3+) for the HER2/ERBB2 protein, as shown by IHC in FFPE tissue, that lack amplification of the HER2/ERBB2 gene. The overall amplification rates for patients in the IHC 3+ group range from 49% to 100%, although most published amplification rates are above 85% with an average of almost 90% showing HER2/ERBB2 gene amplification (Table 27-3). Using an antibody that does not require antigen retrieval for IHC, most of these IHC3+, FISH-negative breast cancers have been shown to have IHC false-positive results (47). As shown in Table 27-3, these IHC3+/FISH-negative breast cancers represent approximately 10% of all IHC3+ cases. This false-positive rate is important because only women with HER2/ERBB2-amplified tumors respond to the HER2/ERBB2-targeted

therapies, trastuzumab and lapatinib (33,46). Indeed, as shown by Mass et al. (33), clinical benefit from trastuzumab therapy in patients diagnosed with metastatic breast cancer is restricted to HER2/ERBB2 FISH-positive patients. Furthermore, inaccurate assessment of HER2/ERBB2 status can lead to the inappropriate treatment of breast cancer patients with trastuzumab, both in the adjuvant and metastatic settings, and subject patients to unnecessary risk. Retrospective evaluation of outcome in the pivotal clinical trials of trastuzumab in women with metastatic breast cancer have shown that these IHC false-positive cases have an approximately 3% (or less) chance of responding to trastuzumab (33) and a similarly low probability of responding to lapatinib (46). Cardiac toxicity is a serious concern in patients with early-stage disease who are treated with both trastuzumab and anthracycline-containing chemotherapy (4-6,105,106). Therefore, as with women diagnosed with 0 or 1+ HER2/ERBB2-negative tumors by IHC, the discordance between HER2/ERBB2 amplification and HER2/ERBB2 overexpression in women with IHC3+/ERBB2-not-amplified tumors can result in inappropriate treatment of patients and, therefore, expose patients to unnecessary risk.

One of the goals of the 2007 ASCO-CAP guidelines committee was to address discrepancies in HER2/ERBB2 testing through standardization of the testing practices. Since publication of these guidelines, the CAP has required adherence to these guidelines for accreditation of HER2/ERBB2 testing laboratories. This has led to a substantial increase in the number of laboratories participating in the CAP proficiency testing programs (58), especially for IHC; however, it has not resulted in a similar reduction in the discrepancies between FISH and IHC testing based on papers published since 2007 (see Table 27-3) or based on single-institution comparisons of testing before and after implementation of the ASCO-CAP guidelines (107).

Inaccurate assessment of HER2/ERBB2 status can lead to inappropriate treatment of breast cancer patients with targeted therapies in both the adjuvant and metastatic settings. This exposes patients to unnecessary risk by either denying HER2/ERBB2-targeted therapies to patients who have a reasonable likelihood of responding to the drugs or by inclusion of patients in HER2/ERBB2-targeted treatment who do not exhibit HER2/ERBB2 amplification or overexpression. These concerns are especially relevant in countries such as the United States where most HER2/ERBB2 testing is performed with IHC assays (36,47,58).

ISSUES RELATED TO RESPONSE OF "HER2/ERBB2-NEGATIVE" BREAST CANCER PATIENTS TO HER2/ERBB2-TARGETED THERAPY

Although a report from the NSABP suggests that *HER2/ERBB2-negative* breast cancer patients in the B-31 trial respond to trastuzumab in the adjuvant setting (108), all of those patients were entered in the clinical trial based on their having *HER2/ERBB2-positive* breast cancer assessed in community laboratories. The NSABP central laboratory HER2/ERBB2-negative breast cancers represent 9.7% of women (174/1787) entered in the trial with follow-up data and this percentage is within the known range of testing variability between selected laboratories (31,43–45,47). Similar observations have been made for HER2/ERBB2-negative metastatic breast cancer patients and response to lapatinib therapy (46). A blinded reanalysis of the HER2/ERBB2-negative metastatic breast cancer patients from the latter clinical trial of lapatinib by a second central laboratory eventually demonstrated that the apparent lapatinib responsiveness of HER2/ERBB2-negative breast cancer patients was due to testing errors in the original large, high-volume laboratory where a medical technician, rather than a board-certified pathologist, assessed HER2/ERBB2 status (46). Since the NSABP has not subjected their central laboratory HER2/ERBB2-negative breast cancers to independent assessment of HER2/ERBB2 status by FISH, these cases could represent HER2/ERBB2 testing errors by FISH, as has already been demonstrated for the EGF 100151 lapatinib clinical trial (46). Nevertheless, the NSABP has initiated the B47 clinical trial of trastuzumab in women with invasive, HER2-low (IHC 1+ or 2+) breast cancer to test this idea.

CONCLUSIONS

Determination of a patient's HER2/ERBB2 status is critical for patients diagnosed with both primary and metastatic breast carcinomas. HER2/ERBB2 status is important for assessment of the patient's prognosis as well as a critically important factor in selecting the optimal chemotherapeutic or biologic treatment for a patient.

MANAGEMENT SUMMARY

Histologic diagnosis of invasive breast carcinoma with evaluation of HER2/ERBB2 status is as follows.

Based on available published evidence as summarized in this chapter we recommend:	Based on consensus of the ASCO-CAP guidelines—committee recommendations:
• Assessment of HER2/ERBB2 status by FISH	• Assessment of HER2/ERBB2 status by either IHC or FISH, although the vast majority (80%) of testing is clearly performed with IHC
• HER2/ERBB2-amplified → ERBB2-targeted therapy (trastuzumab) in combination with chemotherapy (preferably a nonanthracycline (6, 26) chemotherapy regimen)	• HER2/ERBB2-IHC 3+ → ERBB2-targeted therapy (trastuzumab) in combination with chemotherapy
	• HER2/ERBB2-IHC 2+ → reflex to FISH assay to determine HER2 status based on gene amplification
• HER2/ERBB2 not amplified → nonanthracycline (6,26) combination chemotherapy regimen	• HER2/ERBB2-IHC 1+/0 → combination chemotherapy regimen
• FISH failure (1% to 5% of cases) → IHC assessment of HER2/ERBB2 status (0/1+/2+, HER2/ERBB2 low expression; 3+, HER2/ERBB2 overexpression)	

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CHAPTER 28

Clinical and Pathologic Prognostic and Predictive Factors

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CHAPTER CONTENTS

Prognostic and predictive factors and biomarkers are critical to clinical decision-making in oncology. A 1991 NIH Consensus Conference (1) stipulated that clinically useful prognostic and predictive factors in breast cancer must meet the following criteria:

1. They must provide significant, independent predictive value, validated by clinical testing.
2. Their identification and measurement must be feasible, reproducible, and widely available with quality control.
3. The results must be readily interpretable by clinicians and have therapeutic implications.
4. Measurement of biomarkers should not consume tissue needed for other tests, especially routine histopathological evaluation.

Prognostic markers provide information on the biological potential and most likely clinical course of a breast cancer irrespective of treatment (2,3). Insight into the natural history of individual breast cancers may provide valuable information regarding the need for systemic adjuvant therapy, but is uninformative with respect to which specific treatment regimen is most likely to be effective.

Predictive factors inform on the likelihood of response of a breast cancer to specific therapies (3). Hormone receptor status predicts the responsiveness or lack of same of a breast cancer to endocrine therapy.

Some tumor biomarkers are of mixed significance. Estrogen receptor expression, while a strong predictor of response to endocrine therapy, is only weakly prognostic. HER2 expression has highly adverse prognostic implications but is predictive of tumor response to anti-HER2 therapy.

Conventional clinicopathological factors such as patient age, menopausal status, race/ethnicity, tumor size, nodal status, lymphovascular invasion, micrometastases or isolated tumor cells in regional lymph nodes, extracapsular extension of nodal metastases, tumor grade, tumor stage, presence or absence of the inflammatory phenotype, markers of tumor proliferation, and hormone receptor and HER2 status continue to be useful in estimating prognosis. The prognostic implications of the intrinsic breast cancer subtypes (4,5), multigene tumor signature assays (6), and clinicopathological response to neoadjuvant systemic therapy (7) offer further opportunities for refinement of clinical decision making in breast cancer.

Numerous potential breast cancer biomarkers have been cited and characterized over the past several decades. Discerning their true magnitude of effect, reliability and clinical utility has been complicated by deficiencies in biomarker assays and measurement, the quality of evidence supporting the potential biomarker status of the factor(s) under study, and failures in clinical trials design and studied patient cohorts and populations to account for and control confounding variables. A number of expert panels have reviewed available information on breast cancer biomarkers and concluded that limitations in available data allow for only the most guarded recommendations (8). For these reasons, significant efforts have been directed toward standardizing the investigation and establishment of clinically relevant biomarkers.

GENERAL CONSIDERATIONS

For prognostic and predictive factors to be clinically useful, they must be detectable and reproducibly measurable by different laboratories at reasonable cost, yielding results promptly for clinical decision making. Their clinical correlations must be clearly defined in terms of their nature (prognostic, predictive, or both), and assay values, whether continuous or categorical, must be reliably associated with patient outcomes. The relevant clinical information being sought must not be available through another more readily accessible factor. The expected differences in outcomes must be significant and important from the patient's perspective. Finally, useful prognostic and predictive factors must provide information upon which a choice among available treatment options can be based (9).

Pure prognostic and predictive factors are schematically depicted in Figure 28-1, panels A and B, respectively.

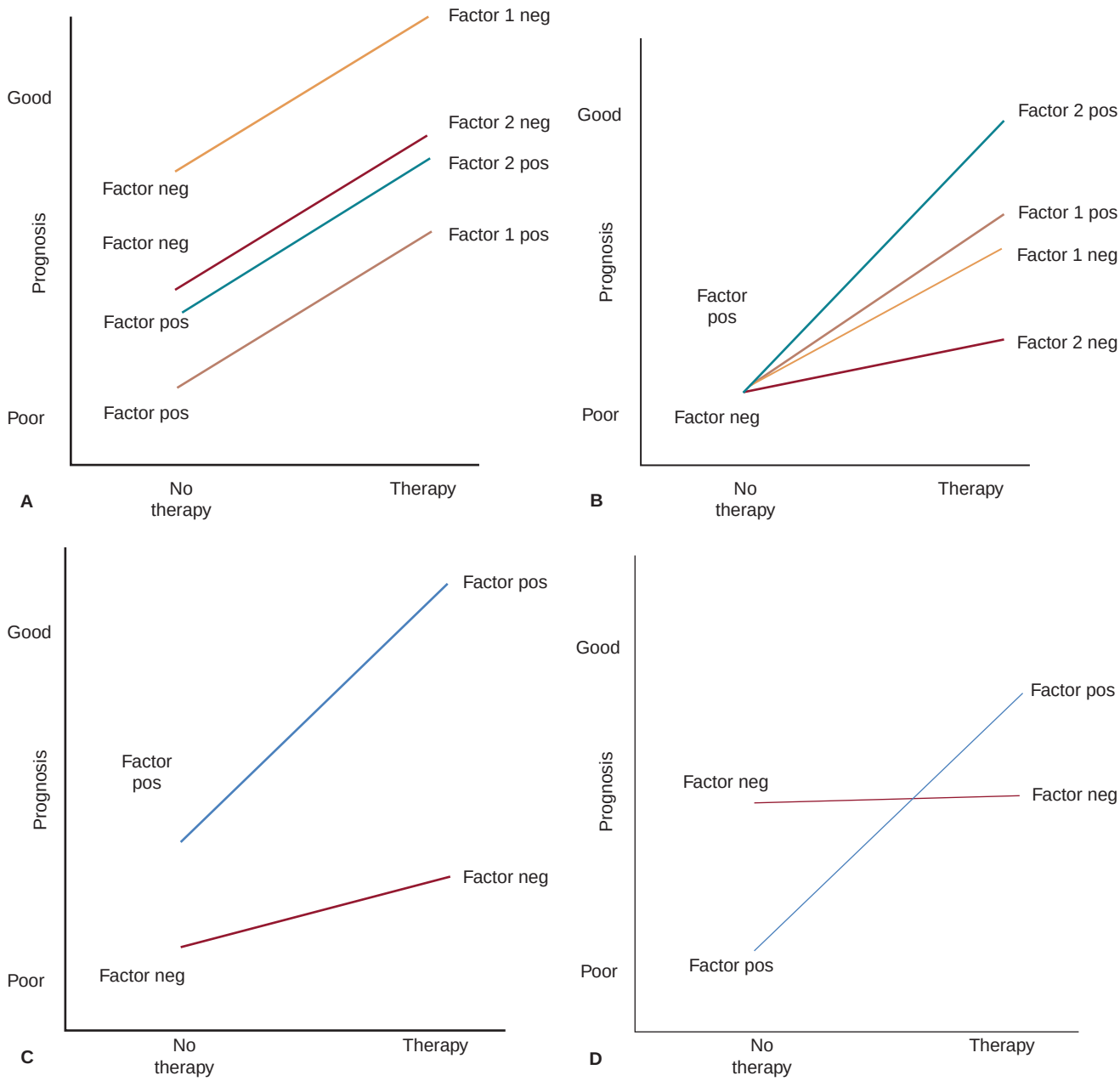

FIGURE 28-1 Schematic representation of prognostic and predictive factors: prognosis versus therapy as binomial variables. **(A)** Pure prognostic factor. **(B)** Pure predictive factor. **(C)** Mixed factor with weakly favorable prognostic effect and strong response to therapy. **(D)** Mixed factor with unfavorable prognosis and strong response to therapy. (Adapted from Henry NL, Hayes DF. Uses and abuses of tumor markers in the diagnosis, monitoring and treatment of primary and metastatic breast cancer. *Oncologist* 2006;11:541–552. Modified from Hayes DF, Trock B, Harris AL. Assessing the clinical impact of prognostic factors: when is "statistically significant" clinically useful? *Breast Cancer Res Treat* 1998;52:305–319, Springer Science and Business Media.)

Prognosis versus therapy are plotted as binomial variables (8,10). A large incremental difference in prognosis related to positive and negative status is observed for factor 1 (a strong prognostic factor such as lymph node status) while that for factor 2 is much smaller (ER status). In panel B, factor 1 is a weak predictive factor while factor 2 is a much stronger one. Hayes et al. (10) proposed that prognostic factors in breast cancer be categorized quantitatively by their associated hazard ratios (HR), HR <1.5 denoting weak factors, 1.5 to 2.0 moderate factors, and >2.0 strong factors. They further proposed a similar rating of the strength of predictive factors by tumor response to and clinical benefit from a specific therapy. "Relative predictive value" (RPV), the ratio of the probability of response to treatment in a factor-positive patient as compared to that in a factor-negative patient, has been proposed as a means of quantifying the strength of predictive factors as weak (RPV = 1 – 2), moderate (RPV = 2 – 4), or strong (RPV > 4).

Panel C in Figure 28-1 represents a mixed prognostic and predictive factor such as ER status, the prognostic effect being weakly favorable and the predictive effect strongly so. Panel D depicts a mixed factor with an unfavorable prognosis but highly responsive to specific therapy, as exemplified by HER2 status.

Statistical significance in marker-positive or marker-negative patient outcomes is not infrequently mistaken for or conflated as evidence of clinical utility. This does not always hold and should never be assumed. Along with the magnitude of the effect and the relevance of the marker, technical reliability and reproducibility are critically important, as is the design and execution of clinical studies (10).

Technical shortcomings related to biomarker assay sensitivity, specificity, reproducibility, and reagent variability can be highly problematic. Standardization of assay methodologies has greatly improved, of late. For example, intra- and interobserver variation, well documented in immunohistochemical assays, has been controlled through automated and semiautomated processes (8).

Determination of cut-off points that distinguish positive from negative results is critical to the development of clinically useful assays. Cut-off points can be set arbitrarily or based on data. Arbitrary cut-off point selection has included the limits of detection of the assay, two standard deviations above the normal mean, the mean value in affected as compared to normal patients, or an arbitrarily defined appropriate percentage of positive cells (8).

Data-derived cut-off points have been based on plots of *p*-values versus outcomes, plots of the magnitude of marker effect versus patient outcome, construction of receiver operating characteristic curves (cut-off points established by determining the optimal trade-offs of sensitivity and specificity in an assay), or subpopulation treatment effect pattern plot (STEPP) analysis (11). The latter methodology evaluates outcomes to specific treatment regimens in subpopulations of patients within randomized trials or meta-analyses (8).

Once established in a test group of patients, cut-off points must be confirmed in a validation patient cohort similar to but completely independent of the initial test group. Having been identified and validated, the clinical value of a new tumor marker relative to well-established prognostic or predictive factors is then confirmed by multivariate analysis. This provides information on the potential clinical utility of the new marker in medical practice.

Study design is key to identifying and establishing new tumor biomarkers. The Tumor Marker Utility Grading System (TMUGS) (12) was developed as a frame of reference for grading the clinical utility of tumor markers based on published evidence. Putative markers are assigned a utility score according to degree of correlation with biological processes and end points (Table 28-1) and favorable clinical outcomes (Table 28-2), as determined by level of evidence (LOE; Table 28-3) (8) and grading of tumor marker studies (Table 28-4) (13).

TABLE 28-1

Scale to Evaluate Tumor Marker for Correlation with Biological Processes and End Points

Utility Scale	*Explanation*
0	Does not correlate with process or expected end point
NA	Data not available on marker correlation with process or end point for that use
+/–	Preliminary data suggestive, but substantially more definitive studies required
+	Assay probably associated with process or end point, but confirmatory studies required
++	Definitive studies show that assay reflects process or end point

From Hayes DF, Bast RC, Desch CE, et al. Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. *J Natl Cancer Inst* 1996;88:1456–1466.

LOE levels I and II are the most robust and objective, the ideal level I clinical trial being prospective, randomized, appropriately powered, and designed specifically to evaluate the clinical utility of a putative tumor marker for a discrete, predetermined use. That noted, a clinical trial adequately powered to determine a clinical end point may be underpowered for analysis of tumor marker subgroups by as much as 25%, even when tissue samples are available for all participating patients (8).

Systematic overviews and pooled analyses of well-conducted LOE II studies are essentially equivalent to LOE I evidence. LOE III studies, with their greater variability in patient characteristics and therapies, are better suited to generating hypotheses than contributing clinically useful information (8).

Attention to detail is critical to clinical trials design and conduct. The appropriate patient population must be selected with particular attention to a similar profile among them in terms of known prognostic factors. Trials focused on predictive factors are ideally prospective, randomized, and controlled, comparing patients receiving the intervention in question to untreated controls (8).

The REMARK tool, a standardized reporting schema for tumor marker data, has been developed by the Working Group of the National Cancer Institute and the European Organization for Research and Treatment of Cancer (EORTC) (14). This project was undertaken to eliminate the highly variable and flawed approaches to tumor marker elucidation and to provide a standard template for investigation of potential markers in the future.

PROGNOSTIC FACTORS—CLINICAL

Age

Breast cancer patients aged 35 to 40 years or less at presentation have a significantly worse prognosis than older premenopausal patients or those over the age of 50.

TABLE 28-2

Scale to Evaluate Utility of Tumor Markers for Favorable Clinical Outcomes

Utility Scale	*Explanation*
0	Marker adequately evaluated for specific use; data definitively demonstrate no utility. Marker should not be ordered for that clinical use.
NA	Data not available for the marker for that use because marker has not been studied for that use.
+/–	Data are suggestive that marker may correlate with biological processes and/or end points, and preliminary data suggest that use of the marker may contribute to favorable clinical outcome, but more definitive studies are required. Thus, marker is still considered highly investigational and should not be used for standard clinical practice.
+	Sufficient data available to demonstrate that marker correlates with the biological process and/or biological end point related to its use and that the marker might affect favorable clinical outcome for that use. However, marker still considered investigational and should not be used in standard clinical practice for one of three reasons: 1. The marker correlates with another marker/test that has been established to have clinical utility, but the new marker has not been shown to clearly provide an advantage. 2. The marker may contribute independent information but it is unclear whether the information provides clinical utility because treatment options have not been shown to change outcome. 3. Preliminary data for the marker are quite encouraging, but the level of evidence is lacking to document clinical utility.
++	Marker supplies information not otherwise available from other measures that is helpful to the clinician in decision making for that use, but the marker cannot be used as the sole criterion for decision making. Thus, marker has clinical utility for that use, and it should be considered standard practice in selected situations.
+++	Marker can be used as the sole criterion for clinical decision making in that use. Thus, marker has clinical utility for that use, and it should be considered standard practice.

From Hayes DF, Bast RC, Desch CE, et al. Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. *J Natl Cancer Inst* 1996;88:1456–1466.

TABLE 28-3

Levels of Evidence for Grading Clinical Utility of Tumor Markers

Level	*Type of Evidence*
I	Evidence from a single, high-powered, prospective controlled study specifically designed to test marker or evidence from meta-analysis and/or overview of level II and III studies. In the former case the study must be designed so that therapy and follow-up are dictated by protocol. Ideally, the study is a prospective controlled randomized trial in which diagnostic and/or therapeutic clinical decisions in one arm are determined at least in part on the basis of marker results, and diagnostic and/or therapeutic clinical decisions in the control arm are made independently of marker results. However, study design may also include prospective but not randomized trials with marker data and clinical outcome as primary objective.
II	Evidence from study in which marker data are determined in relationship to prospective therapeutic trial that is performed to test therapeutic hypothesis but not specifically designed to test marker utility (i.e., marker study is a secondary objective of the protocol).
III	Evidence from large studies from which variable numbers of samples are available or selected. Therapeutic aspects and follow-up of the patient population may or may not have been prospectively dictated. Statistical analysis for tumor marker was not dictated prospectively at the time of therapeutic trial design.
IV	Evidence from small retrospective studies which do have prospectively dictated therapy, follow-up, specimen selection, or statistical analysis. Study may use matched case-controls, etc.
V	Evidence from small pilot studies designed to determine or estimate distribution of marker levels in the sample population. Study design may include "correlations" with other known or investigational markers of outcome but is not designed to determine clinical utility.

From Hayes DF, Bast RC, Desch CE, et al. Tumor marker utility grading system: a framework to evaluate clinical utility of tumor markers. *J Natl Cancer Inst* 1996;88:1456–1466.

TABLE 28-4

Grade of Tumor Marker Studies for Level of Evidence

Grade	*Study Description*
A	Prospective
B	Prospective, using archived samples
C	Prospective, observational
D	Retrospective, observational

Level of Evidence	*Grade*	*Validation Studies Available*
I	**A**	None required
I	**B**	One or more with consistent results
II	**B**	None or inconsistent results
II	**C**	Two or more, consistent results
III	**C**	None or one, consistent or inconsistent results
IV–V	**D**	Not applicable: LOE IV and V unsatisfactory for determination of biomarker clinical utility

From Simon RM, Paik S, Hayes DF. Use of archived specimens in evaluation of prognostic and predictive biomarkers. *J Natl Cancer Inst* 2009;101:1446–1452.

Chemotherapy is especially effective in premenopausal patients. However, those under 35 years of age receiving chemotherapy for endocrine-responsive breast cancer have a significantly higher risk of relapse than older premenopausal patients with such tumors. In contrast, outcomes among younger and older premenopausal patients receiving chemotherapy for endocrine nonresponsive disease are essentially equivalent (15).

In another meta-analysis (16), higher mortality (HR = 1.55; 95% confidence interval [CI] 1.20–2.00) and locoregional recurrence (HR = 2.34; 1.30–4.24) were observed in patients less than 35 years old as compared to those over 50. Mortality in patients aged 35 to 50 years as compared to those over 50 was no different (HR = 1.01; 0.87–1.16) but locoregional recurrence was more frequent (HR = 1.60; 1.14–2.25).

A SEER analysis of 243,012 breast cancer patients (17) reported that those less than 40 years of age (6.4% of the cohort) were more likely to be African American, single, to have presented with advanced disease, and to have undergone total mastectomy. Their tumors were of higher grade, larger size, and more often estrogen receptor-negative (–), progesterone receptor-negative (PR–), and lymph node-positive. The adjusted HR for mortality among younger women was significantly higher as compared to older patients overall (1.39; 1.34–1.45). For stage I disease, HR for mortality was 1.44 (1.27–1.64) and for stage II breast cancer, 1.09 (1.03–1.15). Among patients with stage IV disease, however, the mortality ratio for younger patients, at 0.85 (0.76–0.95), was significantly lower than for those over 40 years of age.

At 11 years median follow-up, a recent EORTC pooled analysis (18) reported that among patients less than 40 years of age, tumor size, nodal status, and intrinsic molecular subtype were independent prognostic factors for overall survival (OS). Among node-negative patients less than 40, only intrinsic subtype was significant. Ten-year survival among patients with luminal A tumors was 94% as compared to 72% for those with basaloid tumors. In a similar analysis of 315 patients less than 35 years of age (19), the excess risk of recurrence (HR = 1.65; 1.30–2.10) and mortality (HR = 1.78; 1.12–2.85) as compared to older patients was significant. Young patients with luminal B, triple-negative or HER2+ tumors were at particular disadvantage with respect to cancer recurrence and mortality.

Menopausal Status

Menopausal status may be a prognostic proxy for age as implied in the foregoing discussion. That noted, the time course of breast cancer recurrence varies as a function of menopausal status (20). Among node-positive premenopausal patients, the hazard function for relapse has two peaks, the first reaching its maximum 8 to 10 months postoperatively and the second at 28 to 30 months. In contrast, the hazard function in node-positive postmenopausal patients is significantly prolonged, peaking at 18 to 20 months. Primary tumor size correlates directly with the height of the hazard peaks in both pre- and postmenopausal patients, but has no effect on time to recurrence. In node-negative patients, the hazard function for recurrence increases to 18 to 24 months, decreasing somewhat thereafter but of much reduced amplitude at all time-points as compared to patients with positive nodes.

Race/Ethnicity

Five-year relative OS for African American breast cancer patients from 1988 to 2001 was 78% as compared to 90% for Caucasians (21). Stage distribution is less favorable among African Americans, but this factor alone does not explain the observed differences in outcomes. Treatment response rates are similar for African Americans and Caucasians, but African Americans are more likely to present with high-grade and triple-negative cancers and at a younger age. Moreover, there is an excess incidence of ER– inflammatory breast cancer in young African American patients (22).

In China, 20% of breast cancer patients are younger than 40 years of age as compared to only 6% of Caucasian patients in the United States. Moreover, the nonluminal HER2+ subtype with its earlier age of onset, poorer prognosis, and more advanced stage at presentation accounts for 26% to 31% of cases in China as compared to only 19% to 23% in Caucasian Americans (23).

Clinical Tumor Size

Clinical and radiographic estimates of primary tumor size tend to overstate the true dimensions of primary invasive breast cancers, especially small lesions, because of tumor-associated desmoplasia and *in situ* disease (24,25).

The pathological dimensions of the invasive component are the accepted standard for determining primary tumor stage.

Clinical Stage

Clinical and pathological stage are critically important in treatment selection and outcomes. At present, the relevance of clinical staging relates primarily to locoregionally advanced disease presenting as a large primary breast tumor with or without one or more of the so-called grave signs (necrotic, fungating, and/or ulcerating tumor eroding through the breast skin with or without localized reactive cutaneous inflammation, *peau d'orange,* tumor invasion of the chest wall, and/or bulky nodal disease in axillary, internal mammary, and supraclavicular lymphatic basins). The most feared clinical presentation by far is inflammatory/T4d breast cancer with its sudden onset and rapid progression, often attended by bulky, fixed, or confluent disease in one or more nodal basins. Detectable distant metastases are present in 40% of these patients at the time of diagnosis (22,26). The inflammatory phenotype, historically a harbinger of profoundly aggressive cancer biology and impending mortality, retains its grim prognostic implications even now, at least in relative terms.

Locoregionally advanced breast cancers are not infrequently unresectable or only marginally operable at presentation. These and inflammatory cancers remain the preeminent indications for neoadjuvant systemic therapy (27).

PROGNOSTIC FACTORS—PATHOLOGIC

In an overview of systematic reviews and meta-analyses published from 1999 through 2007 (28), the American Society of Clinical Oncology (ASCO) updated recommendations on breast cancer tumor markers. The data regarding DNA flow cytometric parameters were insufficient to impute any prognostic value to their routine use. Data on markers of tumor proliferation such as Ki-67, cyclin D, cyclin E (whole or fragments), p27, p21, thymidine kinase, topoisomerase IIα, and others were likewise inadequate to establish prognostic significance.

ASCO recommended assaying for HER2 expression in all primary breast cancers to identify those susceptible to anti-HER2 therapy. While HER2 amplification, overexpression, and the presence of circulating HER2 extracellular domain correlated with poor prognosis, the final consensus statement concluded that circulating HER2 extracellular domain was of no prognostic utility (28).

It was acknowledged that the evidence that anthracycline-based chemotherapy provides greater benefit for HER2+ breast cancer was only LOE II (prospective trials with marker utility as a secondary end point), whereas LOE I evidence had shown that anthracycline and nonanthracycline chemotherapy have equivalent activity in these patients. HER2 amplification and/or overexpression in hormone receptor-positive breast cancers was not deemed a contraindication to endocrine therapy in hormone receptor-positive breast cancer (28) despite resistance to endocrine therapy conferred by HER2 positivity, resulting in reduced efficacy (29–31).

Citing a paucity of evidence, ASCO recommended against p53, cathepsin D, bone marrow micrometastases, or circulating tumor cells for prognostication or therapeutic decision making. Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor 1 (PAI-1) were considered prognostically significant in newly diagnosed node-negative breast cancer. Low levels of both markers correlated with low risk, especially in hormone receptor-positive disease treated with endocrine therapy; chemotherapy was known to provide very little benefit in these circumstances. In patients with high levels of uPA and PAI-1, CMF chemotherapy provided a substantial survival benefit over observation alone. Overexpression of both factors is associated with a twofold to eightfold increased risk for breast cancer recurrence and mortality (28).

In contrast, there was general agreement at the 2009 St. Gallen Consensus Conference that uPA and PAI-1 were of no prognostic utility (32) primarily because of the practical difficulties in measuring them (M. Morrow, personal communication).

Primary Tumor Size

A SEER analysis for 1988 to 2001 on 302,763 patients (21) reported 5-year relative survival rates for all stages and ages as a function of primary tumor size. Among those with tumors 0.1 to 0.9 cm, survival was 100%; 91.8% for tumors measuring 1.0 to 1.9 cm; 75.7% for lesions 2.0 to 2.9 cm; 61.3% for tumors 3.0 to 3.9 cm; 54.2% for tumors 4.0 to 4.9 cm; 45.7% for tumors 5.0 to 9.9 cm; and 27.0% for diffuse primary tumors.

Five-year relative survival in the SEER analysis (21) of patients with primary disease confined to the breast parenchyma was 93%, 71.7% when subcutaneous tissues were invaded, 69.2% when the pectoralis fascia was invaded, 62.2% when tumor invaded the chest wall (ribs, muscle or both), 47.3% when extensive skin involvement was present, and 39.9% in patients with inflammatory cancer. Of those with documented distant disease at the time of breast cancer diagnosis, only 18.7% survived 5 years.

Regional Lymph Node Status

Nodal status is the most powerful clinicopathological prognostic variable for locoregional stage breast cancer (33,34). The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 and B-06 randomized trials (35,36) demonstrated that mortality as a function of number of positive lymph nodes behaves as a continuous variable, with steepening of the upward trajectory of mortality appearing at between three and four positive nodes. Ten-year survival in the B-04 trial with 0, 1 to 3, 4 to 9, and 10 or more positive nodes was 67%, 47%, 30%, and 12%, and, in B-06, 75%, 62%, 42%, and 20%, respectively. The differences in survival between these trials were largely attributable to the use of adjuvant chemotherapy in node-positive patients in B-06; patient accrual to B-04 was completed prior to the advent of adjuvant systemic therapy.

The incidence of positive regional nodes varies directly with primary tumor size. In an analysis of 2,233 breast cancer patients (37), positive nodes were present in 11% of patients with tumors of 0.1 to 0.9 cm, 30% with tumors of 1.0 to 1.9 cm, 40% with tumors of 2.0 to 2.9 cm, 50% with tumors of 3.0 to 3.9 cm, and 52% with tumors of 4.0 to 4.9 cm. The relationship between presence of nodal metastases and primary tumor size varies among the intrinsic molecular subtypes, luminal B and HER2+ tumors being more likely to be node-positive (52% and 57%, respectively) than luminal A or basal cancers (43% and 44%). The incidence of four or more positive nodes also varied from 11% for luminal A and 14% for basal cancers to 20% for luminal B and 28% for HER2+ tumors (38).

A logistical regression analysis of the SEER data (21) on incidence of nodal metastases versus primary tumor size is shown in Figure 28-2. Incidence of nodal involvement increased in direct proportion to primary tumor size up

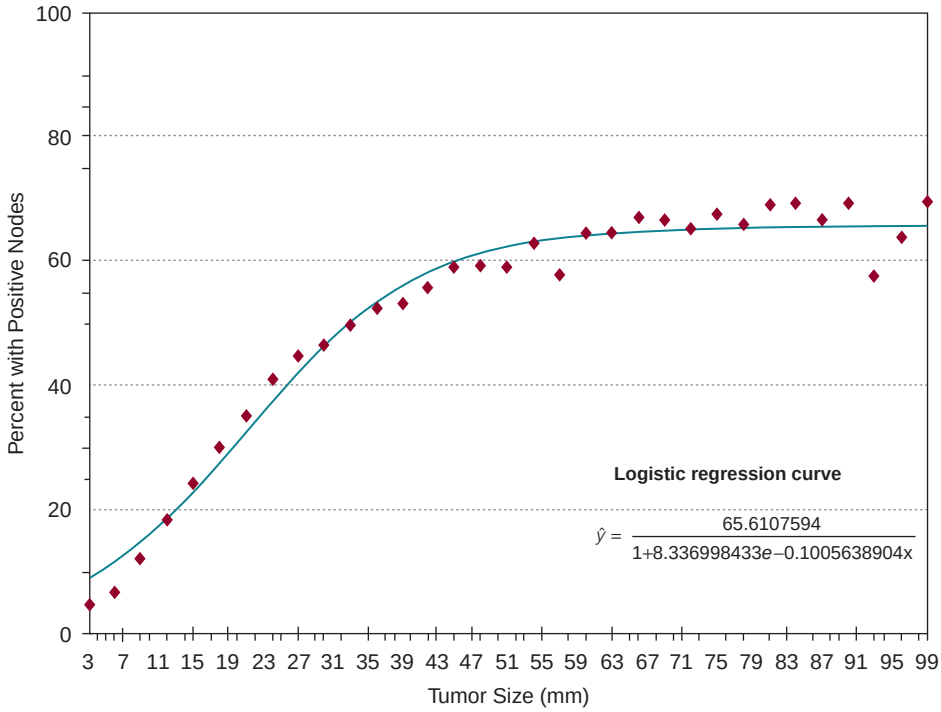

FIGURE 28-2 Presence of positive regional lymph nodes by primary tumor size 12 SEER areas, 1988–2001. (Redrawn from Ries LAG, Young JL, Keel GE, et al., eds. SEER survival monograph: cancer survival among adults: U.S. SEER Program, 1988–2001, patient and tumor characteristics. NIH Pub. No. 08-6215. Bethesda, MD: National Cancer Institute, SEER Program, 2007.)

to 54 mm, reaching a plateau at over 60% thereafter. Five-year relative survival varies inversely as a function of both primary tumor size and number of involved regional lymph nodes (Fig. 28-3).

A "binary-biological" mathematical model of breast cancer and melanoma metastasis reported by Chen et al. (39) incorporated primary tumor size, lymph node status, and other prognostic factors to estimate "cancer lethality" in individual patients. This model was capable of estimating the probability of mortality as a function of all, some, or single independent variables in isolation. In over 375,000 breast cancer patients, positive lymph node status was found to be a strong predictor of breast cancer mortality. Nodal metastasis was associated with intermediate and high tumor grade, ductal histology, African American race, male gender, young age, the inflammatory phenotype, Paget's disease, ER+PR+ and ER–PR– tumors. Nodal metastases were significantly less prevalent among low-grade tumors and cancers of tubular, comedo, medullary, mucinous, cribriform, or papillary histology.

Using a forerunner of the binary-biological mathematical model, an earlier analysis (37) had shown that 15-year Kaplan-Meier death rates were 26% for patients with one positive node, 34%, 37%, and 57% for two, three, and four involved nodes, respectively.

Nodal Micrometastases and Isolated Tumor Cells

The advent of sentinel lymph node biopsy (SLNB) has spawned numerous research initiatives, among them the relationship of prognosis to nodal tumor burden and extent of axillary surgery. Nodal micrometastases (MM - pN1mi), defined as metastatic disease measuring > 0.2 to ≤ 2.0 mm,

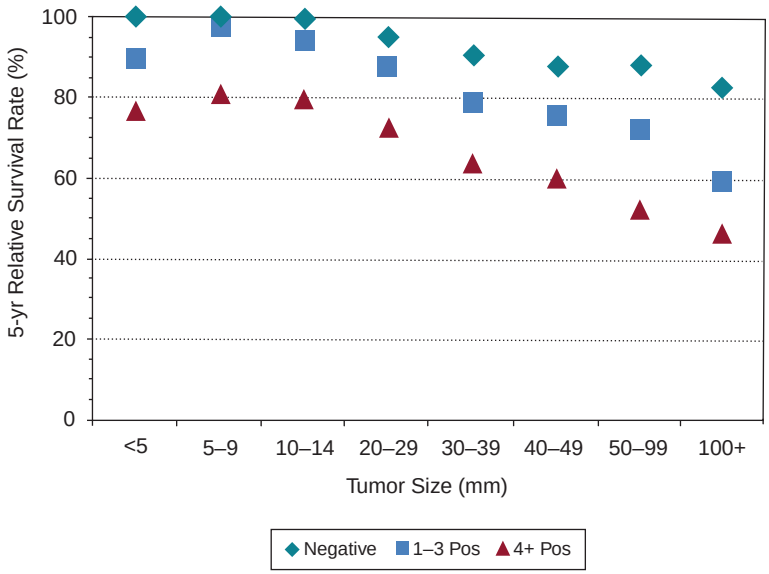

FIGURE 28-3 Five-year relative survival rates by primary tumor size and number of positive lymph nodes: Ages 20+, 12 SEER areas, 1988–2001. (Redrawn from Ries LAG, Young JL, Keel GE, et al., eds. SEER survival monograph: cancer survival among adults: U.S. SEER Program, 1988–2001, patient and tumor characteristics. NIH Pub. No. 08-6215. Bethesda, MD: National Cancer Institute, SEER Program, 2007.)

and isolated tumor cells (ITC - pN0[i+]), defined as single tumor cells or metastatic deposits ≤ 0.2 mm, have been a recent focus of clinical investigation.

Studies of the presence or absence of nodal MM or occult metastases were reported in 297,533 breast cancer patients, 265,638 for whom submitted axillary nodes were evaluated only by single pathological sections, 7,740 in whom retrospective examination of negative nodes for occult nodal metastases by step sectioning and/or immunohistochemistry (IHC) was undertaken, and 4,155 patients in whom intensified workup of sentinel but not nonsentinel nodes was carried out (40). The presence of MM in the first cohort was associated with poor OS (HR for mortality 1.44; 1.29–1.62) while in the two occult metastasis cohorts, the presence of MM portended poor 5-year DFS (HR = 1.55; 1.32–1.82) and OS (HR = 1.45; 1.11–1.88).

The population-based MIRROR study of survival by tumor burden per sentinel lymph node (SLN) compared 856 node-negative patients who did not undergo adjuvant therapy, 856 patients with ITC or MM who also did not receive adjuvant therapy, and 995 patients with ITC or MM who underwent adjuvant therapy (41). At a median follow-up of 5.1 years, adjusted HR for disease events among patients with ITC who did not undergo adjuvant therapy was 1.50 (1.15–1.94) as compared to node-negative patients. Among those with MM, adjusted HR was 1.56 (1.15–2.13). Among patients with ITC or MM who were treated with adjuvant therapy, the adjusted HR for disease events was 0.57 (0.45–0.73) as compared to untreated patients with ITC or MM.

A subsequent analysis (42) of patients completing at least 5 years' follow-up confirmed that among untreated patients, 24.9% had had a disease event as compared to only 16.8% of those receiving adjuvant therapy ($p < .01$). Cost-effectiveness analysis demonstrated that the extrapolated mean cumulative costs per patient beyond 18 years were significantly lower among those receiving adjuvant therapy for sentinel node ITC or MM.

While nodal ITC and MM may be prognostic, whether axillary lymphadenectomy is justified for these remained to be determined. Several LOE I prospective observational and randomized clinical trials of SLNB have reported within the past 2 years. At a median follow-up of 8.4 years, the American College of Surgeons Oncology Group (ACoSOG) Z0010 study (43) of 5,539 patients with T1,T2N0M0 breast cancer reported no differences in locoregional or distant recurrence between the 3,904 patients with negative SLNs and the 1,625 in whom SLN metastases were detected only by IHC. ACoSOG Z0011 (44), a prospective randomized non-inferiority trial of 891 patients with T1-T2 invasive cancer comparing SLNB alone to axillary dissection, demonstrated no significant survival differences between the two treatment arms at a mean follow-up of 6.3 years.

The International Breast Cancer Study Group (IBCSG) 23-01 prospective randomized clinical trial (45) in patients with ≤5 cm breast cancer and nonpalpable nodes recently reported at a median follow-up of 5 years. Patients in whom SLNB revealed one or more MM-involved lymph nodes without extracapsular extension were randomized (1:1 ratio) to observation or axillary dissection. Survival did not differ between the two arms of the study.

The NSABP B-32 prospective randomized trial (46) comparing SLNB alone to SLNB plus axillary dissection reported that occult metastases, defined as tumor found on additional 2.0-mm step-sectioning of negative SLNs, were independently prognostic, but the incremental difference in outcome at 5 years was only 1.2%. A clinically insignificant difference in patient outcomes reached statistical significance solely due to the trial's large sample size (3,887 patients). As compared to no metastases, SLN ITC were associated with an increased HR for mortality, although the associated reduction in OS was only 0.6% at 5 years. ITC were less significant than MM for every outcome evaluated. The concept of degrees of nodal tumor burden was validated and formal lymphadenectomy shown to be unnecessary in the absence of SLN macrometastases.

Most patients in these four prospective trials had indications other than nodal status for adjuvant therapy, and this may have contributed to the absence of survival differences between the surgical treatment arms.

Patani and Mokbel (47) reviewed published studies on the prognostic and biological significance of ITC and MM, highlighting their significant disparities with respect to findings and conclusions. Some studies showed no associations with outcome while others reported that ITC and MM are prognostically adverse and portend an excess risk of distant disease, locoregional recurrence, and up to a 64% likelihood of non-SLN nodal metastases. There is as yet no clear consensus on optimal analytical methods for identifying SLN metastases, particularly cytokeratin IHC and molecular analysis. In considering all available data, it was posited that reliable analytical distinction of ITC from MM in SLNs could make possible a triage of affected patients into node-negative (ITC) and node-positive (MM) treatment paradigms from the standpoint of adjuvant therapy and further axillary intervention.

Extracapsular Extension of Nodal Metastases

Extracapsular extension (ECE) of metastatic tumor in regional nodes is an adverse prognostic factor in breast cancer. Among 263 breast cancer cases in 260 patients with T1 or T2 disease who underwent sentinel node biopsy, 74 had positive sentinel nodes and 70 of these patients underwent completion axillary dissection. Nonsentinel node metastases were found in 29 of these 70 patients. ECE was present in the sentinel nodes of 18 patients and 78% of these had further axillary disease as compared to only 29% of those without ECE ($p = .0003$). ECE was associated with a greater number of positive axillary nodes (7.6 vs. 2.5; $p = .006$) (48).

An analysis of 376 patients with node-positive pT1 and pT2 breast cancer from a prospective database of 1,142 patients reported ECE in 47%. ECE correlated with lymphatic and vascular invasion within the breast parenchyma, an increased risk of regional recurrence (13.4% vs. 6.6%; $p = .37$) and distant metastasis (43% vs. 16.2%; $p < .001$) (49).

At 14 years' median follow-up of 1,475 premenopausal node-positive patients in the IBCSG Trial VI randomized to 3, 6, or 9 courses of CMF, locoregional failure rates among the 933 patients for whom information was retrospectively obtained on the presence or absence of ECE were calculated. ECE correlated strongly with number of positive lymph nodes ($p < .0001$). For patients with and without ECE, local recurrence rates were 14.6% and 11.6% ($p = .05$), axillary recurrences 4.1% and 2.1% ($p = .09$), and supraclavicular failures 9.8% and 5.8% ($p = .004$), respectively. These differences were not significant after adjusting for number of positive nodes and other baseline prognostic factors (50).

Tumor Grade

The most widely used tumor grading schema is the Nottingham method, known in North America as the Elston-Ellis modification of the Scarff-Bloom-Richardson (SBR) breast cancer grading system. Glandular/tubular formation, nuclear pleomorphism, and mitotic count are each scored on a scale of 1 to 3. These are summed to give an aggregate score classifying the tumor as low (3–5), intermediate (6–7), or high (8–9) grade.

In a consecutive series of 2,219 operable breast cancers, Rakha et al. (51) reported that SBR grading was closely associated with patient outcomes, the most marked difference being between grade 1 and grade 3 ($p < .001$ for breast cancer–specific survival and disease-free survival [DFS]). The differences in survival between grades 3 versus 2 and grades 2 versus 1 were also highly significant. SBR grade was an independent prognostic factor relative to tumor size and nodal status and remained significant in multivariate Cox regression, with the exception of DFS for grade 2 versus grade 1 cancers.

The Elston and Ellis modification of the SBR grading system was necessitated by the lack of concordance in tumor grading between pathologists and institutions, and has proven highly salutary (52). Identification and analysis of 97 cell cycle regulation and proliferation genes associated with histological tumor grade demonstrated that a derived "gene expression grade index" was highly associated with histological grades 1 and 3, while the genetic expression grade indices of grade 2 lesions spanned the entire range of values for all grades. Gene expression grade index tended to reclassify grade 2 cancers into two groups, one at high and the other at low risk of recurrence (53).

The SEER analysis (21), using a four-grade schema, reported relative 5-year survival of 100% for grade 1 tumors and 93.2%, 77.6%, and 78.6% for grades 2 to 4, respectively. For stage II, III, and IV patients, histological grade was prognostically significant.

Tumor Histology

Adenocarcinoma of the breast includes a variety of histological subtypes, the commonest being ductal, lobular, mixed ductal and lobular, and "not otherwise specified" (NOS). Five-year relative survival for these histologies from the SEER data (21) was 87.5%, 91.6%, 92.9%, and 62.2%, respectively. The less common indolent histological variants include mucinous (5-year relative survival 98.3%), tubular (100%), adenoid cystic/cribriform (100%), medullary (89.5%), papillary (94.5%), and comedocarcinoma (89.9%). Only 34.2% of patients with inflammatory cancer survived 5 years as compared to 82.6% with Pagetoid cancer, 81.7% with scirrhous adenocarcinoma, and 64.8% of patients with nonadenocarcinomas.

Tumor Stage

Pathological TNM tumor staging is key to prognostication and treatment recommendations. In the SEER analysis (21), the 5-year relative survival for stage 0 and stage I breast cancer was 100%, 86% for stage II, 57% for stage III, and 20% for stage IV (Fig. 28-4).

Lymphovascular Invasion

LVI is an adverse prognostic variable in breast cancer. In a large national cancer registry study of 15,659 patients accrued between 1996 and 2002 (54), LVI was identified in 15%. Median follow-up was 6.4 years for DFS and 7.7 years for OS. Five-year DFS was significantly lower among affected patients at 54.5% (95% CI 52.4–56.6%) as compared to those without LVI (79.5%; 78.7–80.2%). OS was also significantly lower at 66.0% (64.1–67.9%) as compared to 87.3% (86.7–87.8%) among patients without LVI. These differences persisted on multivariate analysis.

However, LVI was associated with adverse outcome only in patients already at high risk of recurrence, and had no adverse effect on patients considered low risk on the basis of other factors. This finding was at odds with the 2007 St. Gallen Consensus (55) which concluded that among patients at low risk for relapse, LVI elevated affected patients into the moderate-risk category.

Lee et al. (56) studied the prognostic influence of LVI in patients with node-negative breast cancer, stratifying them by time period and adjuvant therapy; 990 patients diagnosed in 1974–1988 who received no adjuvant therapy and 1,765 diagnosed in 1988–2000 who did. Median follow-up of the two groups was 13 and 6.8 years, respectively. LVI was identified in 19% of tumors and was associated with larger tumor size, high grade, and young age. On multivariate analysis, OS was independently associated with LVI, tumor grade, and tumor size in both cohorts.

Interobserver variation with respect to LVI in breast cancer can be problematic, and thus five criteria must be satisfied for a diagnosis (57). Historically, retraction artifact due to processing has been cited as a significant cause. Recent research suggests that this entity may not always be due to tissue fixation, but can itself be an indicator of poor prognosis related to tumor–stromal interactions.

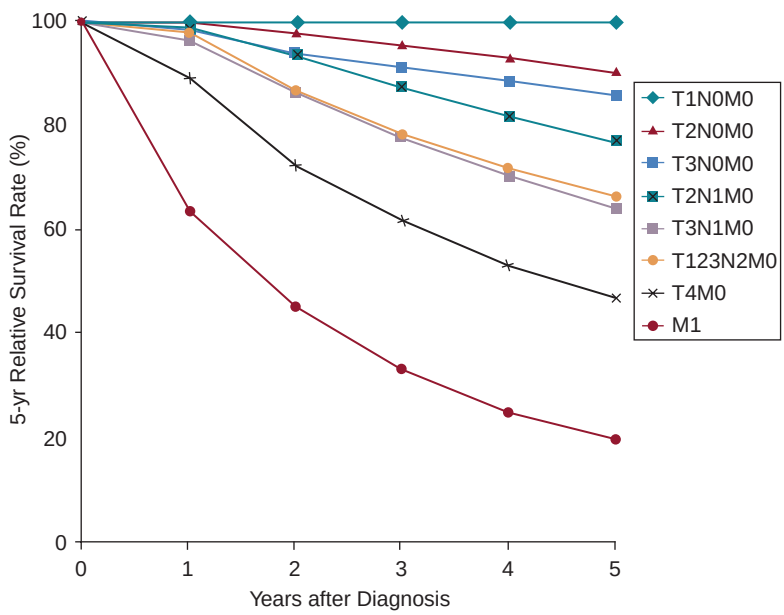

FIGURE 28-4 Five-year relative survival rates by TNM stage. Ages 20+, 12 SEER areas, 1988–2001. (Redrawn from Ries LAG, Young JL, Keel GE, et al., eds. SEER survival monograph: cancer survival among adults: U.S. SEER Program, 1988–2001, patient and tumor characteristics. NIH Pub. No. 08-6215. Bethesda, MD: National Cancer Institute, SEER Program, 2007.)

Hormone Receptor Status

The reader is referred to Chapter 26 for a detailed discussion of the prognostic impact of tumor ER and PR receptor status.

HER2 Amplification or Overexpression

HER2 amplification or overexpression is present in at least 15% to 20% of the annual breast cancer burden and is an independent indicator of poor prognosis (58). HER2 receptor expression augments tumor cell proliferation, mobility, invasiveness, and survival through signal transduction initiated by HER2 homodimerization or heterodimerization with HER1, HER3, and/or HER4, among other mechanisms.

Measures of Tumor Proliferative Activity

Numerous measures of tumor cell proliferation have been studied including thymidine labeling index, flow cytometry and S-phase fraction, thymidine kinase, cyclins D and E and their inhibitors p27 and p21, topoisomerase IIα, p53, bax, bcl-2, and Ki67, among others. Colozza et al. (59) reviewed 135 studies of these tumor proliferative factors in 159,516 breast cancer patients published prior to June 2004.

Methodological shortcomings precluded attribution of prognostic or predictive significance to any of these potential markers. The retrospective status of most of the included studies, disparities in the handling and preservation of archived materials, the small number of patients per study and frequent recourse to subset analysis, confounding heterogeneities within and between patient populations, significant variation in cut-off points and the methods used to measure biomarkers, lack of standardization and quality control methodologies of the various assays used, and the relatively short median follow-up reported in some studies were all contributing factors (59).

Mitotic index (MI), one of the three elements of SBR tumor grading, has been cited as the strongest prognostic discriminant in node-negative breast cancer patients aged less than 71 years in the Multicenter Morphometric Mammary Carcinoma Project, a national database of 3,479 patients (60). Of these, 853 had node-negative, small, and/or low-grade cancers and therefore did not receive systemic adjuvant therapy. In multivariate analysis, MI was the most significant predictor of survival among all variables evaluated, rendering insignificant both pleomorphism and tubular formation, the other two components of the SBR tumor grading paradigm. MI ≥10 identified patients at high risk who should be offered adjuvant therapy. In a subsequent analysis (61), MI was superior to Norwegian Breast Cancer Group guidelines and the online program Adjuvant! in node-negative patients aged less than 55 years. However, in 477 patients analyzed by REMARK criteria who did not receive adjuvant therapy, MI provided no prognostic advantage over standard SBR grade (62).

Ki67 expression in breast cancer has been further investigated for prognostic significance since the analysis of Colozza et al. (59) and the ASCO overview (28). This marker of proliferation has recently been evaluated using the REMARK tool (14) and determined to be an independent prognostic factor for DFS (HR 1.05–1.72) in multivariate analysis of prospective randomized clinical studies. In the neoadjuvant setting, high Ki67 is associated with pathological complete response (pCR) (63).

Luporsi et al. (64) reported a meta-analysis of 71 studies of Ki67, 17 of these prospective. Ten studies of 9,185 patients evaluated this marker for prognostic significance, three studies of 411 patients for prognostic and predictive significance, and four studies of 520 patients for predictive significance. Ki67 was an independent prognostic factor in multivariate analysis of DFS (HR 1.05–1.72) in 7 reports but prognostic for OS only in one trial. The REMARK scores for the included studies ranged from 9 to 18 (median 12), and the LOE for Ki67 as a prognostic factor for DFS was IB as the trials were randomized and slide review was centralized. Only one study with LOE IIB concluded that elevated Ki67 was predictive of chemotherapeutic responsiveness.

Endocrine therapy profoundly inhibits tumor proliferation. Anastrozole suppresses Ki-67 expression at 2 and 12 weeks by 76% and 82%, respectively, as compared to 60% and 62% for tamoxifen and 64% and 61% for combined therapy (63). The IMPACT Trialists Group (65) compared Ki67 expression in tumor biopsy samples procured before and after 2 weeks of presurgical treatment with anastrozole, tamoxifen, or anastrozole plus tamoxifen in 158 patients with ER+ primary disease. On multivariate analysis, high Ki-67 expression after endocrine therapy was significantly associated with reduced recurrence-free survival (RFS), whereas high Ki-67 at baseline was not. Large baseline tumor size and lower ER expression after endocrine treatment also correlated with poorer RFS ($p < .001$ and $p < .04$, respectively).

Response to neoadjuvant chemotherapy and prognosis were analyzed in 552 patients as a function of high versus low tumor Ki-67 expression (66). Ki-67 was an independent predictor of pCR (HR 3.5; 1.4–10.1), 113 of 390 patients (29%) with high Ki-67 attaining pCR status as compared to only 7 of 162 patients (4.3%) with low Ki67. Mean Ki-67 value in patients with pCR was 50.6 as compared to 26.7 in those with less than pCR.

PREDICTIVE FACTORS

In 2007, ASCO recommended that ER and PR always be measured on primary and, when possible, metastatic breast cancer specimens to establish or rule out possible benefit from endocrine therapy. The predictive value of HER2 gene amplification and/or overexpression was affirmed as essential in determining whether trastuzumab and/or newer anti-HER2 agents should be prescribed to individual patients (28).

Hormone Receptor Status

This is discussed in detail in Chapter 26.

HER2 Amplification and/or Overexpression

HER2-positive breast cancer predictably responds to HER2-targeted therapies. These include the monoclonal antibodies trastuzumab and pertuzumab, the dual HER1 and HER2 tyrosine kinase inhibitor lapatinib, and the immunoconjugate trastuzumab-DM1, with other agents in development.

The ASCO overview (28) acknowledged that evidence that anthracycline-based chemotherapy provides greater benefit for HER2+ breast cancer was only LOE II (prospective trials with marker utility as a secondary end point), whereas LOE I evidence had shown that anthracycline and nonanthracycline chemotherapy have equivalent activity in these patients.

In prospective randomized adjuvant and neoadjuvant trials for HER2+ disease, survival was increased and recurrence rates reduced by trastuzumab. At almost 4 years' median follow-up, DFS and OS in patients randomized to trastuzumab plus anthracycline-based chemotherapy were significantly increased as compared to chemotherapy alone ($p < .001$ for both). Mortality in the trastuzumab arm was 39% less than that in the chemotherapy control arm (67).

At 65 months' median follow-up of a three-armed trial of trastuzumab (68), DFS and OS of patients randomized

to docetaxel, carboplatin plus trastuzumab (TCH), anthracycline chemotherapy plus trastuzumab, or anthracycline chemotherapy alone were reported. While there was no difference in survival between the two trastuzumab arms, the anthracycline control arm fared significantly worse. However, cardiotoxicity in the TCH arm was significantly less as compared to anthracycline chemotherapy plus trastuzumab.

Hayes et al. (69) hypothesized that HER2 expression/amplification would predict benefit from high-dose doxorubicin, addition of paclitaxel following adjuvant doxorubicin and cyclophosphamide, or both. In an analysis of 1,500 randomly selected node-positive patients from a cooperative group prospective randomized trial, no interaction was observed between HER+ status and doxorubicin doses above 60 mg/m^2, but HER2 positivity was associated with a significant benefit from paclitaxel (HR = 0.59; p = .01). Paclitaxel provided no benefit for patients with HER– ER+ breast cancers.

In a meta-analysis (70) of 9,117 patients in five prospective randomized trials of adjuvant trasuzumab, the HR for mortality for anti-HER2 treatment was 0.52 (95% CI, 0.44–0.62). Recurrence was significantly lower (HR = 0.53; 95% CI 0.46–0.60) as was the incidence of distant metastasis (6% vs. 10.8%, p < .00001). Another meta-analysis (71) of 515 patients in five randomized neoadjuvant trials of chemotherapy with or without trastuzumab reported an odds ratio for pCR of 1.85 (95% CI, 1.39–2.46) among trastuzumab-treated patients (p < .001).

Pertuzumab and trastuzumab bind to different HER2 epitopes and are complementary in their mechanisms of action. In patients with stage IV breast cancer, pertuzumab plus trastuzumab and docetaxel resulted in improved survival as compared to trastuzumab and docetaxel alone (mortality HR = 0.62; 0.51–0.75, p < .001) (72).

Randomized neoadjuvant trials of the anti-HER2 monoclonal antibodies trastuzumab and pertuzumab and the tyrosine kinase inhibitor lapatinib, singly and in combination, have yielded significant pCR rates when administered with cytotoxic chemotherapy in HER2+ breast cancer. Dual anti-HER2 therapies in the neoadjuvant setting demonstrate additive activity and perhaps synergy as evidenced by the superior pCR rates in patients so treated (71,73).

The loss of HER2 expression in residual disease following neoadjuvant chemotherapy and trastuzumab is associated with a higher rate of relapse, as is high Ki-67 expression in residual tumor following neoadjuvant therapy (74).

Predictive Pathological Factors: Future Possibilities

Predictive biomarkers for the basal-like intrinsic subtype, triple-negative, and claudin-low tumors are lacking. Chemotherapy is the only adjuvant option currently available. Alkylating agents and the platinum salts in particular have shown efficacy through DNA-disrupting activity and interference with tumor cell DNA repair mechanisms (75–77).

Poly(ADP-ribose) polymerase (PARP) identifies DNA damage and promotes repair of single-strand breaks through base excision pathways (77). This enzyme is expressed in all intrinsic breast cancer subtypes. *In vitro,* PARP inhibition is lethal to *BRCA*-deficient cancer (78). The PARP inhibitors iniparib and olaparib have yielded encouraging preliminary results in *BRCA*-associated and triple-negative breast cancer (77).

Despite their low expression of proliferative genes, claudin-low cancers have a particularly guarded prognosis. They overexpress genes related to mesenchymal differentiation and the epithelial–mesenchymal interface, and can exhibit a cancer stem cell phenotype. They present clinically as high-grade infiltrating ductal cancers with metaplastic or medullary features, and 80% are triple negative. They respond poorly to neoadjuvant chemotherapy. Of all the basaloid intrinsic subtypes, these tumors pose an especially difficult challenge. Clinically useful biomarkers are urgently needed for these and other triple-negative cancers within the basal-like and other intrinsic subtypes (75).

Tumor ER, HER2, and Ki-67 expression frequently change in the course of neoadjuvant therapy, with important prognostic and predictive implications. Core needle biopsy of residual tumor with measurement of ER after neoadjuvant endocrine therapy not infrequently reveals reduced ER expression, predicting abrogation or complete loss of susceptibility to endocrine agents. So too, HER2+ breast cancers treated with neoadjuvant trastuzumab and chemotherapy may cease to express HER2, a finding that correlates with significantly increased risk of relapse of disease (74).

Reduced tumor cell Ki-67 expression after 2 to 12 weeks of endocrine therapy correlates with a good clinical outcome while high Ki-67 portends the opposite, as already noted (61,63). Elevated pretreatment Ki-67 expression predicts a high probability of attaining pCR with neoadjuvant chemotherapy (64,66).

In the POETIC trial (63), postmenopausal ER+ patients are randomized (2:1) to 2 weeks of neoadjuvant aromatase inhibition or no presurgical therapy. Tumor Ki-67 expression is assayed 2 weeks before and again 2 weeks following the presurgical intervention. The potential utility of Ki-67 expression before and after endocrine therapy in predicting RFS is a secondary aim. Serial core biopsies of residual tumor for assays of tumor biomarkers during or following adjuvant or neoadjuvant systemic therapy may prove salutary for prognostication and determination of optimal systemic therapy for the individual patient and her tumor.

MANAGEMENT SUMMARY

- Prognostic and predictive factors must provide independent and significant value, validated by clinical testing. Their identification and measurement must be feasible, reproducible and widely available, and the results interpretable and therapeutically useful.
- Prognostic factors inform on the biological potential and probable clinical course of a breast cancer irrespective of treatment.
- Predictive factors provide information on the responsiveness of a breast cancer to specific therapies.
- Clinical prognostic factors currently include young age (less than 35 to 40 years), race/ethnicity, clinical primary tumor size and nodal status, clinical staging, and clinical response to neoadjuvant systemic therapy.
- Pathological prognostic factors currently include primary tumor size (invasive component only), direct extension of primary tumor beyond the breast parenchyma, regional nodal status by degree of metastasis and number of nodes involved, tumor grade, tumor histology, pathological TNM stage, lymphovascular invasion, extranodal extension, tumor hormone receptor status, tumor HER2 amplification/overexpression, tumor Ki-67 expression, and pathological response to neoadjuvant systemic therapy.

- Predictive factors currently include tumor hormone receptor status and HER2 expression.
- Tumor biomarkers are lacking for basaloid, triple-negative and claudin-low breast cancers. Alkylating chemotherapy agents, platinum-based regimens, and PARP inhibitors are under investigation for efficacy related to their tumor DNA-disrupting mechanisms of action.
- ER, HER2, and Ki-67 expression by tumor can change quantitatively over the course of treatment, with consequences both bad and good. Investigation of interval core biopsy of residual tumor for serial measurements of biomarkers in the course of neoadjuvant systemic therapy is currently in progress.

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CHAPTER 29

Genomics, Prognosis, and Therapeutic Interventions

Lisa A. Carey, Maggie Chon U Cheang, and Charles M. Perou

CHAPTER CONTENTS

CURRENT OVERVIEW

The rapid advancement of high-information content technologies has resulted in the completion of numerous molecular profiling studies of breast cancers. Global gene expression profiling, massively parallel sequencing (MPS), array-comparative genomic hybridization (aCGH), and reverse phase protein arrays (RPPA) have allowed scientists to profile RNA, DNA, and proteins in hundreds of human breast tumor tissues in a speedy fashion. To fully decipher the mountains of data generated from these 'omics' approaches, and to translate the findings into the clinical setting is challenging, but, undoubtedly, is also one of the highest research priorities for the next few years. In this chapter, we will review how genomics have informed our understanding of the heterogeneity of breast cancer and how it is currently being used for prognostication and therapeutic decision-making. The promise of gene expression patterns, when possibly coupled with somatic mutational profiles, is the near future when we will be able to use the detailed tumor-specific, and patient-specific, information as a means to personalize therapy for breast cancer patients.

Breast cancer is a known heterogeneous disease comprised of a growing number of recognized biologic subtypes. Clinicians and researchers have noted the variations in risk factors, response to therapy, and clinical behavior according to hormone receptor status (i.e., Estrogen Receptors [ER] and Progesterone Receptors [PR]) for several decades. More recent data has also implicated HER-positive breast cancers as possessing unique characteristics, such as responsiveness to anthracyclines (1). Traditional single marker approaches to biomarker identification is limited by the fact that seldom is one gene/protein responsible for the entire action of a cellular pathway. Even more importantly, single marker studies do not address the important relationships among and within different pathways, which are increasingly becoming needed to predict tumor behavior and response to therapy.

As mentioned earlier, MPS is a new and powerful tool for the study of human cancers. The first commercially available MPS platform was the 454 technology by Roche Applied Sciences (2). As of today, other platforms available in the market include the HiSeq and MiSeq Systems by Illumina, Ion Torrent PGM and Proton by Life Technologies, and PacBio RS by Pacific Biosciences. Each technology uses a proprietary approach to sequence molecules of DNA; however, all result in the generation of tens of thousands, to even tens of millions, of sequence 'reads,' which are then used to reconstruct the genomic DNA sequence (or mRNA sequence) of a gene or genome. Although the clinical integration of targeted sequencing assays may still be a few years away, in 2012, eight published landmark studies all applied MPS and/or other DNA-based 'omic' technologies to create a comprehensive catalog of somatic mutational events that are driving breast cancer pathogenesis (3–10). This new MPS data, and the older gene expression array data, provide the genetic framework for personalized medicine as follows.

GENE ARRAYS

DNA microarrays have been used as a means to better understand tumor biology and to predict outcomes and response to therapy. Gene expression microarrays measure the level

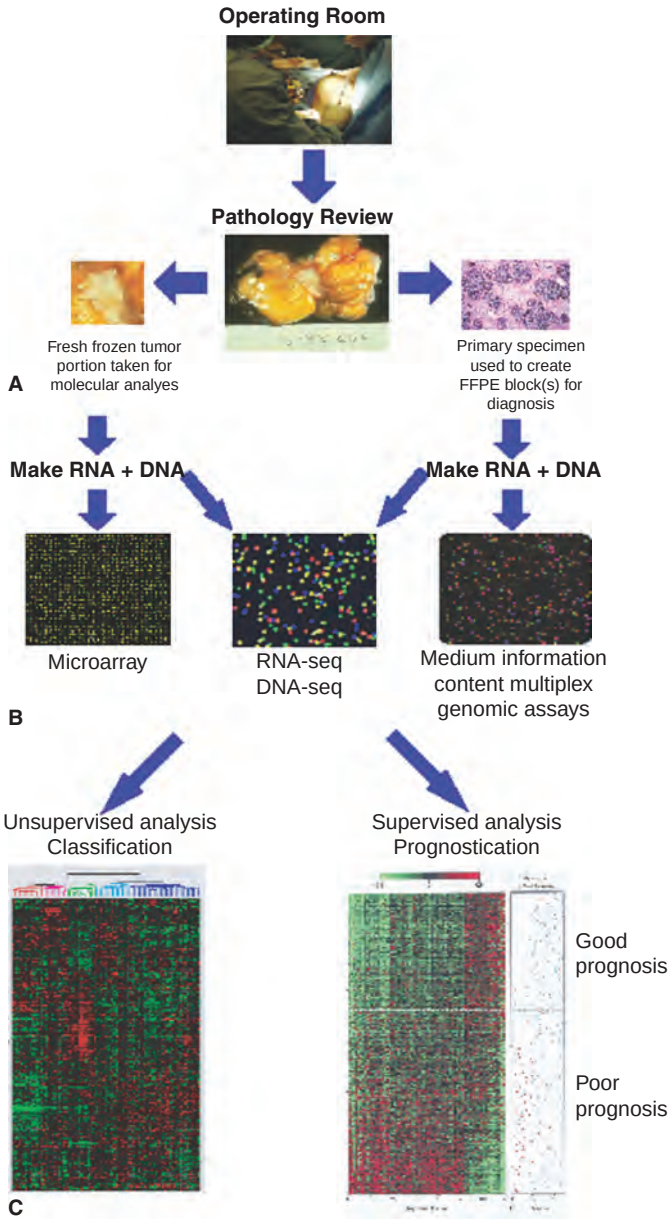

FIGURE 29-1 Overview of gene expression analysis of human tumors. **(A)** Tumors are collected in the operating room and often split into multiple aliquots. **(B)** Nucleic acids (i.e., RNA and DNA) are isolated and can be assayed on a variety of technologies. **(C)** Unsupervised and supervised analyses are performed to identify tumor subtypes and/or to develop predictors of outcomes or response to therapy.

of expression of a particular gene by quantitatively determining the level of mRNA transcripts, which can be initially compared to a reference sample (as in the case of two-color arrays like those produced by Agilent), or directly compared to other tumors or normal tissues (as in the case of one-color arrays like those produced by Affymetrix). The arrays themselves currently include essentially all human genes that are encompassed in thousands to millions of features/probes that are either oligonucleotides, or PCR amplified cDNA inserts. These sequences represent known, unknown but validated, and hypothetical genes, and all approximately 37,000 genes in the human genome can be included (~25,000 protein coding genes, ~12,000 non-coding RNAs). A tumor is processed for RNA, which is used to generate either complementary DNA or RNA, labeled with a fluorescent probe. These fluorescent probes are then either directly applied to a gene array alone (one-color arrays), or combined with a second fluorescently labeled reference sample and then both are applied to an array (two-color array, in which, by convention, the color 'red' is used for the sample of interest and the color 'green' for the common reference sample). The remainder of the assay is basically a Southern blot with nucleic acid hybridization reactions occurring and binding, and with the intensity(s) of the nucleic acids that hybridize to the individual gene probes reflecting the relative amounts of tumor mRNA. In the case of a two-color microarray the 'green' signal predominance reflects low expression and 'red' predominance reflects high expression of that gene in the tumor relative to the reference (Fig. 29-1). Thus, in a two-color array it is not the value of the tumor versus the reference that is of greatest interest, but the ratio of tumor/reference for each gene that is used as a quantitative measure of that gene. This value is then used to compare tumor to tumor, and tumor to normal; in this way, once a two-color microarray gives a tumor/reference value, it is used nearly identically to the one-color microarray absolute intensity values, and thus, once the user gets past these initial different data processing steps, all downstream analysis steps are similar.

MOLECULAR PROFILING OF BREAST CANCERS BY GENE EXPRESSION ARRAYS

Most breast cancer molecular profiling studies have focused upon gene/mRNA expression. Multiple approaches to analyzing gene expression microarrays exist; however, it is self-evident that the answer one gets from genomic analysis depends upon the question one asks. For example, *unsupervised* analyses (which use no external guide) can identify whether there are molecularly identifiable tumor subtypes, also called "class discovery," while *supervised* analyses (analyzed with a particular clinical endpoint in mind) can identify if there are genes correlated with relapsed patients versus those that did not relapse (prognostic profiles), or related to patients who responded to a particular therapy versus those that did not (predictive profiles), which are also called "class comparisons" (11,12). It is tempting to assume that the individual genes that are identified using these methods may themselves be causal in creating the subtype, or the clinical characteristic, and sometimes they are; however, in truth, the identified genes themselves may be mere proxies for genetic events or pathway activation and may not themselves be the cause. A third category of analysis, called "class prediction," first uses a prespecified gene list (typically coming from a supervised analysis) and a given sample set (and classification rule) that is then used to assign a new individual tumor to a particular category, such as a genomic-based class; all genomic tests offered in the clinic should have reached the class prediction stage.

The molecular profiling of breast cancer has provided important information for three major questions: (1) Are there subtypes of breast cancer based on biological differences? (2) Are there gene expression profiles that can distinguish poor from good prognosis patients, thus allowing us to make better-informed decisions regarding adjuvant therapy? (3) Are there gene expression profiles that can predict which tumor will respond to a specific therapy? These questions, and others, will be addressed in the following sections.

BREAST CANCER INTRINSIC SUBTYPES

In 2000, Perou and colleagues used a semi-supervised approach to identify naturally occurring breast cancer subtypes in a population of 40 patients with locally advanced disease treated with neoadjuvant chemotherapy (13). They identified 496 genes termed the "intrinsic gene set" that showed little variance within repeated tumor sample, but high variance across different tumors, and then used this gene set for potential subtype discovery. Among these breast cancers, they found that the patterns of expression of these genes segregated the tumors into four subtypes, and in Sorlie et al. (2001), they identified a fifth possible subtype (14). The five 'intrinsic' subtypes are so-called because the gene list that defines them reflects intrinsic properties of breast cancers rather than being contributed by other cell types or augmented by drugs. These subtypes have been consistently identified in independent datasets using multiple different technologies (15–21), are conserved across ethnic groups, and are present in preneoplasia (21,22). Reassuringly, the intrinsic subtypes are segregated by expression of hormone receptors and the genes they regulate (and actually include ER, PR, and HER2), supporting earlier epidemiologic and biomarker studies suggesting that ER positive and ER negative breast cancer are different. At least two hormone receptor positive subtypes were identified and are called "Luminal A" and "Luminal B." Conversely, there are several subtypes characterized by low expression of hormone receptors, one of which is called the "HER2-enriched" subtype (HER2-E) and another called the "Basal-like" subtype (Fig. 29-2A). The fifth subtype, the normal-like, is less clearly a subtype rather than a likely technical artifact possibly caused by too much normal contaminating tissue. A new possible subtype, named Claudin-low, has been recently identified, which is characterized by low to absent expression of cell adhesion genes including Claudin 3, 4, 7, and E-cadherin (23). Although the intrinsic subtypes were identified without any knowledge of outcomes, these subtypes have strong prognostic implications (Fig. 29-2B); in particular, patients with Basal-like, Claudin-low, HER2-E, or Luminal B tumors demonstrate a significantly worse outcome compared to patients with Luminal A tumors in datasets from patients treated with no systemic adjuvant therapy, and in patient sets treated more heterogeneously including adjuvant and neoadjuvant chemotherapy (15–19,24,25).

A critical aspect of biomarker biology is validation and the intrinsic subtypes have been validated through multiple common findings including similar distributions on many independent datasets, and similar overall risks/prognoses as well (14,17,19,26). Because the clustering methodology for the initial identification of the intrinsic subtypes is suboptimal for everyday clinical classifications, the development

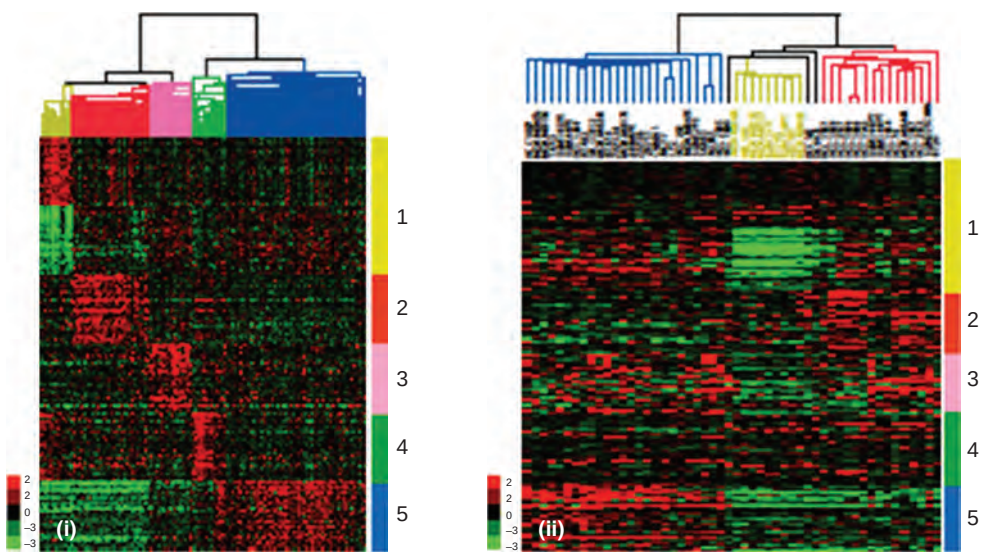

FIGURE 29-2A (A) Gene clusters that characterize each primary human tumor subtype are shown in the human **(i)** and cell line **(ii)** gene expression data sets. In both data sets, array trees have been derived by unsupervised hierarchical clustering using the 1,906 intrinsic genes as described in Parker et al. (29). **(i)** The top 50 upregulated genes associated with each molecular subtype, including the top 50 downregulated genes in Claudin-low tumors, are shown in the UNC337 database that included 320 breast carcinomas and 17 normal tissues. Top genes were selected after performing a two-class Significant Analysis of Microarray (SAM) (false discovery rate = 0%) between each molecular subtype versus others. Luminal A and B subtypes were combined into the luminal subtype. In the tree, the yellow node denotes the Claudin-low tumors. **(ii)** Gene clusters characteristic of each tumor molecular sub-type are shown in 52 breast cancer cell lines. Missing genes have been omitted. In the tree, the yellow node denotes the most highly correlated cell lines that best resemble the Claudin-low subtype. 1 (yellow), Claudin-low gene cluster of upregulated and downregulated genes; 2 (red), basal-like gene cluster; 3 (pink), HER2-enriched gene cluster; 4 (green), normal breast-like gene cluster; 5 (blue), luminal gene cluster. (Reproduced with permission from Prat A, Parker JS, Karginova O, et al. Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer. *Breast Cancer Research* 2010;12:R68.)

(i)

	Claudin-low			Basal-like			HER2-enriched			Luminal B			Luminal A			Normal-like		
	UNC	NKI	MDACC	UNC	NKI	MDACC	UNC	NKI	MDACC	UNC	NKI	MDACC	UNC	NKI	MDACC	UNC	NKI	MDACC
Num.patients	37	21	18	73	42	15	39	49	28	62	69	27	99	84	37	10	30	8
Prevalence	12%	7%	14%	23%	14%	11%	12%	17%	21%	19%	23%	20%	31%	28%	28%	3%	10%	6%
ER+	12%	33%	22%	11%	19%	0%	36%	59%	29%	91%	100%	96%	91%	100%	97%	44%	93%	100%
PR+	23%	–	22%	6%	–	13%	30%	–	25%	53%	–	41%	74%	–	70%	22%	–	63%
HER2+	22%	–	6%	9%	–	13%	66%	–	71%	24%	–	15%	8%	–	11%	67%	–	25%
HER2-/ER-	70%	–	72%	82%	–	87%	25%	–	18%	8%	–	4%	6%	–	3%	13%	–	0%
HER2-/ER-/PR-	71%	–	61%	80%	–	73%	22%	–	14%	9%	–	4%	4%	–	3%	0%	–	0%
Node-	58%	48%	28%	63%	60%	20%	26%	47%	21%	44%	42%	33%	51%	58%	41%	33%	50%	25%
Grade3	77%	38%	61%	88%	86%	93%	55%	61%	89%	62%	41%	46%	30%	13%	27%	63%	20%	50%
Tumor size > 2 cm	74%	38%	78%	77%	62%	80%	93%	57%	79%	85%	52%	69%	66%	36%	91%	89%	40%	88%
pCR	–	–	39%	–	–	73%	–	–	39%	–	–	19%	–	–	0%	–	–	0%

(ii)

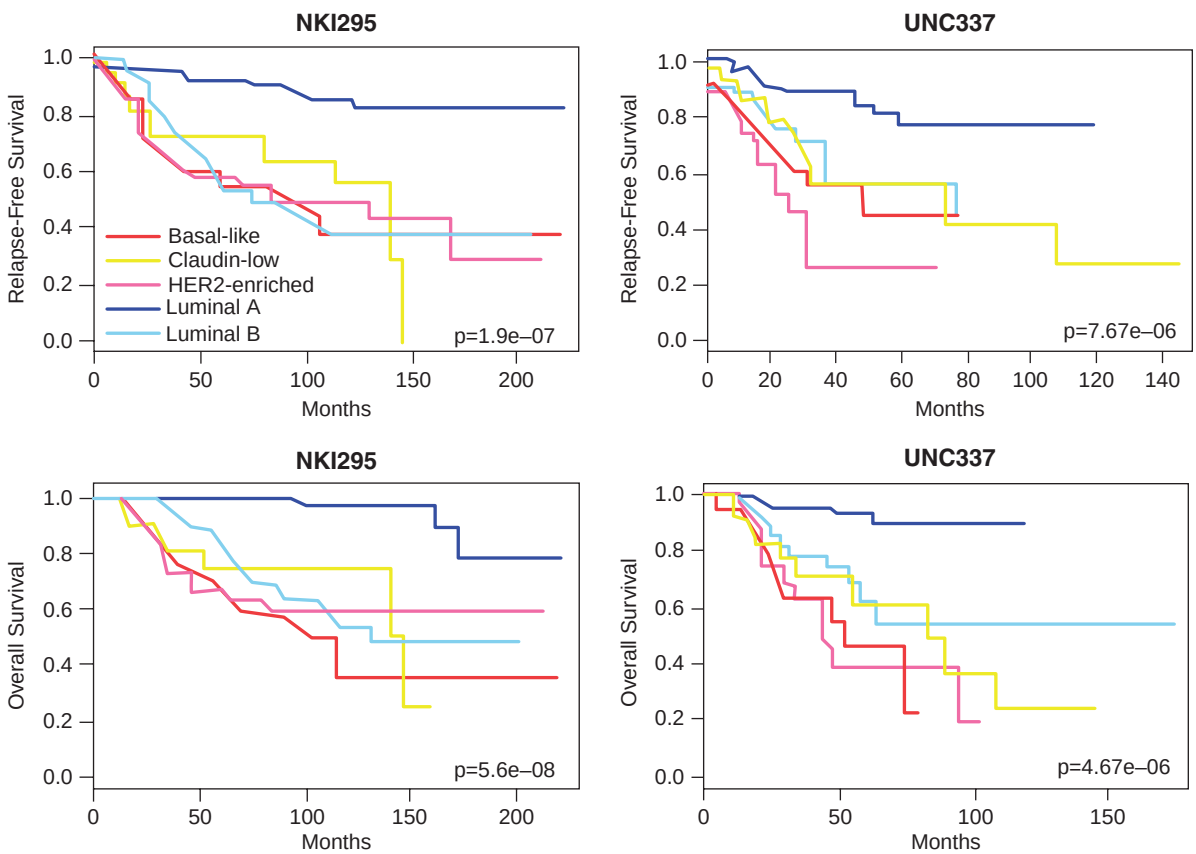

FIGURE 29-2B Clinical and pathological characteristics and prognosis of all intrinsic subtypes, including Claudin-low tumors, across three independent breast cancer data sets. **(i)** Percentages of the different clinical-pathological characteristics in the UNC337 data set and two publicly available data sets (NKI295 and MDACC133 [117]). ER/PR/HER2 scores of the UNC337 database were based on clinically validated methods. **(ii)** Survival data of the different molecular subtypes are shown for the UNC337 database and NKI295 (26,87). Normal breast-like samples have been removed from this analysis. The UNC337 set represents a heterogeneously treated group of patients treated in accord with the biomarker status, whereas NKI295 is predominantly a local therapy only cohort. (Reproduced with permission from Prat A, Parker JS, Karginova O, et al. Phenotypic and molecular characterization of the claudin-low intrinsic subtype of breast cancer. *Breast Cancer Research* 2010;12:R68.)

of a robust subtyping method for individual patient samples has been an area of active research. One of the promising approaches for reproducible subtype classifications is based upon identifying a subtypes mean expression profile, called a centroid (17,18,27). Hu and colleagues developed the Single Sample Predictor (SSP) tool to serve as a first generation, unchanging classifier for individual patient samples; the SSP compares the gene expression profile of an unknown sample to a prototypical profile of each intrinsic subtype and classifies the unknown sample according to the profile it most closely matches. Thus, one sample or hundreds of samples can be objectively classified in a reproducible fashion.

Fresh frozen (FF) tumor samples are usually preferred for microarray experiments, therefore limiting the practicability of these approaches for correlative sciences on clinical trials when often only formalin-fixed paraffin embedded (FFPE) tissues are available. However, Mullins and colleagues demonstrated that there was 94% concordance (33 of 35 matched FF-FFPE pairs) when comparing the subtype assignments by centroid-based algorithm from FF tissue by microarray versus FFPE tissue assayed by real-time quantitative reverse transcription-PCR (qRT-PCR) (28). In 2009, Parker and colleagues developed an improved, open-source intrinsic subtype classifier based on a minimal list of 50 genes, commonly known as the PAM50 (29). In this study, 122 matched frozen-FFPE tumor pairs were subjected to both microarray and qRT-PCR analysis, and a centroid-based predictor was developed that used 50 genes, and which could use either FF RNA (microarray) or FFPE RNA (qRT-PCR). This 50-gene subtype predictor provided significant prognostic value independent of the standard clinical parameters in a test set of 761 patients receiving no systemic therapy, and significantly predicted the pathologic complete response (pCR) in a test of 133 patients treated with neoadjuvant taxane and anthracycline regimens (29).

In the same study, the authors also developed several risk models based upon a Cox Modeling approach, which uses the genomic-determined subtype data and a standard clinical variable (tumor size). A Risk of Relapse (ROR) score could be assigned to each test case (that is, a patient sample) using a Cox model based upon a tumors "distance" to the subtype centroids alone (ROR-S), or using subtype correlation along with tumor size (ROR-T) (29). The most current standard for molecular intrinsic subtyping is the PAM50 50-gene test, which includes the above subtypes except the Claudin-low, and is undergoing extensive clinical validation (30–34).

Other approaches to defining the intrinsic subtypes have been attempted using non-microarray-based methods, most often using immunohistochemistry (IHC) (35,36). However, the accuracy using an IHC-based approach is not as great as the multi-gene expression assays, mostly because IHC assessments can be subjective, and suffer from inter-observer and inter-laboratory variations. Despite the limitations of IHC, performing tumor subtyping via IHC is still valuable and has been adopted as a means of classification by the St. Gallen's consensus conference (37); specifically, the indication is that Luminal A patients as defined by this IHC-based definition (i.e., ER+ and/or PR+, HER2-normal, Ki-67 less than 14%), may not be recommended to receive adjuvant chemotherapy given their overall general good prognosis.

Luminal Intrinsic Subtypes

The most common subtypes of breast cancer are the Luminal subtypes, so-called because they have a gene expression pattern reminiscent of the luminal epithelial component of the normal breast (13). These tumors are characterized by expression of the estrogen receptor (ER), progesterone receptor (PR), and genes associated with ER activation such as LIV1, TFF1, and Cyclin D1, as well as expression of luminal cytokeratins 8 and 18 (13,20,38). Within the luminal tumors family there are at least two subtypes, Luminal A and Luminal B, and there are many relevant differences between these two groups. For example, Luminal A tumors generally have high expression of GATA3, ER-regulated genes including PR, low expression HER2 and of the HER2 amplicon expression cluster, and low expression of proliferation-associated genes including Ki-67 (19,25). Conversely, Luminal B tumors tend to be highly proliferative, are sometimes HER2+, and show lower expression of PR (36,39) and of other ER-regulated genes (36,39).

When compared to other breast cancer subtypes, Luminal tumors have a low frequency (fewer than 20%) of TP53 mutations (20,25), with a rate of 12% in Luminal A and a higher frequency of 29% in Luminal B tumors (4), with the presence of mutant TP53 being strongly associated with endocrine therapy resistance (6). Interestingly, ~30% of Luminal B tumors also have amplification of the TP53 antagonist MDM2 (4), thus suggesting that inhibitors for MDM2-p53 interaction might be a potential treatment approach for a subset of the aggressive Luminal B tumors. In addition, The Cancer Genome Atlas (TCGA) data also reported that phosphatidylinositol-3-kinase (PIK3CA) mutations are the most common Significantly Mutated Gene (SMG) in Luminal breast cancers (~40%), hence another potential therapeutic target. In addition, the site of PIK3CA mutation may be subtype-specific where, for example, almost all the "hotspot" E545K mutations occurred in Luminal A subtype (25/27), whereas the other common hotspot (i.e., H1047R) occurred in all of the subtypes (4). Whether adjuvant studies focusing on PIK3CA mutations should stratify by mutation type and intrinsic subtype is debatable, but should be kept in mind as the high correlation between subtype and mutation type is likely an important biological feature of these Luminal A cancers.

In population-based studies that classified tumors using IHC, Luminal A breast cancer is the most common, representing approximately 40% to 50% of tumors while Luminal B comprises approximately 10% to 15% (16,35,36,40,41). Expression array-based profiling studies suggest that Luminal A comprises approximately 30% to 40% and Luminal B approximately 20% of breast cancers (17,42), with Luminal A breast cancers consistently showing a better prognosis than Luminal B (19,20,25,43). Although life history risk factors for all of the subtypes remain complex, it is increasingly clear that most traditional risk factors are primarily risk factors for Luminal breast cancers (44). In addition, the population-based studies also show that premenopausal women, and African-American (AA) women, tend to develop fewer of the good-prognosis Luminal tumors and more of the poor-prognosis Basal-like tumors (described further later), which may contribute to the worse mortality outcomes experienced by groups (i.e., young women, and/or AA women) (16,41). While clinical gene expression-based assays to identify Luminal A and B are not yet formally available, the OncotypeDx Recurrence Score™ (RS) assay includes many genes (HER2, GRB7, ER, SCUBE2, Bcl2, Ki-67, Survivin, MYBL2, and Cyclin B1) that are also used to define Luminal A vs. Luminal B tumors. To more directly compare intrinsic subtyping to the Recurrence Score, Fan et al. ran a research version of both assays on a single data set of patients and showed that 50% of 123 Luminal A tumors had low RS (associated with good outcome) whereas only 2% of Luminal B tumors had low RS (with almost all Luminal B being called RS high) (42) (Table 29-1). On the other hand, Kelly et al. compared the risk assignments between OncotypeDx RS and the research version of intrinsic subtypes by PAM50 qPCR

TABLE 29-1

Prognostic Profile by Intrinsic Subtype

		Recurrence Score		*70 Gene Profile*		*Wound Response*	
Intrinsic Subtype	*No. of Patients*	*Classification*	*No. of Patients*	*Classification*	*No. of Patients*	*Classification*	*No. of Patients*
Basal-like	53	Low	0 (0%)	Good	0 (0%)	Quiescent	3 (6%)
		Intermediate	0 (0%)				
		High	53 (100%)	Poor	53 (100%)	Activated	50 (94%)
Luminal A	123	Low	62 (50%)	Good	87 (71%)	Quiescent	45 (37%)
		Intermediate	25 (20%)				
		High	36 (29%)	Poor	36 (29%)	Activated	78 (63%)
Luminal B	55	Low	1 (2%)	Good	9 (16%)	Quiescent	4 (7%)
		Intermediate	4 (7%)				
		High	50 (91%)	Poor	46 (84%)	Activated	51 (93%)
HER2+/ER-	35	Low	0 (0%)	Good	3 (9%)	Quiescent	0 (0%)
		Intermediate	0 (0%)				
		High	35 (100%)	Poor	32 (91%)	Activated	35 (100%)
Normal-like	29	Low	7 (24%)	Good	16 (55%)	Quiescent	15 (52%)
		Intermediate	4 (14%)				
		High	18 (62%)	Poor	13 (45%)	Activated	14 (48%)

Adapted from Fan C, Oh DS, Wessels L, et al. Concordance among gene-expression-based predictors for breast cancer. *N Engl J Med* 2006;355:560–569.

classifier on 151 ER positive stage I–II tumors (45). Seventy percent of Luminal As had low RS and 90% of the high RS tumors were Luminal B. These concordant findings from two different genomic assays validate the genomics approach in general, and highlight the biomarker powers of multi-gene expression assays.

HER2-Enriched Subtype

The hormone receptor-negative subtypes are comprised of the HER2-Enriched (HER2-E) and Basal-like subtypes, although it should be noted that not all HER2-E, and not all Basal-like tumors, are ER/PR negative. The HER2-E subtype has elevated expression of HER2 and many other genes that reside near HER2 in the genome including GRB7 (see section on Recurrence Score) because of HER2 region genomic DNA amplification. These tumors also show low expression of the luminal, hormone receptor-related gene cluster, and low expression of the Basal-like cluster. However, it is imperative to note that many, but not all, clinically defined HER2-positive breast cancers fall into the HER2-enriched category; for example, ~55% of the clinically defined HER2-positive breast cancers (30,46) were ER positive tumors that were classified as luminal subtypes, thus, there exists at least two types of clinically HER2-amplified tumors (i.e., HER2-E and Luminal/HER2+).

Another important feature of tumors in the HER2-Enriched subtype is high expression of the proliferation cluster and, befitting this expression pattern, 75% are high grade tumors and over 70% have p53 mutations (4). This subtype is uncommon, comprising only 5% to 10% of all breast cancers in population-based studies (16). In the era before HER2-targeted therapy, the HER2+/ER– subtype carried a poor prognosis (19,20,25,43,47). Given that there is no apparent interaction between the benefit of HER2-targeted therapy such as trastuzumab and hormone receptor status, it is reasonable to presume that the HER2-E subtype has benefited from the HER2-targeting revolution to the same degree as a HER2-positive Luminal breast cancer (48). The risk factor profile for the HER2-Enriched subtype mirrors the other Luminal tumor subtypes (49), and there is no apparent interaction with race or age (16,41). Aside from HER2 amplification and TP53 mutation, other frequent somatic mutation alterations include PIK3CA (39%) and another PI3K-pathway component (PIK3R1), but with a much lower frequency of 4% (4).

In the clinic, it is known that approximately 50% of patients with clinically HER2+ tumors respond to HER2-targeted therapies like trastuzumab. The TCGA data may provide a rationale for this as one subgroup of clinical HER2+ disease showed high levels of epidermal growth factor receptor (EGFR) and HER2 protein phosphorylation, and this subgroup was largely coincident with the HER2-Enriched subtype (4), whereas the other clinical HER2+ tumors showed the luminal phenotype and lower levels of phosphorylated EGFR and HER2. Whether the HER2-E subtype could be a biomarker for trastuzumab and/or lapatinib sensitivity, and/or HER2 and EGFR protein phosphorylation, could serve as predictive biomarkers, is yet to be determined.

Basal-Like Subtype

The Basal-like subtype is characterized by low expression of the hormone receptors and luminal subtype-related genes, and low expression of HER2 (and lack of gene amplification), thus, most of these tumors are of the so-called "triple negative" classification; however, not all Triple Negative Breast Cancers (TNBC) are Basal-like, and not all Basal-like cancers are TNBC (50) (Fig. 29-3). Other expression features of Basal-like cancers include high expression of the proliferation signature, and high expression of a unique cluster of genes called the basal cluster. The basal gene cluster includes typical basal epithelial cytokeratins (CK) such as CK5, 6, 14, and 17, the epidermal growth factor receptor, c-Kit, Vimentin, P-Cadherin, and αB-crystallin. Massive parallel sequencing

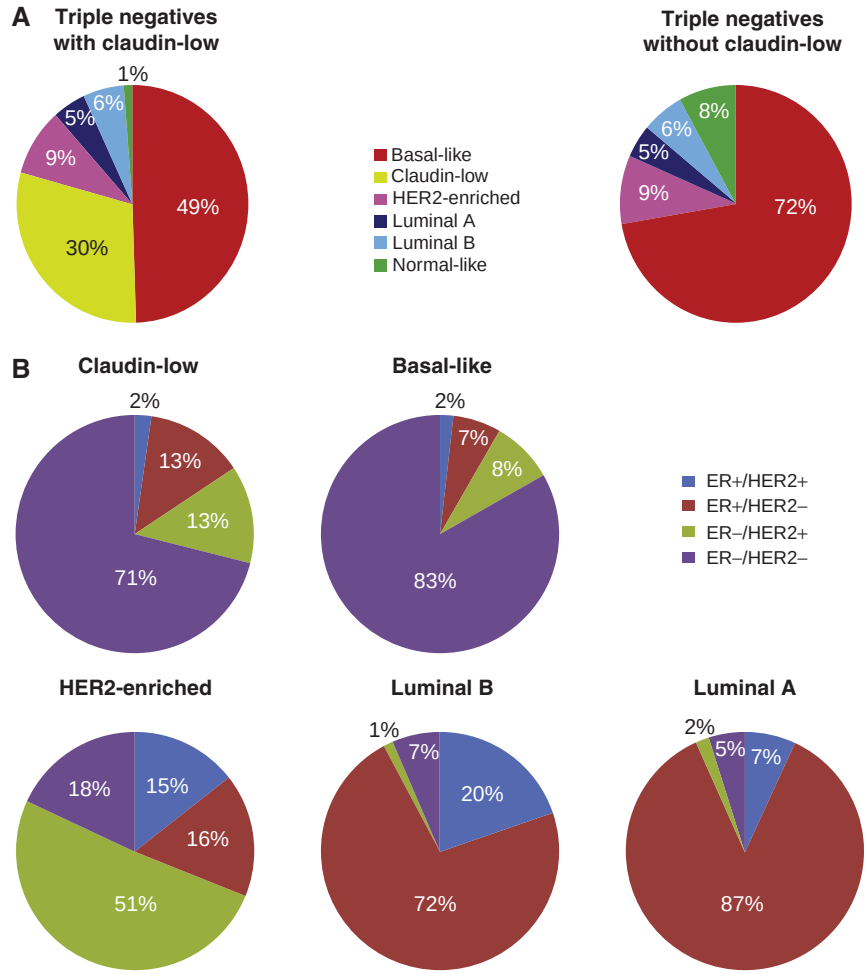

FIGURE 29-3 Distribution of clinical-pathological categories relative to the intrinsic subtypes. **(A)** Intrinsic subtype distribution within the triple-negative tumor category shown with and without Claudin-low tumors. **(B)** Distribution of ER+/HER2+, ER+/HER2+, ER–/HER2– clinical groups in the Claudin-low, Basal-like, HER2-enriched, Luminal B, and Luminal A within each subtype. (From Prat A, Perou CM. Deconstructing the molecular portraits of breast cancer. *Molec Oncol* 2011;5:5–23.)

studies have shown that Basal-like tumors are molecularly distinct from Luminal tumors, and are more similar with tumors arising in the basal layer of epidermis including squamous carcinoma of the lung (51), and epithelial ovarian cancer (4). Although the PIK-pathway appears activated within Basal-like tumors, unlike Luminal subtypes, there is a low frequency of PIK3CA mutations (9%) (4), but higher frequency of PTEN (35%) and INPP4B (30%) loss (i.e., the deletion/mutation of negative regulators for PIK-pathway) (4). Similar to HER2-E subtype, the presence of TP53 somatic mutations (85%) is extremely frequent within Basal-like tumors, which is another property they share with serous ovarian cancers (95% TP53 mutant) (52).

Several risk factors for developing Basal-like subtype tumors have been identified with one of the most intriguing being the link between the Basal-like subtype and *BRCA1* mutation carriers (19,53–55). Women who carry a deleterious mutation in *BRCA1* are at > 50% risk of developing breast cancer, and, when they do, over 80% of the time it is Basal-like. However, while *BRCA1* mutation carriers usually develop Basal-like breast cancer, most Basal-like breast cancers are sporadic and the *BRCA1* gene and protein appear intact in these tumors. A commonly held, but unproven, assumption is that the *BRCA1* pathway is somehow deranged in sporadic Basal-like breast cancer, which, if true, could have important therapeutic implications. From the TCGA data, there is a combined frequency of 20% for *BRCA1* and *BRCA2* mutations (both germline and somatic) in the Basal-like subtype (4). The *BRCA1/2* pathways, which include a number of other genes such as FANC genes, are involved in homologous recombination mediated DNA repair, which is a high fidelity DNA repair pathway. When the homologous recombination pathway is lost or dysfunctional, DNA repair occurs by the more error-prone methods that involve poly (ADP-ribose) polymerase (PARP), which can be inhibited by a novel class of drugs that are being tested in clinical trials (56,57). Loss of normal DNA repair is also implicated in sensitivity to chemotherapy, particularly to DNA-damaging agents such as platinum drugs (58), although recent studies suggest that Basal-like breast cancers may have a general sensitivity to chemotherapy (30,47,59). Gathering the commalities between Basal-like subtype and high-grade serous ovarian cancers together, one might predict that platinum-based chemotherapy might be a potential therapeutic option for Basal-like tumors.

Another notable Basal-like tumor association is between this subtype and race and age. Several independent population-based studies have shown that the Basal-like subtype is more frequent in young women, and in African-American women (16,40,41,60,61). In the Carolina Breast Cancer Study, the Basal-like breast cancers were the most common among premenopausal African-American women (27%), and least common among postmenopausal non– African-American women (9%) (41,62). Basal-like breast cancer carries a poor prognosis in multiple datasets (16,17,19,63) and this has raised the question of whether an excess of this subtype might contribute to the worse outcomes suffered by African-American women with breast cancer.

A variety of methods to identify Basal-like breast cancer have been suggested including gene expression-based methods (17,29), specific IHC-based immunoprofiles (63,64), and the "triple negative" (ER, PR, and HER2) phenotype that is already available in the clinic (47). Each approach has strengths and weaknesses; however, it is important to note that while the majority of TNBC are Basal-like (~75%), up to 25% of Basal-like breast cancers identified by gene expression are positive for either ER, PR or HER2, and thus will be misclassified by the TNBC method (39,65) (see Fig. 29-3); therefore, the use of positive markers to identify Basal-like tumors will likely be needed, and multiple redundant biomarkers for the Basal-like subtype would give the most robust assay possible.

The categorization of breast cancers into Luminal and Basal-like subtypes arises from similarities of their gene expression patterns based upon their inferred normal cell types of origin. These observations raise the question of whether these subtypes arise from different progenitor cells rather than being derived from a common progenitor and acquiring variations during progression. Several lines of evidence support that breast cancer heterogeneity is an early phenomenon with distinct lines of progression for each subtype; these data include the finding that Basal-like, Luminal, and HER2+ subtypes are found in the ductal carcinoma *in situ* stage (22,66,67) Gene copy number aberrations also have characteristic patterns within these invasive subtypes and in DCIS (68,69), and are more frequent in Basal-like breast cancer even at DCIS diagnosis (70).

OTHER BREAST CANCER SUBTYPES

A new and more rare intrinsic subtype (prevalence ~10%), namely Claudin-low, has recently been identified in human tumors, mouse models, and human cell lines (23). The majority of these tumors are high grade, metaplastic and/or TNBC phenotype, and carry a poor prognosis. Claudin-low tumors share some similar gene expression patterns with Basal-like tumors, such as low expression of the Luminal genes (*ESR1, GATA3*, keratins 8 and 19) and HER2 amplicon genes. They differ, however, from Basal-like tumors through the low expression of the proliferation signature, low expression of cell-cell adhesion proteins including Claudin-3, 4, -7, and E-cadherin (23). In comparison to Basal-like as well as other subtypes, Claudin-low tumors are enriched for immune system response genes (*CD4, CD79a*, interleukin 6, or *CXCL2*). Based on genomic analyses, *in vivo* Claudin-low tumors and the human cell lines that show the Claudin-low phenotype (i.e., BT549, MDA-MB231, MDA-MB157, SUM159PT) also have characteristics similar to metaplastic tumors, mammary stem cells (71), and an Invasiveness Gene Set (IGS)/Cancer Stem Cell (CSC) signature (72). The association of Claudin-low tumors with CSC is further supported by limiting dilution transplantation analysis of mouse Claudin-low tumors, where a large proportion (30%–40%) of the tumor cells showed Tumor Initiation Cell activity (73). The best predictor of this subtype to date is a ~800-gene based signature, and there is no robust immunohistochemical surrogate for this subtype, thus imposing a practical challenge to studying this subtype in clinical trials.

Over the last few years, efforts have been made to identify additional possible subtypes within Triple Negative Breast Cancer (TNBC) by applying MPS and/or global gene expression profiling analyses (7,74). When compared with the existing known heterogeneity present within TNBC, the results of one particularly interesting study from Lehmann et al. are highly concordant with intrinsic subtyping in that a Basal-like group is identified, a luminal/Androgen-Receptor positive group is found, as is a mesenchymal/Claudin-low like group; extending these results, Lehmann et al. goes on to show that there exists significant heterogeneity within the tumor microenvironment, namely that there exists TNBC with significant immune cell infiltrates and others without, and some with significant fibroblast invasion and others without. Thus, the heterogeneity within TNBCs included tumor-specific subtypes, as well as potentially important differences within the cellular composition of the microenvironment.

PROGNOSTIC APPLICATIONS OF GENOMICS

Over 90% of breast cancers are identified at a non-metastatic clinically curable stage;, however, all are at risk of subsequent development of metastatic disease. Identifying those at greatest risk of progression is crucial in order to limit the use of potentially toxic drugs to those most likely to benefit. This has been the purpose of prognostic indices in breast cancer. The traditional prognosticators include the Nottingham Prognostic Indicator (NPI), the St. Gallen criteria, the NIH consensus guidelines, and Adjuvant! Online, all of which use criteria like tumor size, grade, lymph node status, and hormone receptor status to predict a patient's clinical outcome. The advent of genomics technology has allowed biology-based prognosticators to be developed. Only a handful of gene expression-based prognosticators, described in the following paragraphs, have been validated and are in clinical use, and in general, these complement, but do not replace traditional prognostic factors like stage.

A separate question is, does a study establishing prognostic relevance also establish therapeutic relevance? In adjuvant therapy, prognostic relevance is often translated into therapeutic relevance simply because risk crosses a threshold for use of conventional adjuvant therapies to reduce risk. There are two caveats to keep in mind when considering multi-gene, expression-based assays in this regard. First, unlike anatomic prognosticators, there may well be an interaction between the nature of the genes included in a particular profile and the benefit of systemic therapy. The most obvious analogy is the interaction between hormone receptor status and benefit of chemotherapy (75). This may mean that the interpretation of benefit may vary by expression profile, and should give warning to clinicians about excessive extrapolation. Second is that establishing therapeutic relevance is typically harder to do than prognostic relevance. Therapeutic relevance requires either a prospective randomized clinical trial designed to test the marker (the holy grail of biomarker levels of evidence) or studies performed in a fairly homogeneous population with prospective ascertainment of clinical data, excellent representation of tumor samples, and *a priori* defined profile definitions (76).

With these caveats in mind, the most clinically relevant scenario for prognostication by genomic signatures is within node-negative breast cancer, as most of these patients do not relapse, yet most receive adjuvant therapy. Five prognostic profiles have shown promise in this arena and are relatively well-characterized, and of these, two are in clinical use in node-negative breast cancer: the Amsterdam 70-gene Mammaprint™ profile, and the OncotypeDX Recurrence Score™. As mentioned earlier, another prognostic profile is the intrinsic subtypes ROR score, which was trained for prognostic purposes on node-negative disease (Table 29-2). It is increasingly clear that the biologic pathways identified by these profiles are independent of anatomic extent of disease, and they may also provide useful information about identifying good-prognosis patients within the node-positive subset (77).

TABLE 29-2

Prognostic Profiles

Profile	*Training Population*	*Validation Population*	*Endpoint*	*Adjusted Hazard Ratio*	*Clinical Use and Notes*
Recurrence Score (Oncotype Dx™) (78)	N = 447 (78) N– or N+ ER+ and ER–, heterogeneous Rx	✓ Subset of prospective clinical trial (NSABP B14) ✓ N= 668 (of 2,617) ✓ N0, ER+ ✓ Tamoxifen only ✓ Followup > 10 years	Distant metastasis at 10 years	3.21 (2.23–4.61)	✓ Predictor of distant relapse in ER+ node-negative. ✓ Predictor of likelihood of chemotherapy benefit in ER+ node positive ✓ Can be performed in fixed archival tissue.
		✓ Subset of prospective clinical trial (ATAC) (79) ✓ N = 1231 (of 5,216) ✓ N0 or N+, ER+ ✓ Tamoxifen or Anastrozole alone ✓ Follow-up > 10 years	Distant metastasis at 10 years	N0: 5.25 (2.84–9.73) N+: 3.47 (1.64–7.38)	
		✓ Subset of prospective clinical trial (SWOG-8814) (77) ✓ N = 367 (of 927) ✓ N+, ER+ ✓ Tamoxifen and CAF–tamoxifen ✓ Follow-up > 10 years	Disease-free survival at 5 yrs vs. tamoxifen only:	Low RS: 1.02 (0.54–1.93) CAF High RS: 0.59 (0.35–1.01) CAF	
Amsterdam 70-gene profile (26) (Mammaprint®)	N = 78 N0, age < 55 years, Followup> 5 years (26)	✓ Retrospective ✓ N = 295 (61 from training set) ✓ N- or N+, age < 53, T1–2, any ER ✓ Heterogeneous Rx ✓ Followup > 5years (87)	Distant metastasis 1st event	4.6 (2.3–9.2)	✓ Predictor of distant metastasis in Stage I–II. ✓ Can be performed in both frozen and fixed archival tissue
		✓ Retrospective ✓ N = 302 ✓ N0, age < 61, T1–2, any ER ✓ No adjuvant systemic therapy ✓ Followup > 10 years (88)	Time to distant metastasis Overall survival Disease-free survival	2.13 (1.19–3.82) 2.63 (1.45–4.79) 1.36 (0.91–2.03)	
		✓ Retrospective ✓ N = 148 ✓ N0, age 55–70, T1–2, any ER ✓ Majority no adjuvant systemic therapy (18% received endocrine therapy) ✓ Follow-up > 10 years (89)	Breast cancer specific survival at 5 years	14.4 (1.7–122.2)	

Breast Cancer Index (94**)**	N = 236 Heterogeneous Rx N– or N+	✓ Retrospective ✓ N = 239 (94) ✓ N0-1, ER+, T1–2 ✓ Tamoxifen Rx and Tamoxifen + chemotherapy Rx	Distant metastasis	24 (4.3–135.2)	✓ None at this time ✓ No consistent methodology so not yet validated ✓ Focus is on hormone receptor-positive ✓ Can be performed in fixed archival tissue
		✓ Different algorithm (not true validation) ✓ Subset of prospective clinical trial (Stockholm trial) ✓ N = 314 ✓ N0, T1–2, ER+, post-menopausal ✓ Tamoxifen Rx for 2–5 years ✓ Follow-up > 10 years (98)	Distant metastasis at 10 years vs. BCI Low:	4.2 (1.5–12.1) Intermediate 4.4 (1.4–13.7) High	
		✓ Different model building (not true validation) ✓ Subset of prospective clinical trial (ATAC) ✓ N = 665 (of 5,216) ✓ N0 or +, ER+ ✓ Tamoxifen or Anastrozole alone ✓ Follow-up > 10 years (99)	Distant metastasis at 10 years vs. BCI Low	2.89 (1.55–5.4) Intermediate 4.86 (2.58–9.17) High	
Wound Response signature (104)	Core serum response genes in serum-stimulated fibroblasts	✓ Retrospective ✓ N = 295 (87) ✓ N0 and N+, age < 53, T1–2 ✓ Heterogeneous Rx ✓ Followed for > 5years	Metastasis 1st event Overall survival	7.25 (1.75–30.0) 11.18 (2.52–49.6)	✓ None at this time ✓ Requires frozen tissue
Invasiveness Gene Set (122)	186 genes differentiating CD44+/CD24– cells from normal breast epithelium	✓ Retrospective ✓ N = 295 (87) ✓ N0 and N+, age < 53, T1–2 ✓ Heterogeneous Rx ✓ Followed for > 5yrs	Metastasis-free survival Overall survival	1.2 (1.1–1.4) 1.2 (1.0–1.4)	✓ None at this time ✓ Requires frozen tissue
Intrinsic Subtype and PAM50 ROR (17,19,25,29**)**	N = 220 N– or N+ ER+ and ER–, no adjuvant systemic Rx	✓ Retrospective ✓ N = 786 (33) ✓ N0 and N+, ER+ ✓ Tamoxifen Rx ✓ Follow-up > 15 years	Breast cancer specific survival at 5 years vs. Luminal A: Breast cancer specific survival at 5 - 10 years vs. Luminal A:	1.99 (1.09–3.64) Luminal B 3.65 (1.64–8.15) Her2-enriched 17.7 (1.7–183) Basal-like 1.7 (1.13–2.55) Luminal B 1.52 (0.72–3.18) Her2-enriched	✓ Primary interest for stratification rather than prognostication ✓ Predictor of distant relapse in ER+ ✓ Predictor of likelihood of chemotherapy benefit in ER+ ✓ Can be performed in both frozen and fixed archival tissue

(Continued)

TABLE 29-2 *(Continued)*

Prognostic Profiles

Profile	*Training Population*	*Validation Population*	*Endpoint*	*Adjusted Hazard Ratio*	*Clinical Use and Notes*
		✓ Subset of prospective clinical trial (ATAC) ✓ N = 1007 (of 5,216) (32) ✓ N0 or N+, ER+ ✓ Tamoxifen or Anastrozole alone ✓ Follow-up > 10 years	Distant metastasis at 10 years Distant metastasis at 10 years vs. Luminal A:	**Node 0:** 7.16 (4.07–12.61) ROR **Node 0:** 4.78 (2.97–7.7) Luminal B **Node 1-3:** 2.2 (1.1–3.61) Luminal B **Node 4+:** 3.40 (1.60–7.22) Luminal B	
		✓ Subset of prospective clinical trial (NCIC MA.12) ✓ N = 398 (of 672) (31) ✓ N0 and N+, ER any, premenopausal ✓ Heterogeneous chemotherapy ✓ Tamoxifen Rx vs. placebo	Relapse-free survival vs. placebo:	**Luminal A/B**: 0.52 (0.32–0.86) Tamoxifen Rx **Non-Luminal subtypes:** 0.80 (0.50–1.29) Tamoxifen Rx	
		✓ Subset of prospective clinical trial (NCIC MA.5) ✓ N = 476 (of 716) (30) ✓ N+, ER any, premenopausal ✓ CEF vs. CMF	Relapse-free survival vs. CMF	**Luminal A:** 1.14 (0.70–1.88) CEF **Luminal B:** 0.76 (0.47–1.24) CEF **Her2-enriched:** 0.56 (0.34–0.93) CEF **Basal-like:** 1.12 (0.60–2.08) CEF	

N0, lymph node negative; N+, lymph node positive; Rx, treatment; CEF, cyclophosphamide, epirubicin, 5-fluorouracil; CMF, cyclophosphamide, methotrexate, 5-fluorouracil.

The Recurrence Score

The 21-gene Recurrence Score assay (RS, OncotypeDx™) was developed using unique methods and represents one of the most validated gene expression assays yet developed (78). Using 447 patients from three available datasets of mostly node-negative, hormone receptor-positive patients, and using a qRT-PCR-based approach that allows examination of limited numbers of genes from formalin-fixed tissue, they correlated gene expression with distant recurrence. From the 250 candidate genes selected based on prior knowledge, 16 cancer-related and 5 reference genes were chosen to be included in the RS assay. This assay can be performed on fixed tumor samples and does not require frozen samples.

The RS was validated in an independent dataset derived from samples collected in the National Surgical Adjuvant Breast and Bowel Project (NSABP) cooperative group B-14 trial, which examined the benefit of adjuvant tamoxifen in patients with hormone receptor-positive, lymph node-negative breast cancer (78). In those patients classified as low risk by the RS (RS <18) only 7% relapsed despite adjuvant tamoxifen, compared to high risk patients (RS > 31) among whom 31% relapsed. Currently, postmenopausal women with ER-positive tumors are often treated with aromatase inhibitors. The prognostic value of RS was further confirmed in the retrospective analysis of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) Trial (79), which evaluated the efficacy and safety of 5 years of anastrozole, tamoxifen, or the combination of both treatments in over 4,000 postmenopausal women (80). The RS was significantly associated with distant metastasis for both node-positive and node-negative tumors, and provided significant independent prognostic information beyond Adjuvant! Online. In the node-negative tumors, the adjusted HR between high and low RS groups was 5.2 (95% CI 2.7–10.1), and the HR between intermediate and low RS groups was 2.5 (95% CI 1.3–4.5). In the node-positive tumors, the adjusted HR between high and low RS groups was 2.7 (95% CI 1.5–5.1) and the HR between intermediate and low RS groups was 1.8 (95% CI 1.0–3.2). The distant metastasis rate for RS low group was 17%, and whether chemotherapy can be spared or needed for patients with node positive/low RS group is a pressing clinical question being addressed in a prospective clinical trial, the RxPONDER trial, described in the following paragraphs.

The RS was further validated in homogeneous patient populations of node-negative or positive, hormone receptor-positive, and endocrine therapy treated women. For this reason, it was not clear if its prognostic ability reflects true prognosis, prediction of lack of tamoxifen benefit, or both. In a population-based case-control study, the RS provided independent prognostic information in untreated patients suggesting a pure prognostic role in addition to the previously suggested predictive one for endocrine sensitivity (81). Fortunately, in addition to predicting worse outcome despite endocrine therapy, a high RS also predicts benefit of chemotherapy (82,83). In SWOG 8814, 1,477 postmenopausal women with node-positive, hormone receptor-positive breast cancer were randomized to tamoxifen alone, cyclophosphamide, doxorubicin, plus fluorouracil (CAF) chemotherapy plus tamoxifen concurrently, or CAF chemotherapy followed by tamoxifen (77); the overall trial revealed a benefit of chemotherapy particularly given sequentially with tamoxifen. The RS was performed in 367 tumors from the sequential CAF-tamoxifen arm of the study, and revealed that in the node-positive population the RS was prognostic across nodal categories. Moreover, the benefit of the addition of CAF to tamoxifen was only seen in those with high RS (Fig. 29-4). The caveat to clinical application of this finding to node-positive breast cancer is that this is an older regimen, and even in the "good risk" low RS group, the long term disease-free survival was only 60%.

The Treatment (**Rx**) for **Po**sitive **N**ode, **E**ndocrine **R**esponsive Breast cancer (RxPONDER) Trial (SWOG S1007, ClinicalTrials.gov identifier NCT01272037) is a large Phase III clinical trial designed to answer the earlier question concerning a possible lack of chemotherapy benefit in low RS and node-positive patients. The study is expected to enroll approximately 4,000 patients with node-positive (1–3 nodes), hormone receptor positive, and HER2-negative tumors and have RS ≤ 25 (i.e., low to intermediate) by Oncotype Dx, with patients being randomized to receive hormonal therapy (tamoxifen citrate, anastrozole, letrozole, or exemestane) with or without chemotherapy. The study also aims to determine the optimal cut off for RS score within node-positive patients.

The OncotypeDX RS assay is recommended as a clinical decision-making tool for patients with hormone receptor-positive, node-negative breast cancer by the American Society of Clinical Oncology (84) and the 2011 St. Gallen International Expert Consensus (37). Meanwhile, the final results from the **T**rial **A**ssigning **I**ndividua**L**ized **O**ptions for Treatment (**Rx**) (TAILORx) is nearing reporting. In this large, multicenter, randomized study, more than 10,000 women diagnosed with hormone receptor-positive, HER2-negative, node-negative breast cancers were accrued. Briefly, patients with RS < 11 received standard hormonal therapy, while patients with RS > 25 received both chemotherapy and hormonal therapy (standard of care), and lastly, patients with RS 11–25 were randomized to receive hormonal therapy alone or chemotherapy followed by hormonal therapy. Results from this study will likely help to determine if patients with intermediate RS will have improved survival outcome by receiving both adjuvant chemotherapy and hormonal therapy rather than hormonal therapy alone.

Finally, the main reclassification effect of the RS when compared with classic biomarkers is from high risk to low risk (85); befitting this effect a recent report confirms that, at least in largely academic practices, the main clinical effect of the RS is to change from planned chemo endocrine therapy to endocrine therapy alone (86). This study was a prospective cohort study, so is without many of the biases of a retrospective study, and can be considered level II evidence of the utility of the RS. Based upon these data, the RS has been accepted by many U.S. insurers and oncologists.

Amsterdam 70-Gene Profile

The Amsterdam 70-gene prognostic profile (Agendia Mammaprint®) was created by supervised analysis of gene expression array data using frozen tumor samples from the Netherlands Cancer Institute. The initial 98 tumors included 78 from node-negative patients under the age of 55 at diagnosis, 34 of 78 (44%) had developed distant metastasis within 5 years and 44 of 78 (56%) had not developed any distant disease. By comparing the gene expression profiles of the tumors with and without subsequent distant metastasis, a signature 70-gene set was identified. Since this initial publication, there have been at least six external validation studies of the 70-gene prognostic profile. The first was a retrospective analysis of 295 patients from the Netherlands Cancer Institute who were under the age of 53 years at diagnosis with T1–2 tumors, either lymph node negative (151 patients) or lymph node positive (144 patients), heterogeneously treated with or without adjuvant therapy and followed for nearly 7 years (87). Of the 295 patients, 180 were classified as having a poor 70-gene signature and 115 as having a good 70-gene signature. The mean five-year survival for the poor 70-gene signature group of patients was 74% versus 97% for the good 70-gene signature patients. This signature was able to predict prognosis regardless of lymph node status and remained significant in multivariate analysis of first

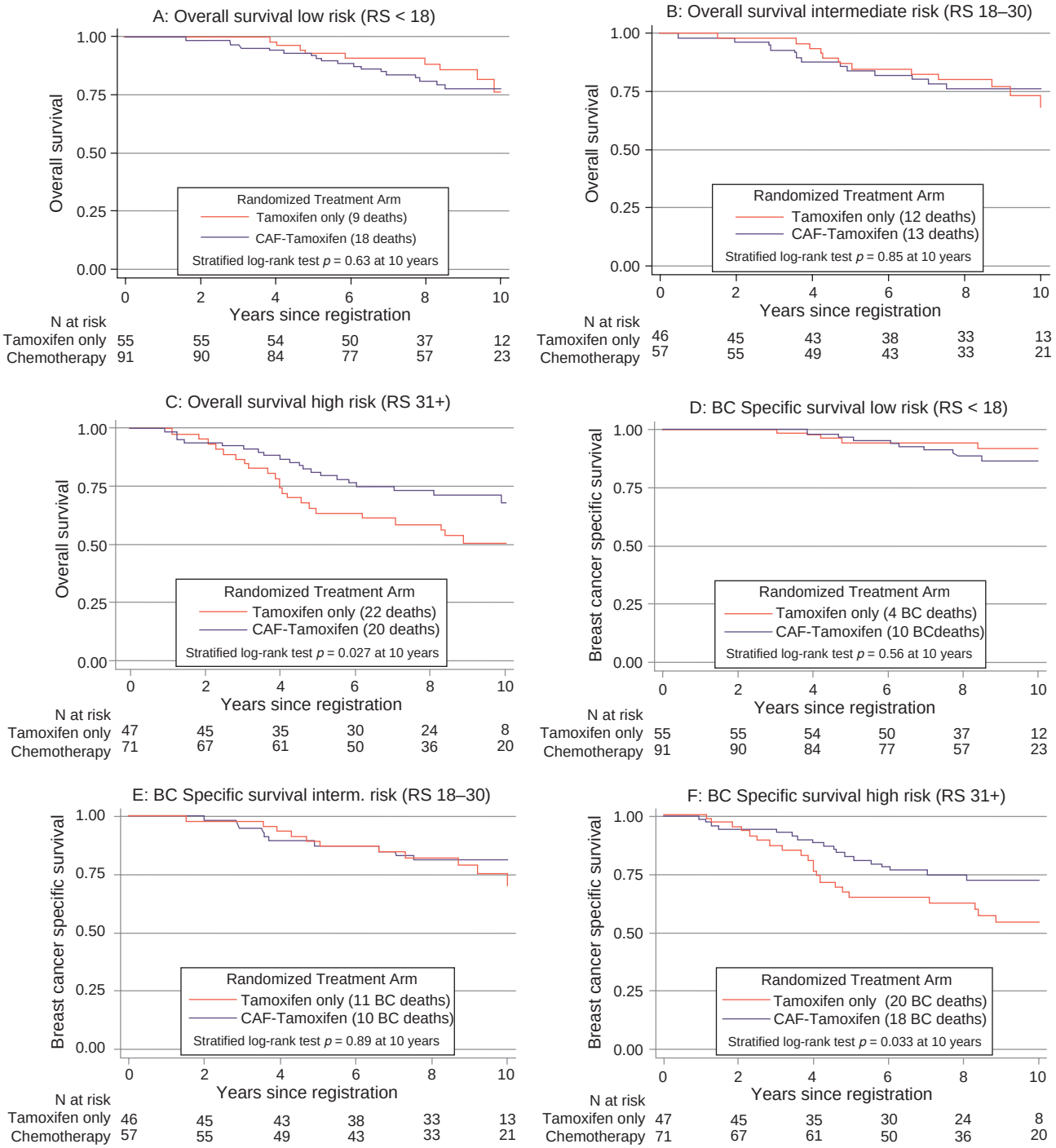

FIGURE 29-4 Secondary endpoints of overall survival by Recurrence Score™ (RS) groups **(A, B, and C)** and the exploratory endpoint of breast cancer specific survival by RS groups **(D, E, and F)**, all adjusted for number of positive nodes on SWOG 8814. (From Albain KS, Barlow WE, Shak S, et al. Prognostic and predictive value of the 21-gene recurrence score assay in postmenopausal women with node-positive, oestrogen-receptor-positive breast cancer on chemotherapy: a retrospective analysis of a randomised trial. *Lancet Oncol* 2010;11:55–65.)

event, as did the traditional prognostic criteria of tumor size, nodal involvement, and use of adjuvant chemotherapy.

A second, less heterogeneous, and truly independent retrospective validation study of the 70-gene prognostic signature was performed in 302 women treated at several European institutions (88). Adjusted for clinical risk as assessed by Adjuvant! Online, the 70-gene prognostic indicator effectively predicted time to distant metastasis (hazard ratio [HR] 2.13, 95% confidence intervals [CI] 1.19–3.82) and overall survival (HR 2.63, 95% CI 1.45–4.79); however, it did not significantly predict disease-free survival (HR 1.36, 95% CI 0.91–2.03) (Fig. 29-5) (88). In additional studies,

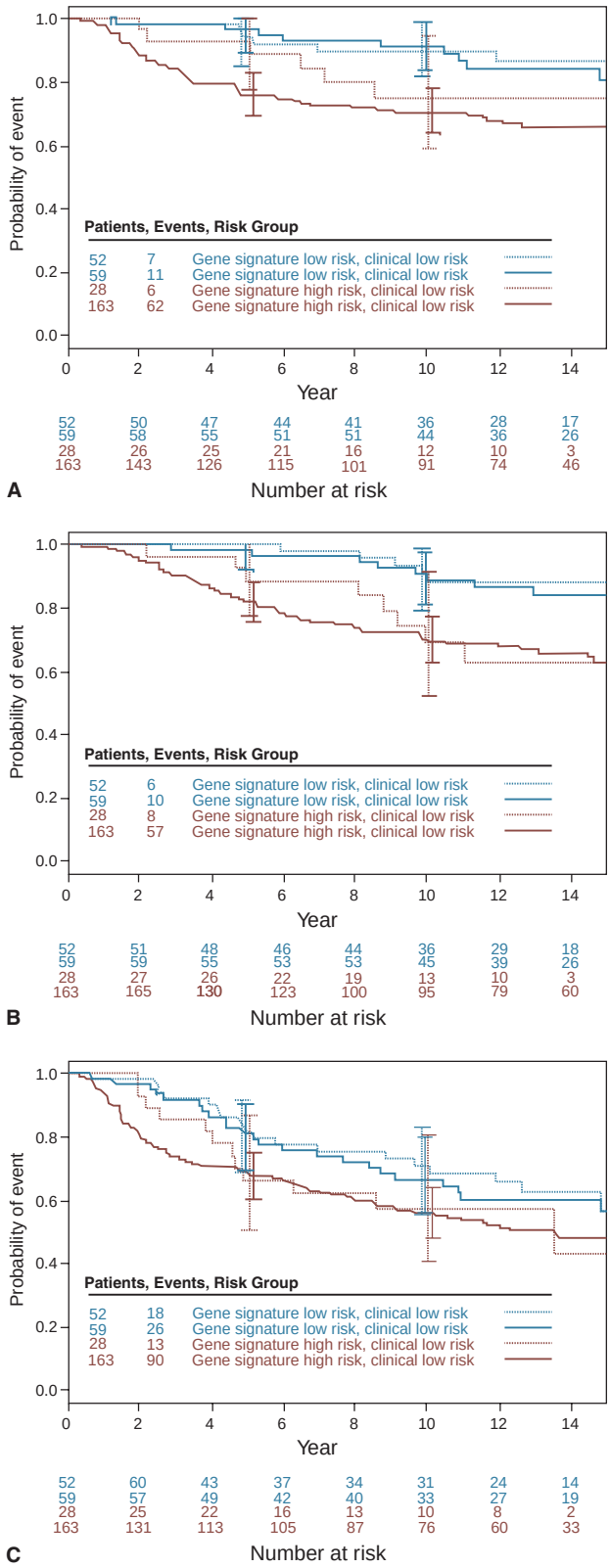

FIGURE 29-5 Outcome among 302 node-negative patients by 70-gene profile and clinical risk (with 95% confidence limits in bars). **(A)** Time to distant metastasis. **(B)** Overall survival. **(C)** Disease-free survival. (From Buyse M, Loi S, van't Veer L, et al. Validation and clinical utility of a 70-gene prognostic signature for women with node-negative breast cancer. *J Natl Cancer Inst* 2006;98(17):1183–1192.)

the 70-gene prognosis signature also predicted metastasis in patients (n = 148) aged 55–70 years, with node negative, T1–2 tumors diagnosed from 1984–1996 (89). Adjusted for the clinical risk features, the signature was again a strong prognostic factor for distant metastasis, especially for the first five years (HR 14.4, 95% CI 1.7–122). The performance of the 70-gene signature was also evaluated in 241 patients with node-positive (1–3 nodes), T1–3 breast tumors diagnosed between 1994 and 2001 at several European institutes (90). Ninety patients (44%) were classified as having good prognosis by the 70-gene signature, and again, the 70-gene signature was significantly prognostic in predicting breast cancer-specific survival beyond the standard clinical variables (HR 7.17, 95% CI 1.81–28.43). There is a strong time dependence of the 70-gene profile, befitting the way it was developed, as it far better predicts early (before 5 years) than later relapse (91). Notably, this profile is also more useful in ER-positive versus ER-negative disease; among ER-positive tumors 50% had low profiles, whereas among ER-negative only 6% showed the favorable profile. These validation studies provided the evidence needed for the development of the MINDACT trial, which is described in the following paragraphs.

One previous obstacle to large-scale use of the 70-gene signature has been the need for a significant amount of frozen tissue, which was a major impediment for use in the United States (92). The Mammaprint assay is now also available for use on FFPE tissues, although there is no information on the concordance with the microarray data from frozen tissue samples. Level I evidence of its clinical utility awaits reporting of the MINDACT Trial (Microarray in Node-Negative and 1 to 3 node positive Disease May Avoid Chemotherapy, Clinical Trials.gov identifier NCT00433589), in which 6,600 women with node-negative (and also node-positive with 1 to 3 nodes affected) breast cancer underwent clinical risk assessment via Adjuvant! Online and the 70-gene prognostic signature, and when these two tests disagreed, patients were randomized to be treated according to the risk assessment by Adjuvant! Online or by 70-gene signature. The two prediction methods will be compared in this randomized subset (93). Based on its development and prognostic validation, the Mammaprint® assay was FDA-approved for use in prognostication in small- to intermediate-sized, node-negative breast cancers in 2007.

Breast Cancer Index

The Breast Cancer Index (BCI) is a prognostic assay for the risk of developing distant metastasis in patients with ER-positive, node-negative tumors. This assay is a combination of a previously identified 2-gene signature (HOX13:IL17BR) and a five-gene tumor molecular grade index ([MGI] *BUB1B, CENPA, NEK2, RACGAP1*, and *RRM2*) (94). The development of the 2-gene signature for outcome predictions started from 22,000-gene arrays performed in 60 node-positive women with hormone receptor-positive breast cancer treated with tamoxifen and followed for at least 5 years (95). HOXB13 was associated with recurrence, while IL17BR was associated with remaining disease-free, making the ratio even more strongly associated with recurrence with an adjusted odds ratio of approximately 7. The MGI was built upon on 39 genes with elevated expression in high-grade tumors (96), and 5 genes functionally involved to different cell cycle phases were eventually picked. Using supervised principal component analysis, an MGI score was calculated based on the expression patterns of these five genes on a population-based series of 236 heterogeneously treated patients (94). Using another similar cohort of 159 patients,

the MGI score was significantly associated with tumor grade and patient outcome. In comparison to the Genomic Grade Index (GGI) (described in the following), both the MGI (AUC = 0.90) and GGI (AUC = 0.92) assays performed equally well to discriminate grade 1 and grade 3 tumors. The GGI is a microarray-based assay based on 97 differentially expressed genes from grade 1 versus grade 3 breast tumors (97). In a retrospective case-control study of 239 ER positive tumors, Ma and colleagues evaluated the individual prognostic value of MGI and the 2-gene HOXB13:IL17BR measured by qPCR TaqMan assay using heterogeneously treated tumors at one institution from 1991 to 1999 (94). The MGI discriminated the grade 1 and grade 3 tumors with 86% accuracy and was found to complement HOXB13:IL17BR in predicting distant metastasis. Patients were classified into three risk groups based upon two cut points (MGI = 0 and HOXB13:IL17BR = 0.06): (a) **low** if low for MGI and low or high HOXB13:IL17BR, (b) **intermediate** if high MGI and low HOXB13:IL17BR, and (c) **high** if high for both MGI and HOXB13:IL17BR. Most notably, when compared to the low risk group, the high risk patients were eight times more likely to develop distant metastasis among the 84 patients with ER positive tumors treated with adjuvant tamoxifen. The prognostic value of this assay for distant recurrence on ER positive tumors was then confirmed using a subset of 588 patients from the randomized Stockholm trial (98).

Subsequently, the Breast Cancer Index (BCI) was developed to provide individual risk assessment. The BCI is a continuous score combining MGI and HOXB13:IL17B using a multivariable Cox model with cubic spline function fit on the 314 tamoxifen-treated patients from the Stockholm trial (98). Tumors were categorized into three risk groups as low risk if BCI < 5, intermediate if 5 ≤ BCI < 6.4, and high risk if BCI ≥ 6.4. The BCI risk-classifier identified patients with significantly different distant metastasis rates at 10-years from the untreated arm from the Stockholm trial (98), with an absolute difference of 20% between the low high-risk groups.

The performance of the BCI assay in predicting risk of distant recurrence beyond standard clinical and pathological variables was further evaluated on the HR-positive and node-negative tumors in the ATAC trial (99). The primary planned endpoints for the BCI were marginally significant (p = .05). Therefore, a new BCI was developed using a different multivariable Cox linear model trained on the untreated patients (n = 274) from the Stockholm trial and re-evaluated on the ATAC trial. Based on the new BCI-linear model, 58% of patients (n = 390) were classified as low, 25% as intermediate (n = 166), and 17% as high (n = 109). The 10-year adjusted HR between high risk and low risk was 4.86 (95% CI 2.58–9.17). Both BCI and RS provided independent prognostic information to predict early recurrence (0–5 years). Although RS did not retain significant prognostic value for late recurrence (>5 years) while the BCI did, the RS algorithm was fixed but the BCI had been modified after the primary analyses on the ATAC trial. Therefore, strictly speaking this cannot be considered a true validation study of the BCI assay. This signature can be performed in FFPE tissue, which makes it of considerable clinical interest, however, given the varying methodologies and cut points in the studies to date, this combinatorial assay of MGI and HOXB13:IL17BR remains intriguing but further implementation awaits ongoing validation studies.

Intrinsic Subtypes and Risk of Recurrence

Using a multivariable Cox Model and a Ridge regression fit, the ROR predictor from the PAM50 assay (29) was trained on a cohort of patients with node-negative tumors who did not receive adjuvant systemic therapy (87). A ROR score can be assigned to each patient sample using (a) correlation to subtypes only (ROR-S) (29), (b) subtype correlation along with tumor size weighted model (ROR-T, previously known as ROR-C) (29,33) and (c) subtype correlation along with proliferation signature and tumor size (ROR-PT) (33). The prognostic value of ROR models were first validated using a heterogeneously treated cohort of 279 patients with old FFPE archival materials and further confirmed on 786 patients with ER-positive tumors homogeneously treated with tamoxifen only (33). Among the node-positive tumors of the tamoxifen-only treated cohort, the ROR-T and ROR-S scores provided the best prognostic models for both relapse free survival and breast cancer specific survival beyond the standard clinical pathological variables and Adjuvant! Online. The 10-year relapse rates for the low-risk groups were between 15% and 20% among these node positive tumors. On the other hand, among the 197 node-negative tumors, among the 31 patients who were classified as low risk, there was only one patient who developed relapse and died of breast cancer over the 15 years of follow-up. The intermediate (n = 145) and high (n = 21) risk groups were significantly associated with worse outcome when compared to the low-risk group. Therefore, similar to the RS and the 70-gene prognostic signatures, the PAM50 ROR score is able to identify a very low-risk group among women with ER positive, node-negative tumors who were treated with adjuvant tamoxifen only.

Both RS and PAM50 ROR assays are optimized to work on FFPE assays. The next logical clinical interest was to perform a direct comparison between the PAM50 ROR scores and RS for prognostication on the same cohort of patients. The translational component of the ATAC trial described earlier with 10-year follow up again proved itself to be an important resource in assessing the performance of PAM50 ROR scores in predicting the risk of distant relapse (32). A total of 940 tumors had been evaluated with both genomic assays (RS and PAM50) as well as the immunohistochemical-based classifier IHC4 (including ER, PgR, Ki-67 and HER2). The PAM50 ROR-defined risk groups were significantly associated with the 10-year distant recurrence in all pre-planned analyses on the whole population, node-negative tumors, and node-positive tumors. Among the 683 node-negative tumors, the addition of ROR provided significant independent prognostic information to the RS (change in likelihood ratio statistics = 8.4), whereas the RS did not provide significant additional prognostic information to the ROR (change in likelihood ratio test statistics = 1.6). Nevertheless, both assays classified a comparable number of patients as low risk, 428 as ROR-low and 434 as RS-low. Even more interestingly, the 10-year distant relapse survival estimates were almost equivalent between these low risk groups of patients (32). Therefore, both PAM50 ROR and RS performed well in identifying patients with ER-positive tumors who may just need endocrine therapy. The prognostic value of PAM50 assay to predict risk of distance recurrence in postmenopausal women with HR-positive tumors who received endocrine therapy has also been recently validated on 1,400 patients from the Austrian Breast & Colorectal Cancer Study Group 8 (ABCSG8) trial (34).

EndoPredict

Another new multi-gene qPCR-based signature known as EndoPredict (EP) had been developed to predict the risk of recurrence within ER-positive, HER2-negative tumors (100). This assay is based on the expression of eight genes, primarily representing proliferation and hormone receptor-related signaling, developed to work on FFPE materials. Using a combined cohort of 1,702 ER-positive, HER2-negative tumors

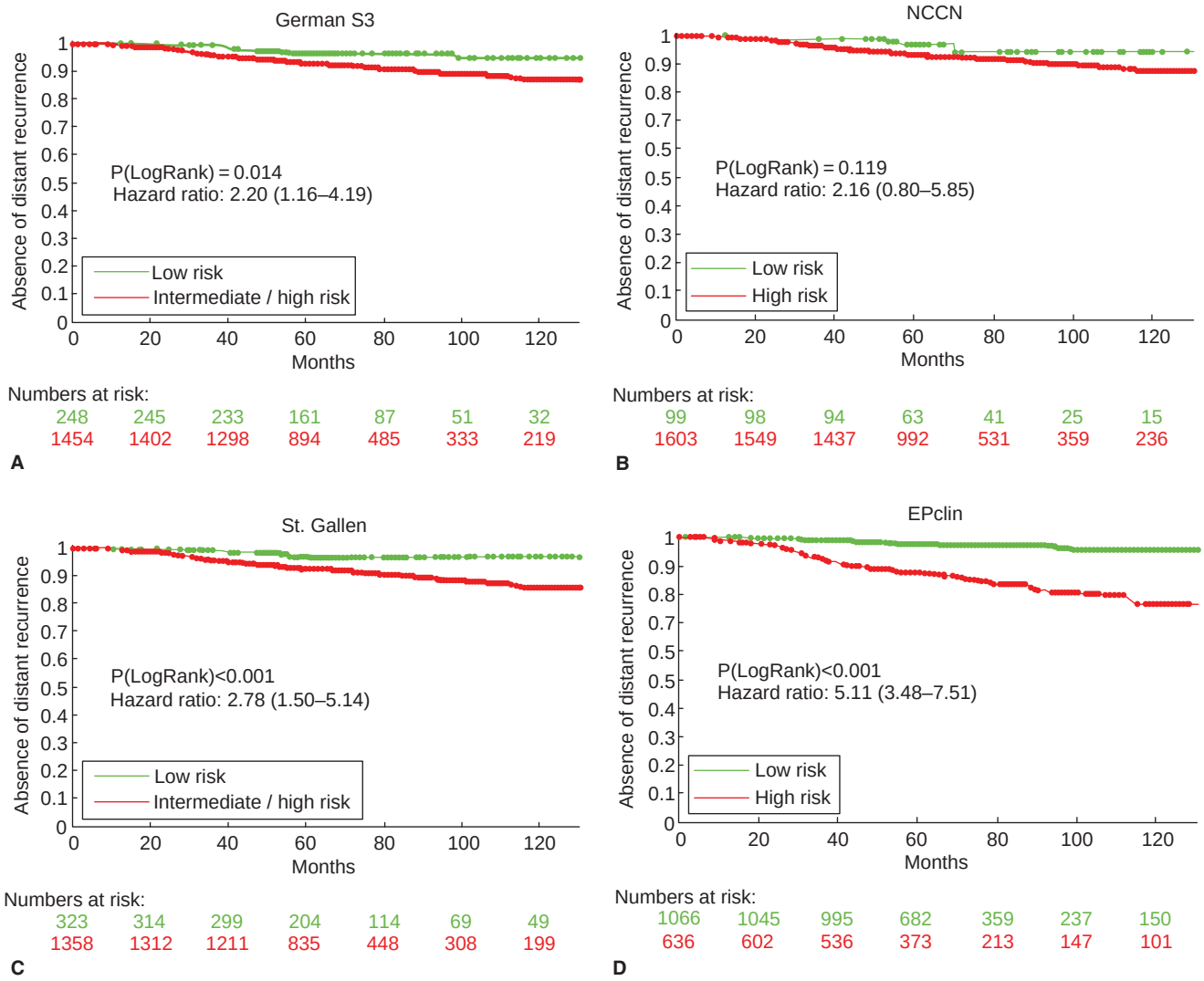

FIGURE 29-6 Kaplan-Meier plot of distant metastasis-free survival by **(A)** German S3, **(B)** National Comprehensive Cancer Center Network (NCCN), **(C)** St. Gallen guidelines, and **(D)** EPClin risk groups. Ninety-five percent confidence intervals (CI) of hazard ratios (HR) are indicated. (From Dubsky P, Filipits M, Jakesz R, et al. EndoPredict improves the prognostic classification derived from common clinical guidelines in ER-positive, HER2-negative early breast cancer. *Ann Oncol* 2013;24(3):640–647.)

treated with endocrine therapy only from two large Phase III trials (ABCSG6 and ABCSG8), ER and the EP assay improved prognostication. Using the clinical guidelines, the 10-year absolute risk differences between the high- and low-risk group were from 6.9% to 11.2%, whereas there was 18.7% difference according to EPClin classification (101) (Fig. 29-6). Of note, the EPClin prognostic signature includes EP, tumor size, and number of nodes in the algorithm. Clearly additional validation is needed; however, it is clear that multiple different gene expression profiling assays are being developed for ER-positive breast cancer patients, most of which are proving valuable information that is not provided by the standard clinical variables.

Other Prognostic Signatures

Of note, the clinical utility of all of the aforementioned prognostic signatures are shown mostly in ER-positive/HER2-negative breast cancers. There are still no similar signatures available for hormone receptor negative or HER2+ positive tumors (102). There have been a very large number of prognostic signatures identified and in development for breast cancer patients and all cannot be discussed in detail here, however, many are related to proliferation. For example, the Genomic Grade Index includes 97 differentially expressed genes between Grade 1 and Grade 3 tumors (97). This histological grade predictor was subsequently validated to be strongly prognostic among patients with grade 2 tumors (43). Another biologically interesting signature is the "wound response" signature that is derived from a set of genes, termed core serum response (CSR) genes, which changed in expression when cultured fibroblasts were activated with serum. Evaluation of the CSR genes suggested that they represented important processes in wound healing like matrix remodeling, cell motility, and angiogenesis, all of which are predicted to play a role in cancer invasion and metastasis (103). Subsequent evaluation of the CSR genes in the same 295-patient dataset used to validate the

Amsterdam 70-gene profile suggested that an activated wound response signature was associated with decreased survival and increased probability of distant metastasis in both univariate and multivariate analyses (104). Lastly, there are literally more than 100 described prognostic signatures for breast cancer, which are too many to detail here. This large number of signatures does suggest that there are common and robust patterns of gene expression that are of biological and clinical value.

PREDICTIVE ARRAY-BASED PROFILES

An area of great interest is the potential of gene expression arrays to predict response, or non-response, to particular regimens, with the hope for individualizing therapy by examining the tumor at the time of diagnosis. A number of predictive genomic signatures that have been, or are being, developed will be summarized here and in Table 29-1. Many of these are often mindful of a particular indication, such as tamoxifen resistance, so are mentioned with predictive signatures, although in many cases these were developed as prognostic as well as predictive profiles.

Prediction of Endocrine Therapy Sensitivity

Because hormone receptor-positive breast cancer is virtually always treated with adjuvant endocrine therapy, identifying how much of an impact upon outcome is prognostic versus predictive can be difficult. The Recurrence Score is both prognostic in the untreated cohort and predictive of tamoxifen benefit in NSABP B-14 (105). The PAM50 Luminal subtypes were also predictive of adjuvant tamoxifen benefit in the NCIC CTG.12 trial, which is a randomized study examining tamoxifen versus placebo in premenopausal women treated with adjuvant chemotherapy (31). Other predictive profiles for endocrine therapy include the 81-gene tamoxifen resistance profile (106), the BCI, and the Sensitivity to Endocrine Therapy (SET) index (107). The SET index was based on the expression of 165 genes that are ER-related and was significantly associated with relapse in patients treated with tamoxifen alone (HR 0.70, 95% CI, 0.56–0.88) and chemotherapy plus endocrine therapy (HR 0.19, 95% CI 0.05–0.69).

An assumption is that predictive profiles developed on tamoxifen will equally predict response to aromatase inhibition. Endocrine sensitivity at this time appears to be a general phenomenon. Comparison of the aromatase inhibitor and tamoxifen arms in ATAC suggested that both RS and PAM50 ROR performed equally well to predict risk of distant recurrence, but could not be used to choose one endocrine approach over another (32,79).

Patients with node-negative and HR+ tumors have good response to endocrine therapy, and hence, typically long survival times. Given extended adjuvant endocrine therapy options, it is important to identify patients who may be associated with increased risk to develop late recurrences, typically defined as those occurring beyond 5 years. Studies using both tamoxifen alone and tamoxifen followed by AI have found that patients treated with extended endocrine therapy for 10 years had better survival than those treated with 5-years of tamoxifen alone. Both the BCI and EPClin score were recently reported to predict late recurrences. In the TransATAC study, the BCI provided additional prognostic information to predict late distant recurrence beyond the standard clinical variables (99), while IHC4 and Recurrence Score did not. Similarly, in a study consisting of 1,702 tumors from patients treated with adjuvant endocrine therapy on the ABCSG6 and ABCSG8 clinical trials, the EPClin score provided significant independent prognostic information for predicting late recurrences. Within the low-risk subgroup of patients, 98% of the patients remained free of distant metastasis (101). In a retrospective study of 222 patients with node negative tumors treated with adjuvant tamoxifen only, the PAM50 ROR-PT score was significantly correlated with 10-year survival, outperforming the Adjuvant! Online and standard clinical variables. The ROR-PT identified a subgroup of patients in whom 5 years of tamoxifen may be adequate treatment given the extreme low rate of late relapses (<2%) in both the 0–5 and 5–10 year window (33). With further validation, it is likely that the clinical utility of extended endocrine therapy could be weighted using EPClin, BCI, or ROR score assignments.

Neoadjuvant endocrine/chemotherapy has been endorsed as an effective research approach to identify or validate biomarkers to predict pathological complete response. In the means of clinical utility, neoadjuvant endocrine therapy has been shown to improve surgical outcomes for postmenopausal women with ER-positive, stage 2 and 3 breast cancer (108). A Preoperative Endocrine Prognostic Index (PEPI) for risk of relapse has been developed on 228 tumors from postmenopausal women with ER+ stage 2 and 3 breast cancers in the P024 neoadjuvant endocrine therapy trial, a study that compared letrozole and tamoxifen for 4 months before surgery (109). The PEPI score integrates the posttreatment ER status, Ki-67 proliferation index, histological grade, pathological tumor size, and node status to predict relapse. Patients with a PEPI score of 0 and low pathological stage (stage 1 or 0) at surgery after neoadjuvant endocrine therapy had a low rate of relapse, and those with a high PEPI score, had a high rate of relapse. Although PEPI score is not a genomic assay, it is a similar 'multi-analyte' tool because it includes multiple variables to predict outcomes. In the ACOSOG Z1031 neoadjuvant aromatase inhibitor trial, there was a significant higher rate of PEPI score 0 in Luminal A versus Luminal B tumors. This again shows the inter-relatedness of multiple genomic and proteomic signatures.

Prediction of Chemotherapy Sensitivity

Chemotherapy efficacy differs according to tumor subtype, in particular between ER-negative and ER-positive subtypes (75), so multi-gene predictors must provide information beyond the available clinical assays. The most clearly developed predictive profile for chemotherapy sensitivity is the Recurrence Score (RS), which is also the only profile tested in the kind of prospectively annotated large datasets that provide reliable evidence of efficacy. In a subset of over 600 tumors from ER-positive node-negative patients in NSABP B-20, the RS predicted sensitivity to methotrexate plus fluorouracil with or without cyclophosphamide (MF/CMF) added to tamoxifen in hormone receptor-positive, node-negative patients (83). Another subset from the SWOG 8814 study examined 367 tumors, and found that the benefit of CAF added to tamoxifen in hormone receptor-positive node-positive disease was primarily among high RS (110). These studies suggest that the RS predicts general sensitivity, or resistance, to chemotherapy, but cannot help to select one regimen over another. The clinical utility of the RS in adding chemotherapy to endocrine therapy in intermediate (11–25) RS scores is being prospectively examined in the TAILORx and RxPONDER trials; however, recognizing the lack of regimen-specificity in the studies to date, the choice of chemotherapy is left to the discretion of the treating physician.

In a recent report, Hatzis et al. reported a chemosensitive prediction algorithm for pathologic response (pathologic complete response or residual burden index I) for patients with HER2-negative tumors treated with sequential neoadjuvant taxane and anthracycline-based regimens (followed

by endocrine therapy if ER-positive), which was developed on a discovery cohort of 310 tumors and tested on a validation cohort of 198 tumors (111). The predictive signature was a combination of probe sets for ER-positive and negative tumors. In the validation cohort, the chemopredictive signature had a positive predictive value (PPV) of 56% and negative predictive value (NPV) of 73% for pathologic complete response; when Luminal B and Basal-like breast cancers were grouped, the PPV was 40% and NPV 78%. The predictive value of intrinsic subtype for neoadjuvant chemotherapy benefit has been demonstrated in multiple datasets, with Luminal A tumors rarely achieving a pathological complete response (pCR), Luminal B tumors showing approximately 10% to 15% pCR rate, and Basal-like and HER2-E subtypes showing high pCR rates (up to 35%) (29,47,59). Chemotherapy specificity was tested on 476 tumors from the NCIC MA.5 trial of premenopausal women with node-positive breast cancers, who were randomized to anthracycline (CEF [cyclophosphamide-epirubicin-fluorouracil]) versus non-anthracyline (CMF [cyclophosphamide-methotrexate-fluorouracil]) chemotherapy (30). The PAM50 assay, particularly the HER2-E subtype, demonstrated the greatest benefit of CEF over CMF with an absolute 5-year RFS and OS difference exceeding 20%, whereas there was a less than 2% difference for the non-HER2-E tumors (i.e., all other subtypes including Basal-like). While these results might be intriguing, additional and larger studies are needed to confirm this finding and the predictive independence of intrinsic subtype over high quality hormone receptor, HER2, and grade assessments in predicting pathologic response to chemotherapy.

The area of greatest interest is in the development of chemotherapy regimen- or agent-specific predictive signatures. There have been several different predictive profiles for docetaxel sensitivity; an 85-gene signature (with cellular redox genes overrepresented) that was approximately 80% accurate in predicting clinical response to the single agent in the neoadjuvant setting (112), a similarly derived 92-gene signature that was nearly 90% accurate (113), and a 50-gene signature derived from cell lines that was 92% accurate when applied to a small neoadjuvant dataset (114). A qRT-PCR-based method for the 92-gene signature plus other candidate genes allowed testing in fixed tissue and found 14 genes predictive of clinical complete response to neoadjuvant docetaxel; however, the false discovery rate (likelihood of finding these genes by chance) was high (115). In a recent report, Martin et al. demonstrated that an 11-gene proliferation score might potentially be useful to identify those with benefit from weekly paclitaxel. In this study, using 820 tumors from the GEICAM/9906 phase III trial that compared adjuvant FEC to FEC followed by weekly paclitaxel (FEC-P), a benefit from paclitaxel was only observed in a group of patients with low PAM50 proliferation score with an unadjusted HR of 0.23 (interaction test $p = .006$). In an independent dataset of tumors from 222 metastatic patients treated on CALGB 9342 and 9840 clinical trials studying weekly versus every-3-week paclitaxel, the low proliferation score had numerically higher benefit from the weekly regimen but this interaction did not reach significance (116). Most of these studies are limited by size, heterogeneity in tumor types, lack of independent validation, and in some cases by endpoints of unclear clinical significance.

A 74-gene predictor of an anthracycline and taxane-based regimen was developed from permutation modeling of a neoadjuvant dataset treated with paclitaxel, fluorouracil, doxorubicin, and cyclophosphamide (24). The investigators developed a 30-probe set predictor that was applied to an independent set of 51 patients. Interestingly, the best predictive model included both genomic and clinical data (117). The same group that identified the 92-gene signature also examined a cohort of patients treated neoadjuvantly with doxorubicin plus cyclophosphamide (AC), and identified 253 genes associated with clinical response (118). As detailed earlier, there are multiple prior and ongoing efforts to develop gene expression signatures of chemotherapy response. It should be noted that most rely upon the neoadjuvant setting for training and discovery, which assumes that the gene sets related to response will also relate to the development of distant disease. Given the tight association of pathologic response to outcome, this may be a reasonable assumption; however, it is unproven. In addition, in assays used for decision-making regarding the use and selection of chemotherapeutic agents, even 10% to 20% inaccuracy may be unacceptable as even a modest benefit of a regimen may be valuable.

PITFALLS AND LIMITATIONS OF APPLIED ARRAY TECHNOLOGIES

The most important pitfall of gene expression based prognostic and predictive profiles has already been highlighted—namely that these are mostly works in progress. Even the most validated assays have been studied in relatively small datasets or as subsets of larger clinical trials. None have met level I criteria for use in clinical decision-making, although both the Recurrence Score (TAILORx and RxPONDER) and the Amsterdam 70-gene prognostic profile (MINDACT) have completed large adjuvant trials and are awaiting results that could be of Level I evidence. Of concern is that the field of breast cancer therapy is rapidly changing, and evidence of prognosis or efficacy of a particular approach can become obsolete during the performance of prospective validation studies. For example, it may take 2 to 3 more years to get the final results of the MINDACT trial that is prospectively testing the value of the 70-gene assay in determining benefit of chemotherapy, and so the difficult question is do we wait until these trial(s) are completed to begin everyday use of these assays? Approaches that will make development and validation of gene expression signatures more nimble are crucial, and the treating oncologist must ask whether retrospective validation is enough evidence to support current clinical use.

Other caveats for genomic studies include the need for exceptional rigor, as always, in the tumor collection, processing, data management, and statistical methods used to analyze gene expression arrays. High dimensional multi-analyte data (like microarrays) are prone to overfitting due to the very high number of genes analyzed, high false negative rates due to the sheer volume and hypothesis-generating nature of arrays, and bias introduced by non-independence of genes from one another and from clinical variables (119). Gene expression pattern reproducibility can also be an issue (120), as can data processing variability and tumor enrichment (53). In fact, one interpretation of the "normal-like" intrinsic subtype is that these are samples with an excess of stroma, and thus these assays may be more sensitive to tumor cell content versus other biomarker methods like IHC. Another methodologic issue is the generalizability and robustness of profiles developed in a certain population when applied to a different population. The importance of the studied population is also highlighted by the Recurrence Score studies demonstrating that while the prognostic implication of the Recurrence Score remains across tumor sizes and nodal categories, smaller tumors have lower risk even if the Recurrence Score is high (81), while node-positive

breast cancer carries a poor prognosis even if the profile is low (110). In other words, biology is not entirely destiny, which again suggests that a combination of genomic and classic biomarker assays is best.

FUTURE DIRECTIONS

The ongoing MINDACT, and the RxPONDER and TAILORx trials could provide level I evidence of the clinical utility of the 70-gene prognosticator and the Recurrence Score assays, respectively; however, even these large scale genomic studies have not addressed all relevant questions. For example, no prognostic profile has yet been developed for hormone receptor-negative breast cancer, and because these tumors also have a heterogeneous prognosis, this would be a clinically valuable direction for researchers to take. Another example might be pharmacogenomics assays aimed at predicting effectiveness or toxicity of drugs based upon inherited variability in drug activation or metabolism, e.g. by cytochrome p450 enzymes (121). Assays for clinically relevant individual cytochrome p450 genes already exist, and investigators and diagnostic companies are developing drug metabolizing enzyme gene arrays that detect genetic variations in multiple genes. These single nucleotide polymorphism (SNP) chips, which detect actual gene variants (rather than gene expression variation), hold great promise, not only for individualizing medicine choices, but also for detecting multiple gene interactions for the risk of breast cancer. As stated before, the future of prognostication and prediction lies in the integration of classic biomarkers like ER status and stage, with genomic biomarkers of the tumor, and with genetic biomarkers of the host, which is occurring and resulting in more accurate outcome predictions for breast cancer patients.

Lastly, with the advent of Massively Parallel Sequencing, it is likely that many of the above mentioned assays will change technologies, moving from microarray-based to sequencing-based. For example, gene expression profiling can now be accomplished using the sequencing and counting of mRNA molecules, which is called mRNA-seq; this approach is more quantitative, more sensitive, and also provides sequence information such that alternative splicing and single nucleotide variants can be simultaneously detected. Thus, as is typically the case, the technology may change, but the basic biomarker that is a gene expression pattern will remain. We are in the age of personalized medicine, and gene expression-based assays helped to bring us here and they are here to stay.

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Disclosure

C.M.P is an equity stock holder, and Board of Director Member, of BioClassifier LLC/University Genomics and GeneCentric Diagnostics. C.M.P and M.C.U. Cheang are listed inventors on a patent application for the PAM50 molecular assay.

CHAPTER 30

Bone Marrow Micrometastases and Circulating Tumor Cells

Costanza Paoletti, Jeffrey B. Smerage, and Daniel F. Hayes

CHAPTER CONTENTS

INTRODUCTION

The development of distant metastases is the result of the spread of tumor cells through the lymphatic and vascular compartments. In breast cancer, the most important example of this process is the identification of tumor cells in the axillary lymph nodes. Therefore, lymph node staging continues to be one of the most important prognostic variables in early-stage breast cancer. However, axillary staging is far from definitive. Women with newly diagnosed breast cancer who have uninvolved axillary lymph nodes still have a 20% to 30% chance of recurrence. Conversely, even in the absence of adjuvant systemic therapy, roughly half of women with node positive cancer will not have recurrence of their cancer (1). This observation suggests that micrometastatic process might be independent of lymphatic involvement. Therefore, development of new methods to detect and characterize micrometastatic disease might improve the ability to make clinical treatment decisions.

Detection of micrometastases in visceral organs, such as liver or lung, is fraught with considerable logistical and safety concerns. In this regard, bone marrow and blood have been the most commonly studied non-lymphatic sites of micrometastases. The finding of micrometastases in bone marrow or blood is designated as "minimal detectable disease" (MDD). When detected in the bone marrow, MDD has also been called "disseminated tumor cells" (DTCs), while the term "circulating tumor cells" (CTCs) has been used to refer to micrometastases in the blood.

CLINICAL VALUE OF DETECTION OF MICROMETASTASES

Detection, enumeration, and characterization of MDD might have several clinical uses relative to breast cancer. However, to date, few if any practice guidelines have recommended either screening for or monitoring DTCs or CTCs in patients at risk for or affected by breast cancer (2,3).

Why are these guidelines so conservative? There are several criteria that must be met before any tumor biomarker test, including those for MDD, are introduced into clinical care (4–6). First, the specific use must be defined—risk categorization or screening of an unaffected person, or prognosis and/or prediction of benefit from therapy in the adjuvant or metastatic settings, or monitoring for occult metastases or for response or progression in patients who are either free of disease or are being treated for metastatic breast cancer. Second, the assay must have been shown to have analytical validity, which requires evidence of accuracy, reliability, and reproducibility (7). Finally, the biomarker test must have clinical utility. Clinical utility is defined as demonstration that use of the assay to direct patient care improves a patient's outcome when compared to care of the patient without knowledge of the assay results (5,6). High levels of evidence are required to established clinical utility. It is important to distinguish "clinical utility" from "clinical validity." The latter implies that the biomarker test has been shown to separate two subgroups within a population according to outcome or biological characteristics, but the

assay may or may not be useful to care for patients. Taking these considerations in mind, the remainder of this chapter will review methods of detection of MDD and their analytical validity, and the potential clinical uses and evidence for clinical utility of tests for MDD.

METHODS OF DETECTION OF MINIMAL DETECTABLE DISEASE

The greatest barrier in detecting MDD is the accurate separation and identification of cancer cells from other cells that are found within the hematopoietic environment. In this regard, over the past two decades, several methods have been developed to enrich these cells from the bone marrow or hematopoietic environment. These methods have been based on either physical or biological properties, or both, that distinguish MDD from normal hematopoietic cells. Moreover, once the capture step has been concluded, further characterization is required to confirm that the presumed isolated cells are indeed at least epithelial, if not malignant. The most commonly used strategy is to demonstrate that the captured cells are epithelial in origin is by monitoring expression of cytoplasmic cytokeratin (CK) (8). Additional molecular evaluation can be conducted, investigating other established or putative biomarkers that might provide further biological or clinical insight.

Methods to Detect and Characterize DTCs in Bone Marrow

Detection and characterization of DTCs in marrow has involved an initial separation of nucleated cells through density centrifugation, followed by immunostaining for cytokeratin versus hematologic markers. The latter is usually performed on smears on glass slides. Further characterization for other markers of interest, such as tumor-associated antigens, can be performed using immunostaining, reverse transcriptase polymerase chain reaction (RT-PCR), or other molecular techniques (9–16). Standardized guidelines have been developed to reconcile different approaches of DTC quantification (17,18).

Methods to Isolate and Detect CTCs

Although malignant cells were identified in human blood over 150 years ago (19), the technology to capture and characterize CTCs with high analytical validity has only been available over the last decade. Over 40 different devices have been reported to isolate and characterize CTCs from whole blood (20). These are based on exploiting the differences between epithelial CTCs and normal hematopoietic cells in size, weight, electric charge, or flow characteristics or expression of epithelial or cancer-specific markers. Table 30-1 provides a description of these devices as of the publication of this chapter. A more detailed description of these devices is available in a recent review (20).

Currently, the most commonly used strategy to capture CTCs involves coating a solid phase matrix of some sort (magnetic or plastic beads, microposts, fluidic channels, etc.) with an antibody directed against a surface-expressed epithelial marker, usually the epithelial cellular adhesion molecule (EpCAM) (21–23). The only FDA-approved, commercially available assay based on this strategy has been designated CellSearch® (Veridex, LLC; Raritan, NJ), and has been shown in several studies to be associated with worse prognosis in breast as well as colorectal and prostate cancer (24–26).

However, this strategy is not perfect. EpCAM is only expressed by approximately 80% of all breast cancers, and the intra-patient expression of EpCAM by CTCs can be highly variable (27,28). In this regard, EpCAM may be lost by cancer cells that are undergoing epithelial to mesenchymal transformation (EMT), a recently recognized process that may be a fundamental property of the metastatic phenotype (29). Nonetheless, of all the markers studied to date, this strategy is the most clinically practical method to capture epithelial CTCs, and, although not ideal, assays based on this strategy are associated with poor prognosis and can be used to monitor patients with metastatic breast cancer.

After the CTCs have been captured, they must be further characterized to prove that they are non-hematopoietic cells. In the case of most solid cancers, this additional characterization involves demonstration that they are of epithelial origin. Again, the most common strategy has been staining with 4, 6-diamidino-2-phenylindole (DAPI) to demonstrate

TABLE 30-1

Characteristics and Techniques to Isolate and Identify CTCs

	Cellular Characteristics	*Techniques*
Physical		
	Size	Filtration
	Weight/mass	Density Gradient Centrifugation
	Morphology	Light Microscopy
Biology		
	Membrane proteins	Immunomagnetic Isolation
		Flow Cytometry
		Immunofluorescent Microscopy
	mRNA	RT-PCR
	Gene mutation or duplication	PCR
		Comparative Genomic Hybridization
		Microarray
	Cytogenetic abnormalities	FISH

FISH, fluorescence *in situ* hybridization; mRNA, messenger RNA; PCR, polymerase chain reaction; RT-PCR, reverse transcription PCR.

the presence of nuclei, and then with fluoresceinated antibodies directed toward CK and CD45 to demonstrate that they are epithelial and not hematopoietic, respectively.

Over 30 other strategies to capture and characterize CTCs have been reported (20). These include use of membrane micropore filters or other devices that separate larger and more rigid epithelial cancer cells from smaller and more flexible hematopoietic cells (30). CTC have also been separated based on microfluidics techniques, which may also incorporate anti-EpCAM capture or not (31). An alternative method has involved smearing whole blood onto a specially charged slide and then identifying the epithelial cells (presumably CTC) by immunofluorescent staining (32,33). Another approach is based on detection of specific proteins secreted only by viable cells using an adaptation of enzyme linked immunoassay technique (Epithelial ImmunoSPOT (EPISPOT) (34). This strategy permits generation of a "protein fingerprint" at the individual cell level.

CTCs can also be presumptively identified by determination of expression of epithelial or cancer-associated genes using RT-PCR (35–37). Quantitative real-time RT-PCR (qRT-PCR) may increase the specificity of this approach by differentiating mRNA derived from non-tumor and tumor cells. This strategy may be used with or without a prior epithelial enrichment. For example, in one commercially available assay (AdnaTestBreastCancer™), epithelial cells are isolated by immunomagnetic beads labeled with antibodies against MUC1 and EpCAM. Real-time PCR is then applied to quantify mRNA transcripts for a variety of epithelial-specific markers such as GA73.3, EpCAM, and human epidermal growth factor-2 (HER2) (38–40).

As with bone marrow, the EPISPOT strategy has also been applied to whole blood to detect CTCs (41). This novel approach appears to have reasonable sensitivity and specificity relative to what has been reported with EpCAM capture, yet may provide an opportunity to characterize non-EpCAM expressing cells with greater clarity.

Each of these methods is predicated on evaluation of a certain volume of blood drawn from the patient and evaluated *ex vivo*. In order to monitor large volumes of blood, Eifler et al. have reported the high recovery of cultured human ovarian cancer cells that had been spiked into whole blood mononuclear fractions separated by leukapheresis (42). However, this approach is not terribly practical as a routine diagnostic assay. Recently, European investigators have reported pilot studies using an indwelling, intravascular guidewire coated with EpCAM monoclonal Ab (NanoDetector®, GILUPI, Greifswald Germany) (43). The catheter remains *in vivo* for 30 minutes, interrogating up to 1,500 mL of blood. This strategy permits collection of a substantially higher number of CTCs over a longer time window than is possible with a single blood draw. Direct comparisons to CellSearch® suggest increased sensitivity, but no data regarding clinical outcomes or clinical utility are available.

SENSITIVITY VERSUS SPECIFICITY IN DTC AND CTC ASSAYS

DTCs and CTCs are rare events in the bone marrow and circulation, respectively. For example, in bone marrow only 1 DTC can be detected for every 10^5 to 10^6 leukocytes (44). Likewise, CTCs are estimated to be present in a ratio of roughly one tumor cell per $1 \times 10^{5-7}$ peripheral mononuclear cells (45). Therefore, it is challenging to reliably separate DTCs and CTCs from the bone marrow and the blood, respectively. Sensitivity might be reduced for one of many reasons. First, most of the available strategies involve *ex vivo, in vitro* assays, limiting the volume of blood that can be interrogated. Second, any *in vitro* assay is fraught with cell loss due to device manipulation, such as flow through the device, incubations, and washings. Efforts to increase sensitivity may, with any assay, be hampered by loss of specificity, as discussed below.

Sensitivity of DTCs

Collection of DTCs requires a bone marrow aspirate and/or biopsy, which can easily be done at the time of surgery. However, for patients not undergoing surgery, bone marrow aspirate and biopsy is not terribly practical. Therefore, most DTC data are derived from patients with newly diagnosed breast cancer, and little if any data are available to estimate the incidence of DTCs in patients with metastatic breast cancer. Using standard techniques, DTCs can be detected in approximately one-third of patients with newly diagnosed, early-stage breast cancer, ranging from 12% to 42% depending on the study and the population selected (46). Following primary and adjuvant systemic therapy, it appears that the incidence of DTCs declines, presumably coincident with efficacy of therapy, although the clinical implications of this effect are not proven (46–48).

The scant data available in metastatic patients suggest that approximately one-fifth or more have DTCs, even without documented bone metastases. Using the EPISPOT assay, the detection of cells that secret MUC1 and/or cytokeratin 19 allowed the detection of viable DTCs in 90% and 54% of patients with metastatic breast cancer and non-metastatic breast cancer, respectively (34).

Sensitivity of CTCs

CTCs are less commonly detected than DTCs in patients with early-stage breast cancer, regardless of the currently available assays used. Several investigators have reported that, using the CellSearch® system, sensitivity ranges between 10% and 25%, when positivity is defined as one or more CTC/7.5–22.5 mL whole blood (49,50). RT-PCR methods appear to detect CTCs in approximately 41% (35,51). Too few studies have been performed with the other assay techniques to provide reliable estimates.

In contrast, CTCs are commonly found in patients with metastatic breast cancer. Using CellSearch®, approximately 70%, 60%, and 50% of patients with metastatic breast cancer have one, two, or five or more detectable CTC/7.5 mL whole blood, respectively. Sensitivity using other assays may be higher.

Specificity of DTCs and CTCs

Specificity has both technical and biologic distinctions. Technically, it is essential to distinguish an identified cell from both normal constituents of the surrounding bone marrow or blood environment. Most assays accomplish this task with accuracy by staining for epithelial and hematopoietic markers, although it is essential to use non-specific quenching techniques to avoid false-positive staining of granulocytes (if using immunohistochemistry) and plasma cells (any technique with a secondary antihuman antibody step). To circumvent these issues of specificity, multiple markers are used for the positive identification of CTCs and dismissal of leukocytes.

It is important to appreciate that some presumed epithelial markers may also be transiently expressed by normal or undifferentiated hematopoietic components of the marrow and blood. For example, MUC1, which is the soluble protein captured by the commonly used CA15-3 and CA27.29

circulating assays, has been shown to be expressed by precursor bone marrow hematopoietic cells (52).

Even with careful attention to separation of epithelial from hematopoietic cells, on occasion, normal subjects are found to have circulating epithelial cells. For example, the CellSearch® assay captures epithelial cells in 1% of normal subjects (21,53). However, analysis by fluorescence *in situ* hybridization (FISH) with multiple chromosomal markers has shown that captured epithelial cells from normal subjects are eusomic, while cells captured by CellSearch® in patients with metastatic breast cancer are almost always aneusomic (54,55). Furthermore, each of the capture strategies described above is really only an imperfect enrichment step. Even if the assay clearly captures well-defined epithelial or malignant cells, secondary analytical steps that do not directly visualize the interrogated cell, such as omics-based multi-gene RT-PCR, may well include contaminating white blood cells that have either simply not been removed or may even be phagocytosing, and therefore nearly covalently attached to, the CTCs.

Even single gene specific RT-PCR methods are plagued by false positive findings, ranging from 10% to 40% (22). These false-positive results are attributed to issues with laboratory technique, primer selection, and illegitimate expression of the target genes in leukocytes. For example, cytokeratin 19 and CEA overexpression can be induced in leukocytes by cytokines and growth factors (56–58). Many strategies have been used to increase the specificity, such as the use of qRT-PCR, which increases specificity compared to nested RT-PCR. As with whole-cell capture devices, qRT-PCR methods are positive in approximately 2% to 6% of normal control populations (59).

In addition to technical specificity, biologic specificity hampers clinical studies of MDD. Biological specificity refers to the detection of DTCs or CTCs that are morphologically malignant, yet may not have the capacity to produce lethal metastases. In this case, the clinician runs substantial risk of overdiagnosis. Indeed, not all MDD has malignant potential. Although detection of MDD in lymph nodes (60), bone marrow (46), and blood (21,50) is consistently associated with a statistically significantly higher risk of a future event, patients with positive findings are not absolutely destined to suffer recurrence, progression, or death in the future. For example, Wiedswang et al. have reported that approximately 15% of women who are free of any evidence of disease 2 to 3 years after initial diagnosis and treatment have positive bone marrow aspirates (47). Although this finding is associated with a statistically significant increase in subsequent relapse and death, many of these women did not suffer recurrence over the succeeding several years of follow-up. Likewise, Meng et al. have identified aneusomic CTCs in blood of approximately one-third of women who were 7 to 15 years after diagnosis but who were free of disease (55). These data suggest that one can identify morphologically distinct, viable DTCs and CTCs, but for one of many reasons they may not have long-term malignant potential. Thus, clinical studies demonstrating robust separation in outcomes are essential before a new assay claiming increased sensitivity is applied to patient care.

MINIMAL DETECTABLE DISEASE AND CLINICAL OUTCOMES

Over the last two decades, several studies have demonstrated that the presence of detectable DTCs or CTCs in patients with both primary and metastatic breast cancer is indicative of a worse prognosis. These studies establish clinical validity of the respective assays. However, only recently have appropriately designed studies been reported that begin to provide insight into clinical utility of these assays for their intended use; in other words, whether and how this information can be used in routine clinical care to improve patient outcomes. Many of the available studies are pilot in nature or conducted as correlative studies of convenience, in which the specimens happened to be available for a given assay. Most of these studies have significant limitations in their ability to assess the value of MDD as either a prognostic or predictive factor in breast cancer. These limitations are largely due to the small size of studies, retrospective acquisition of samples, and wide variations in treatments received by the patients. Thus, while analytical validity and clinical validity have been established for some of the assays (in particular, the CellSearch® system), high levels of evidence demonstrating clinical utility are still lacking.

Prognosis in Early-Stage and Metastatic Stage of Disease for DTCs

Almost all of the data regarding DTCs present in the literature have been generated in early-stage breast cancer and not in the metastatic setting. In a pooled analysis of all available studies, Braun et al. reported that approximately one-third of 4,703 patients with stage I–III breast cancer had detectable DTCs prior to surgery. They showed that the presence of occult cytokeratin positive metastatic cells in early breast cancer is associated with a statistically significantly higher risk of distant metastases and death from death-related causes ($p < .001$) (46). In multivariate analysis, the presence of DTCs was the strongest and most highly significant predictor of death (hazard ratio [HR] = 1.81), disease recurrence (HR = 1.85), and the development of distant metastases (HR = 2.03) (Fig. 30-1). These increased risks were seen in all treatment groups, including patients who only received hormonal therapy, or chemotherapy, and low-risk patients (TNM stage T1N0M0) who did not received any adjuvant systemic therapy.

However, although the pooled analysis demonstrates clinical validity, the clinical utility of these findings is not clear. Given the nature of the pooled studies, adjuvant treatments were variable, representing the local standard of care. Furthermore, although statistically significant, the results may not be clinically relevant. For example, the magnitude of difference in outcomes between those with versus those without MDD was highest in patients who received adjuvant systemic therapy (AST), in particular chemotherapy (Fig. 30-2C and D). Because these patients already received AST, and in the absence of data supporting further or different therapy for such patients, knowledge of this residual risk is of little clinical value.

The most obvious clinical use would be to use DTCs to determine whether to give AST. In this regard, in patients who did not receive AST, the magnitude of the difference in breast cancer–specific survival (BCSS) and disease-free survival (DFS) (Fig. 30-2E and F) between those with positive versus negative nodes is quite small, although still statistically significant. Indeed, even though those with positive DTC had a slightly worse prognosis, it was still quite favorable even without AST. These observations suggest that detection of bone marrow micrometastases in early disease is simply recanting what the clinicians already suspected from analysis of the primary and lymph node status: that patients who received AST had a worse prognosis. Unfortunately, in the very patients for whom further prognostic information would be valuable, the assay was

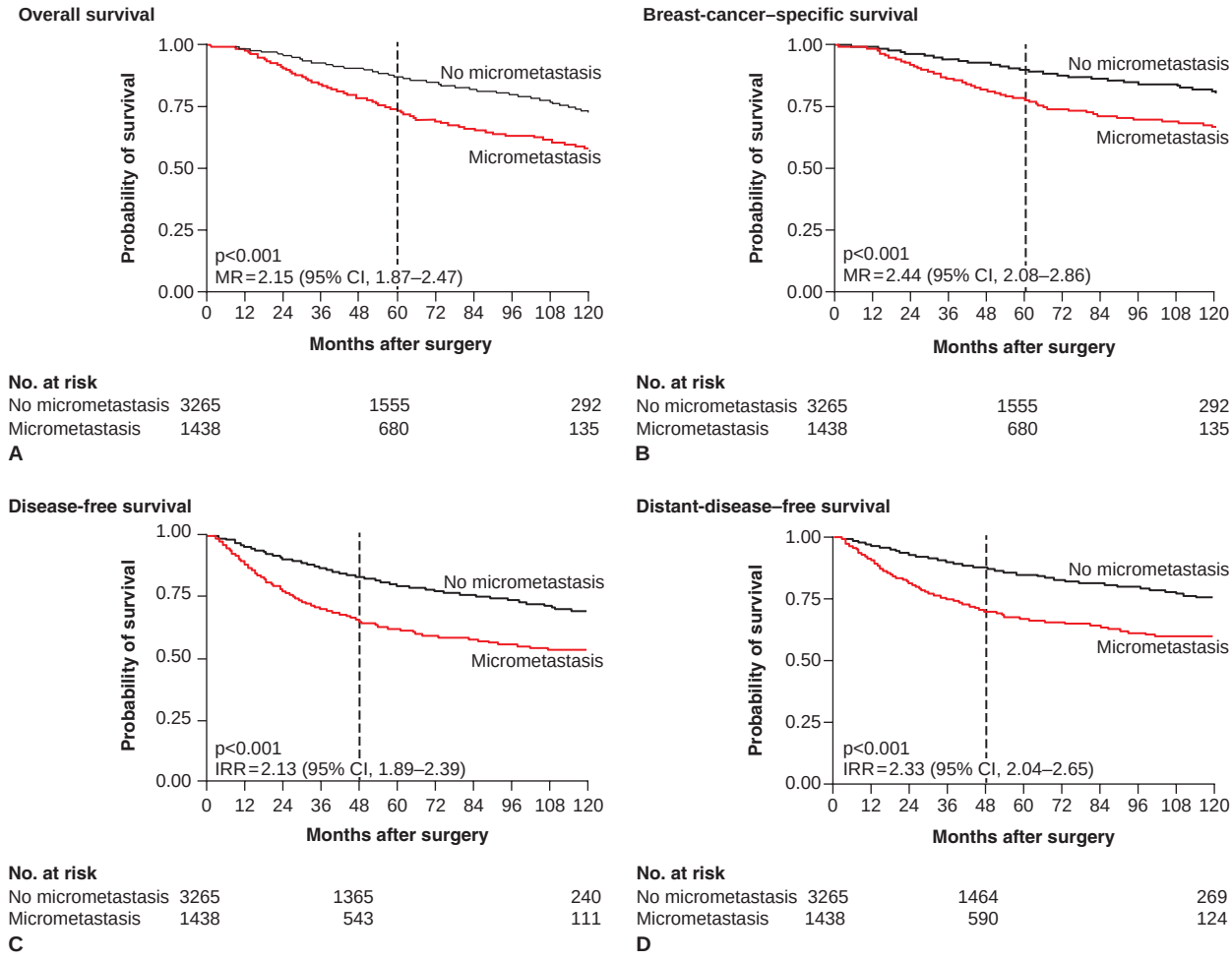

FIGURE 30-1 **Outcome of patients with early-stage breast cancer patients based on disseminated tumor cells. (A)** Overall survival. **(B)** Breast cancer–specific survival. **(C)** Disease-free survival. **(D)** Distant disease–free survival. (From Braun S, Vogl FD, Naume B, et al. A pooled analysis of bone marrow micrometastasis in breast cancer. *N Engl J Med* 2005;253(8):793–802. Copyright © 2005 Massachusetts Medical Society. All rights reserved [46].)

not very informative. Furthermore, because these studies were not conducted to specifically address clinical utility, one cannot determine if lack of MDD might have identified patients whose primary and lymph node status suggested high risk of recurrence but who actually would have done well without AST.

Another appealing use of DTCs in the clinical setting might be to monitor therapeutic efficacy and assessment of response to prior therapy or identify ongoing residual risk during event-free follow-up. In this regard, Wiedswang et al. have reported that of 920 stage I and II patients followed for 0.5 to 85 months, 32% of patients with positive DTCs at any time suffered relapse, compared to 14% of those who remained persistently negative (61). In addition, they and others have reported that the persistence of DTCs after primary and adjuvant therapy was associated with a very poor prognosis (47,62). A pooled analysis has shown that approximately 15% of patients have persistence of DTCs after primary and adjuvant chemotherapy and have a statistically significant higher risk of subsequent recurrence and death during the first 5 years following cancer diagnosis (long-rank test $p < .001$ values for all investigated endpoints) (48).

A more detailed assessment of the potential clinical utility of monitoring MDD (DTCs and CTCs) over time in patients with locally advanced disease undergoing neoadjuvant chemotherapy has been performed in the NeoTax Study. The presence of ≥1 DTC 12 months after the start of neoadjuvant therapy, but not at other time points, was associated with reduced disease-free survival (DFS), breast cancer–specific survival (BCSS), and overall survival (OS). In multivariate analysis, DTC status (</≥1 DTC) at 12 months after the start of neoadjuvant therapy remained as a prognostic factor, and presence of DTCs after neoadjuvant therapy indicated high risk for relapse and death, irrespective of the DTC-status before treatment (63). Although these data need to be confirmed, they suggest that perhaps DTCs might provide additional information to that gained by determination of pathological complete response of the primary breast cancer, which is currently the gold standard surrogate endpoint in this setting (64).

However, once again, the clinical utility of these findings is not clear. The obvious corollary to identification of persistent DTCs is that further alternative, or extended, AST should be delivered. No prospective randomized trial data support additional or alternative therapy to patients who

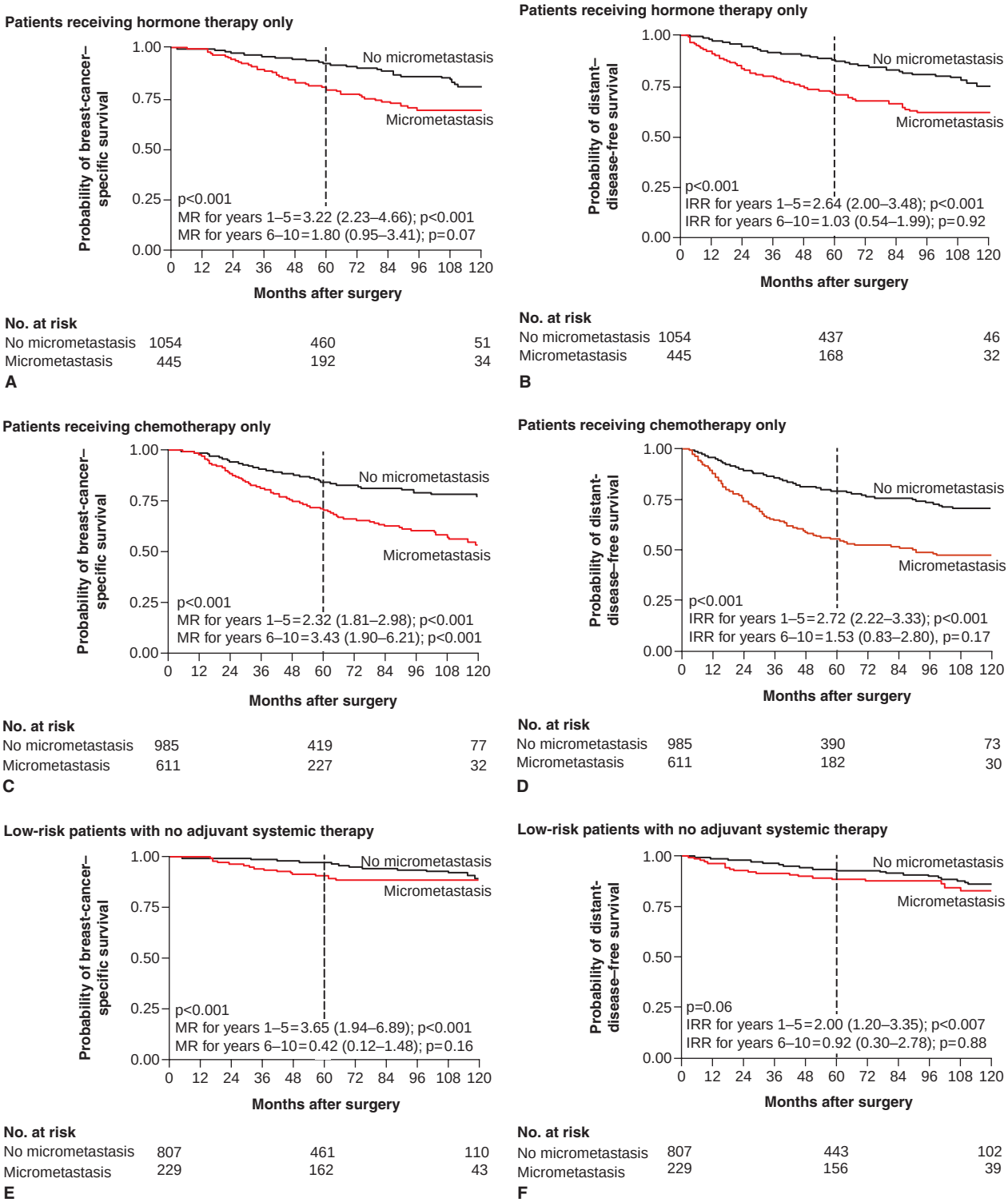

FIGURE 30-2 Outcome of patients with early-stage breast cancer based on disseminated tumor cells among patient subgroups who received adjuvant hormone therapy only, adjuvant chemotherapy, or no adjuvant systemic therapy. (A), (C), (E) Breast cancer–specific survival. **(B), (D), (F)** Distant-disease progression-free survival. A, B: Adjuvant endocrine (hormone) therapy only. **(C), (D)** Adjuvant chemotherapy. (E), (F) No adjuvant systemic therapy. (From Braun S, Vogl FD, Naume B, et al. A pooled analysis of bone marrow micrometastasis in breast cancer. *N Engl J Med* 2005; 253(8):793–802. Copyright © 2005 Massachusetts Medical Society. All rights reserved (46).)

either do not have a pCR or who have MDD after neoadjuvant chemotherapy. In this regard, one trial has been conducted (Norwegian NBCG9 [NCT00248703]) in which 1,121 breast cancer patients with pN1-3 or pT1c/T2G2-3pN0 status were analyzed for the presence of DTCs 8 to 12 weeks and 6 months after six cycles of a taxane-free, antracycline-containing adjuvant chemotherapy regimen. If DTCs were present at the second bone marrow biopsy, subsequent taxane-containing chemotherapy was administered, followed by routine clinical and DTC monitoring (65). Preliminary results demonstrate that DTCs were no longer detectable in the majority of patients after docetaxel treatment, but true clinical outcomes (RFS, OS) are pending. Unfortunately, since this trial did not contain a concurrent, randomized untreated control arm, it will be difficult to determine if the addition of the taxane truly improved clinical outcomes.

DTCs might evade the effect of chemotherapy by remaining in a dormant nonproliferative state. Therefore, beside treatment such as chemotherapy, other studies have investigated the therapeutic efficacy of different drugs such as bisphosphonates or novel targeted agents (66–69). For example, results of a phase II pilot trial suggested a reduction in DTCs after 6 months of zoledronate therapy (66). In a separate trial, 96 patients with early-stage breast cancer who had positive bone marrow after cytotoxic treatment were randomly assigned to zoledronate or observation only. The treatment with zoledronic acid was associated with lower incidence of persistently positive bone marrow after treatment, but additional investigation is required to determine whether the reduction in DTCs portends clinical benefit (67). Likewise, an open-label, randomized, phase II trial conducted in locally advanced breast cancer has shown elimination of DTCs by the administration of zoledronic acid (70).

Taken together, these accumulated results suggest that detection of DTCs either before or after therapy is associated with worse prognosis. However, although these data are promising, they only represent clinical validity, but not clinical utility, for any specific intended use. At present, DTCs should not be routinely collected or used to guide therapy in patients with breast cancer.

Prognosis in Early-Stage and Metastatic Stage of Disease for CTCs

Because serial bone marrow sampling is not easily performed within a single patient, serial collection of blood for measurements for CTC enumeration and monitoring might be a better alternative for sequential analysis of MDD. There are only few studies comparing DTC and CTC detection within the same time point, and for the most part they suggest that the detection of DTCs is higher than for CTCs (71–74).

Nonetheless, isolation, enumeration, and characterization of CTCs is an appealing strategy and might have clinical utility. Among the several reported CTC assays, the CellSearch® system or assays that use RT-PCR-based techniques are the most broadly used.

CTCs in Early-Stage Breast Cancer

Both EpCAM-capture based assays and RT-PCR-based assays may provide prognostic information in the early breast cancer setting. A series of studies have been published in which blood samples were prospectively collected and tested, using RT-PCR-based assays, from patients being treated on a variety of clinical trials (35,51,75). The chemotherapies varied, but the criteria for hormonal therapy and for clinical follow-up were all identical. For example, in one study of 167 patients with node-negative breast cancer, those who were CK-19 positive had a higher risk of recurrence (44% vs. 3%, $p = .000001$) and death (19% vs. 1%, $p = .00005$) (Fig. 30-3) after a median follow-up of 55 months (75). In a second study

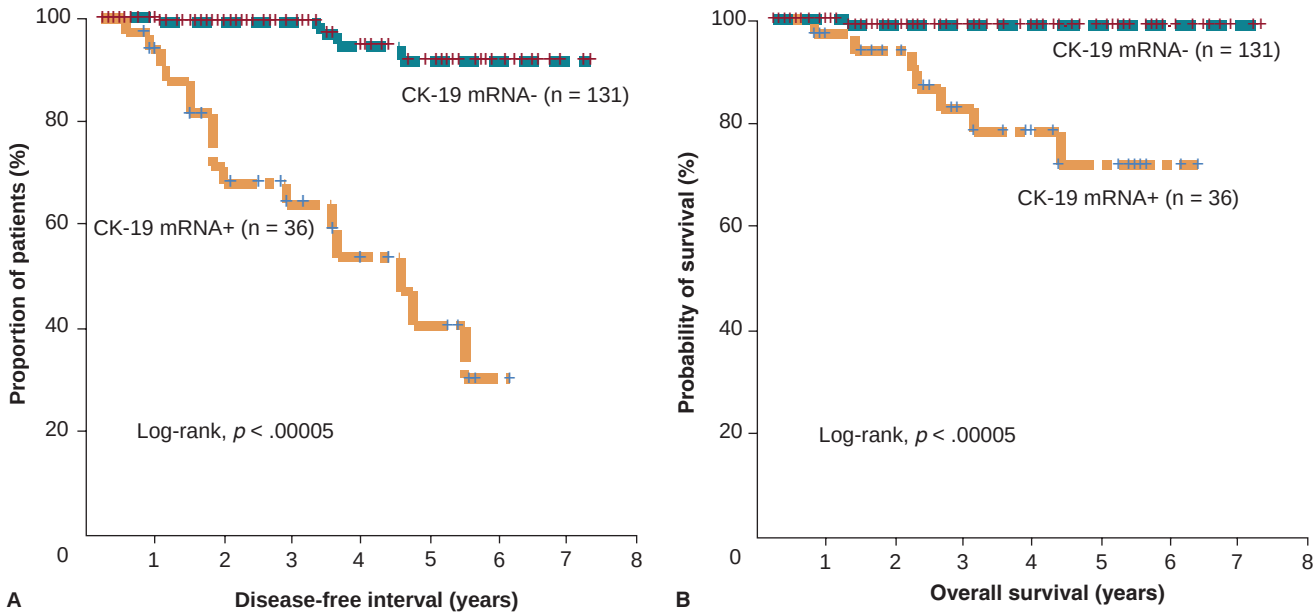

FIGURE 30-3 Outcome of patients with early-stage breast cancer based on circulating tumor cells detected by reverse transcription-polymerase chain reaction assay. (A) Disease-free survival. **(B)** Overall survival. (Adapted from Xenidis N, Perraki M, and Kafousi M, et al. Predictive and prognostic value of peripheral blood cytokeratin-19 mRNA-positive cells detected by real-time polymerase chain reaction in node-negative breast cancer patients. *J Clin Oncol* 2006; 24(23):3756–3762, with permission. Copyright © 2006 American Society of Clinical Oncology. All rights reserved (75).)

by the same investigators but including a higher risk population of 444 patients, CK-19 positive patients were again found to be at significantly higher risk of relapse compared to CK-19 negative patients (30% vs. 15%, $p < .0001$) and death (15% vs. 6%; $p = .001$). In multivariate analysis that included tumor size, lymph node status, and histologic grade, CK-19 positivity was the strongest independent predictor of DFS (HR = 2.4, $p < .001$) and OS (HR = 2.5, $p = .007$) (51).

Other investigators have reported that CTCs as detected by the CellSearch® system are prognostic in early-stage disease (49,50). For example, Lucci et al. reported that 24% of 302 patients with stage 1–3 breast cancer had one or more CTC/7.5 ml whole blood, and that these patients had a higher risk of early recurrence and decreased overall survival (OS) (Fig. 30-4). However, like so many studies in this setting, they did not control for treatment or other variables. Therefore, while this study clearly indicates clinical validity of a highly analytically validated assay for CTCs, it fails to demonstrate clinical utility, as it is not clear exactly who should or should not receive adjuvant systemic therapy.

Several studies have investigated the role of CTCs in the neoadjuvant setting. For the most part, these investigators have shown that persistent detection of CTCs, regardless of the assay, is associated with worse outcome (76–78). However, as with DTCs, none of these studies were designed to determine if this knowledge could or should be used to direct subsequent additional or alternative therapy.

In summary, CTCs appear to be prognostic in early disease in a fashion similar to DTCs, but the clinical utility of this finding is unclear. The results reported to date have been generated in prospective or retrospective registry studies, with no control of primary or adjuvant systemic therapy and no indication of how one might use the data to direct patient care. Although the clinical validity of these findings is of interest, one cannot recommend measurement or use of CTCs in early-stage breast cancer outside of a clinical trial. Indeed, neither the American Society of Clinical Oncology (ASCO) nor the National Cancer Center Network (NCCN) guidelines panels recommends the enumeration of CTCs as either for staging or CTCs in assisting patient care in the non-metastatic setting.

CTCs in Metastatic Disease

Currently, perhaps the most well-established intended use of CTCs is to monitor patients with advanced disease. In this setting, the available assays are reasonably sensitive, and in certain situations, elevated CTCs may be used to help guide clinical decisions.

The majority of clinical outcomes data in the metastatic setting are derived from studies utilizing the CellSearch® assay. In a seminal prospective registry study, 177 patients with metastatic breast cancer who were beginning a new therapy had CTCs determination by CellSearch® and were monitored for outcomes (21). From a training set of 102 patient samples, a level of ≥5 CTC/7.5 mL of whole blood was identified as the threshold that best distinguished progression free survival (PFS) between the two groups. This threshold and its prognostic value were then confirmed in an independent, prospectively collected set of 75 patient samples. Elevated CTCs at baseline predicted extremely short median PFS and OS of 3 and 10 months, respectively. In contrast, patients with <5 CTC/7.5 mL whole blood had median PFS and OS of 7 and 22 months, respectively ($p = .005$). The cumulative effect on prognosis of CTCs at baseline of all patients enrolled in the trial is shown in Figure 30-5A and B.

Although these results are interesting, it is not clear how a pretreatment, baseline CTC prognostic estimate would guide therapy. Based on the worse prognosis inherent in having elevated CTCs at baseline, one might consider an alternative therapy from a previously chosen treatment plan. For example, one might treat a patient with ER-positive breast cancer whose apparent prognosis is quite poor (for example, if she has rapidly progressive visceral disease with end-organ dysfunction) with chemotherapy rather than less toxic endocrine therapy. Likewise, for a patient with hormone refractory disease and very poor prognosis, one might choose to use combination rather than single agent chemotherapy. However, the overall prognosis of patients with elevated baseline CTCs is not as dire as for those with rapidly progressive visceral metastases, and no studies have demonstrated that such an approach is clinically warranted.

Perhaps more interesting, CTC values obtained after one cycle of therapy were associated with even more

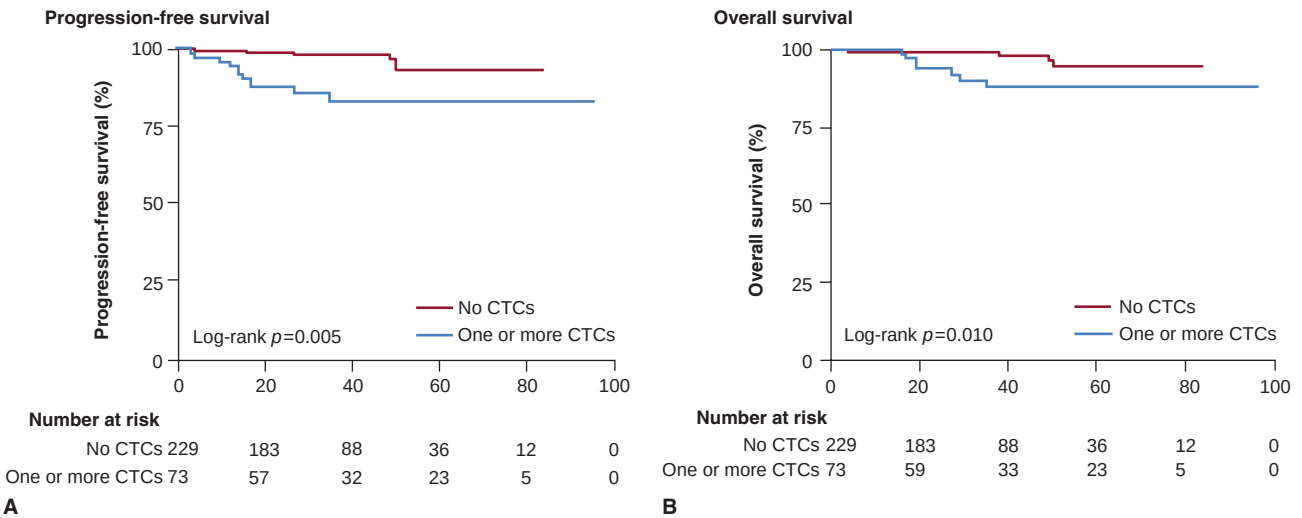

FIGURE 30-4 **Outcome of patients with early-stage operable breast cancer based on circulating tumor cells detected by CellSearch®. (A)** Progression-free survival. **(B)** Overall survival. (Adapted with permission from Lucci A, Hall CS, Lodhi AK, et al. *Lancet Oncol* 2012;13:688–695 with permission Copyright © 2012 Elsevier limited. All rights reserved (50).)

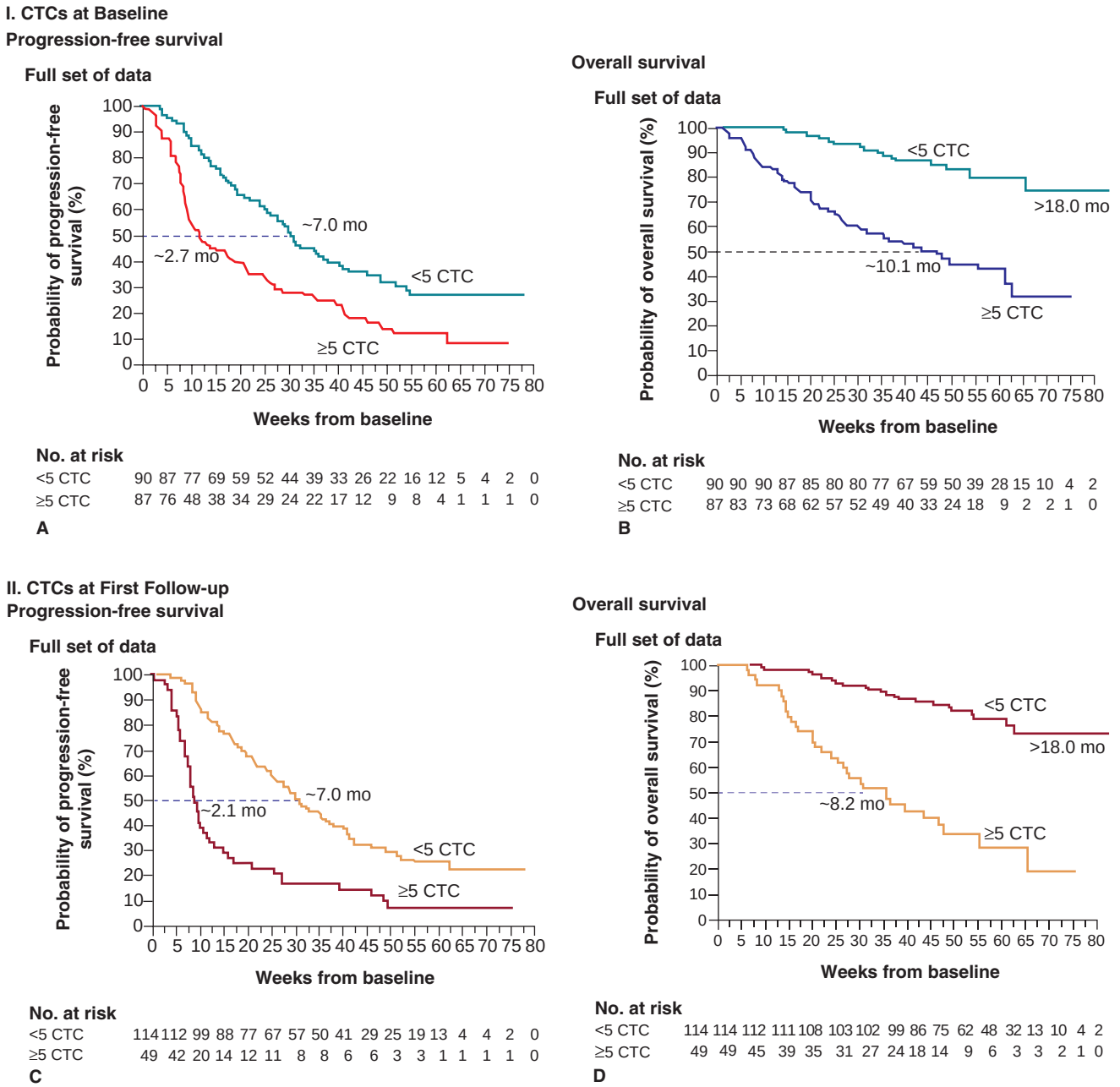

FIGURE 30-5 Outcome of patients with metastatic breast cancer based on circulating tumor cells detected by CellSearch®. I: Baseline before initiation of a new treatment. II: First follow-up after one cycle of a new treatment. **(A), (C)** Progression free survival. **(B), (D)** Overall survival. (Adapted with permission from Cristofanilli M, Budd GT, Ellis MJ, et al. *N England J Med* 2004;351:781–797 with permission Copyright © 2004 Massachusetts Medical Society. All rights reserved (21).)

robust differences in outcomes, suggesting that those with persistent CTCs were likely on ineffective therapy. The incidence of elevated CTCs (≥5 CTC/7.5 mL whole blood) declines from 50% at baseline to approximately 30% at first follow-up after initiation of therapy (3 to 5 weeks) (21,79). In the original Cristofanilli et al. study, those patients with elevated CTCs at this early time point, regardless of whether they had elevated CTCs at baseline, have a substantially shorter median PFS (2.1 vs. 7 months; $p < .001$) and OS (8.2 vs. > 18, $p = .001$) than those who still had elevated CTCs (Fig. 30-5C and D).

The prognostic role of baseline and follow-up CTC results first observed by Cristofanilli, et al. has been confirmed by several other investigators (79–84). A large pooled analysis (80) including 841 patients coming from six different clinical studies has confirmed the prognostic and predictive validity of CTCs assessed before and during therapy. A high level of CTCs before and during treatment was strongly associated with treatment failure irrespective of clinical variables, disease subtype, type, or line of therapy.

The intriguing observation that failure to rapidly clear CTCs early in the course of therapy has led to speculation

that they might be useful to direct an early change to an alternative treatment plan, rather than persisting until classic clinical and/or radiographic evidence of progression. In this regard, a prospective randomized clinical trial has been conducted in the Southwest Oncology Group (SWOG S0500) to test whether women with metastatic breast cancer who have elevated CTCs after one cycle of first line chemotherapy have improved outcomes as a result of switching early to an alternate therapy (Fig. 30-6). This trial is based on the hypothesis that these patients will have improved outcomes by minimizing the time and toxicity spent on ineffective therapies and by spending more time on effective therapy. Results from this study are expected in late 2013 or early 2014. A similar study is currently ongoing in France (85).

Although preclinical studies have suggested that anti-EpCAM capture strategies such as CellSearch® might be less sensitive or prognostic in basal, or "triple negative," breast cancers, the results from several clinical studies suggest a similar likelihood of having elevated CTC levels and worse outcomes regardless of the hormone receptor or HER2 status of the patient's primary cancer (21,80). However, the assay may not be as prognostically robust for selected subsets. For example, in the original Cristofanilli et al. study, PFS and OS for patients initiating hormonal therapy were similar regardless of baseline CTC levels (21). However, CTCs evaluated at first follow-up in this subset after initiating hormonal therapy predict substantial differences in median PFS (2.3 vs. 8.3 months, p = .15) and OS (10.9 vs. >18 months, p = .002). Although the PFS comparison was not statistically significant, it suggests that CTCs may be able to distinguish patients who are on ineffective hormonal therapy. The subset of patients starting hormonal therapy was small (n = 53), so, the analysis in patients on hormonal therapy was likely unpowered and requires further investigation. Because of the lack of strong statistical significance in the hormonal therapy group, the FDA cleared indication for the CTC assay limited to women undergoing chemotherapy for metastatic breast cancer.

Further analysis of these data suggests that the prognostic value is independent of the line of chemotherapy. The original Cristofanilli et al. (21) publication presented combined data for all patients receiving any line of therapy. Approximately half of these patients were receiving first-line therapy, and a subsequent publication demonstrated that the prognostic information was the same in patients receiving first-line therapy (86).

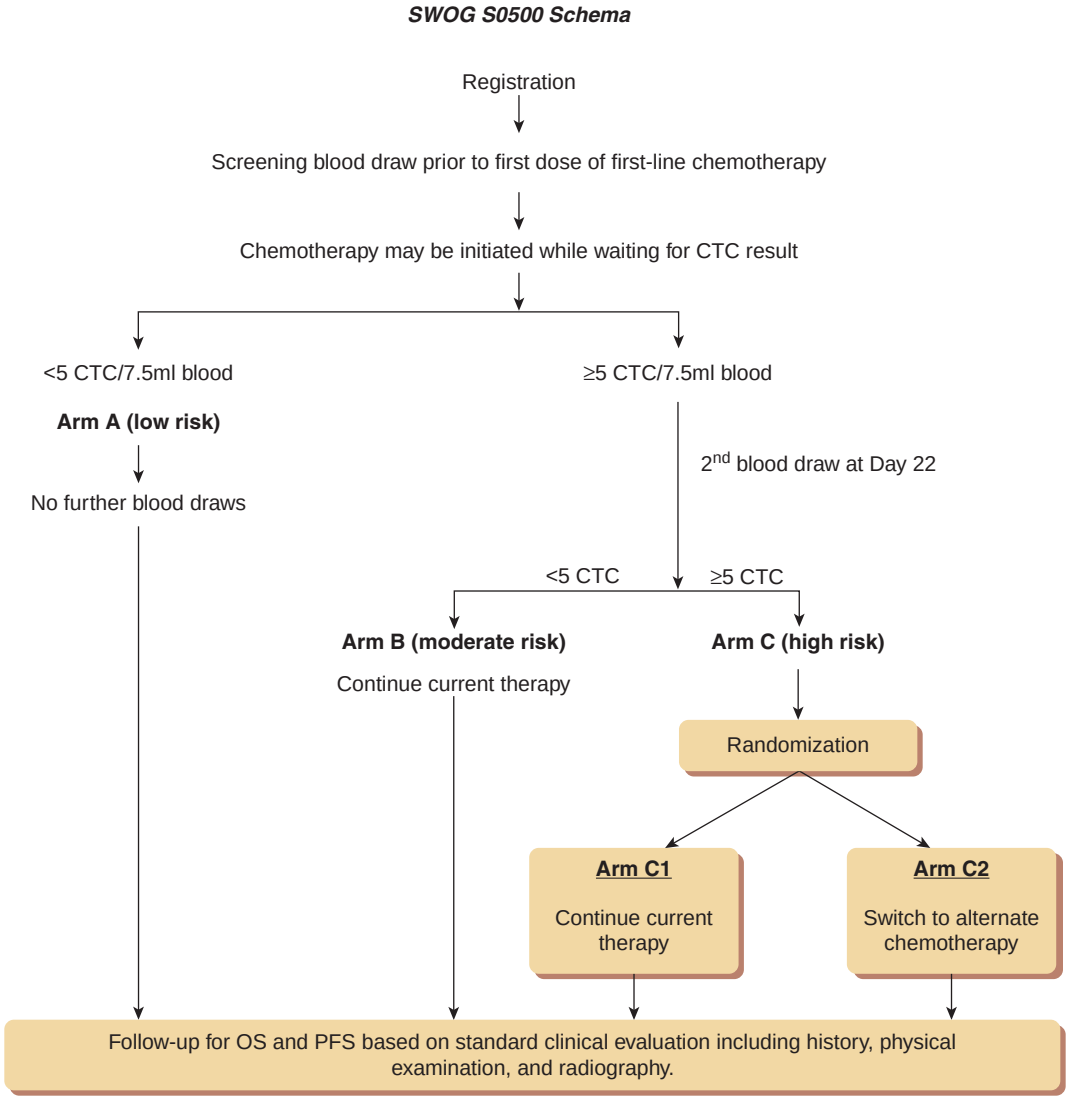

FIGURE 30-6 Schema for Southwest Oncology Group (SWOG) S0500.

Subsequent reports have suggested that elevated CTC levels at any time point are associated with a much higher likelihood of rapid progression (within the succeeding few months) when compared to patients who do not have elevated CTC (79,83). CTC data may be of particular utility as an objective measure to determine progression in patients with non-measurable forms of metastatic breast cancer, which is often subjective, subtle, and difficult. De Giorgi et al. (87) reported that CTC enumeration at follow-up correlated with ^{18}F-FDG PET/CT findings in 78% of the 55 evaluable patients. ^{18}F-FDG-PET/CT findings and follow-up CTC counts were found to be significantly associated with both PFS and OS. Although in multivariate analysis, ^{18}F-FDG PET/CT findings remained as the only predictive factor for OS, the combination of ^{18}F-FDG PET/CT and CTC count might be a potential tool to monitor response to therapy in patients without measurable disease. Rather than performing serial radiographic or scintigraphic imaging, one might use history, physical examination, standard serology (in particular liver function tests), circulating tumor markers (such as MUC1 and/or carcinoembryonic acid assays), and CTCs. If all of these are negative, it appears that the odds of image-documented progression within the next few months are very low, and it is very unlikely that additional inconvenience and cost of imaging would be of value.

More than 50% of patients with metastatic breast cancer do not have measurable disease. Thus, determination of response is quite difficult, and the eligibility requirements for many phase II clinical trials exclude such patients. CTC levels reductions during follow-up may be more predictive of subsequent OS than classically used measures of response, such as history, physical examination, or staging radiographs, even when read by independent reviewers (88). This observation suggests that, in the future, CTC levels might be used in clinical trials to determine response to new drugs or strategies, thus opening accrual to patients who do not have RECIST-defined measurable disease and are currently excluded from participation.

In summary, taken together, the data at present suggest that there is a limited role for monitoring CTCs in the metastatic setting, and the ASCO Tumor Marker Guidelines Committee did not recommend this utility. However, the accumulated data support using CTCs to complement standard circulating markers such as CA15-3, CA27.29, and CEA to monitor patients who have been on a given therapy for some time to help guide whether treatment should be continued without interruption or whether the patient should have restaging imaging to determine if she does or does not have progression (83).

DTCS AND CTCS: PHENOTYPING AND GENOTYPING AND FUTURE RESEARCH

The preceding discussions all point to the potential importance of enumerating DTCs and CTCs in patients with breast cancer. They also, however, highlight the concerns about sensitivity and, in particular, technical and biological specificity. Indeed, the ability to characterize captured CTCs may give insight into which detected cells have true malignant potential and which are more likely impotent, terminally differentiated cells that are detected but have no biological importance.

Breast cancer, perhaps of all the known and treatable malignancies, is a disease for which targeted therapies have been most useful, in particular directed against the estrogen receptor (ER) and ERBB2 (formerly HER2). For example, several recently reported studies have demonstrated that up to 15% of metastases in patients whose original cancer was considered HER2 negative are HER2 positive (89). Taken together, these considerations illustrate the need to not only count *events*, but better characterize the genotype and phenotype of these cells.

Many investigators have developed methods to detect and monitor biologically important markers in both DTCs and CTCs. Genetic changes can be detected in CTCs, including abnormal telomerase activity (90), allelic loss, and/or amplification of multiple oncogenes (91), and aneuploid changes in cellular chromosome content based upon FISH analysis similar to those seen in the primary tumor (54). Indeed, using genome-wide copy number analysis, Magbanua et al. have demonstrated that when compared to matched archival primary tumor, copy number aberrations in CTCs from over 100 patients with metastatic breast cancer have both conserved and divergent genomic alterations (92). Moreover, a recently reported study has demonstrated that overall levels of free DNA are prognostic compared to control levels; that specific mutations in important genes, such as PIK3C can be detected and monitored over time; and that these mutations seemed to correlate with those detected in the patients' cancer (93). In this small study, serial levels of free DNA appeared to be more robust than serial levels of either circulating MUC1 protein (CA15-3) or CTC (CellSearch®). These exciting preliminary results require further conformation to determine whether they have clinical utility for a specific clinical use (94).

Cancer-associated protein expression by DTCs and CTCs can be also be determined, such as HER2 (55,77,95–102), ER (40,103–106), epidermal growth factor receptor (EGFR) (107), MAGE, phosphorylated FAK, the PI3K protein (108), androgen receptor (109), insulin-like growth factor (110), and BCL2. Moreover, using a monoclonal antibody (M30) that detects a neo-antigen exposed in fragmented but not full-length cytokeratin, CTCs undergoing apoptosis can be identified and monitored (111,112).

These molecular markers might be used either as pretreatment predictors of response to targeted therapies, such as antiestrogen or anti-HER2 strategies, or as pharmacodynamics indicators that the therapy is hitting its target, if it results in a known biomarker change such as downregulation (108,113). Investigators have also demonstrated early successes in gene expression profiling (114) and multiplex RT–PCR (115) from CTCs. As each of these methodologies becomes more sophisticated, the ability to isolate, detect, and phenotype these cells will continue to improve.

Characterization of CTCs may also provide insight into the biology and heterogeneity of the metastatic process (116). For example, dormancy and late relapse, especially in patients with luminal cancers, have presented a particularly enigmatic circumstance to clinicians caring for breast cancer patients. As noted previously, DTCs and CTCs can be detected in patients long after prior treatment for early-stage breast cancer. Although this finding is prognostic, many such patients remain free of clinical recurrence (47,55,95,117). Furthermore, many investigators are examining putative stem cell markers, and markers of EMT, that might distinguish CTCs with malignant potential versus those that are impotent (118–122). None of these has as yet gained clinical utility, but they promise to provide even more specific diagnostic tools and perhaps avenues of research for targeted therapies.

Taken together, these results further emphasize the importance of understanding the concept of "biological" false positive findings. In other words, these patients appear to have detectable CTCs but no evidence of progressive disease, living in symbiosis with apparently dormant

metastatic cancers. A more sophisticated understanding of the subsequent changes that may be responsible for late relapses either in the cancers cells themselves or surrounding microenvironment could help select patients who might benefit from extended adjuvant therapy with standard agents, such as antiestrogen therapies, or even novel strategies directed toward the potential driving factors.

SUMMARY

Detection and enumeration of MDD in patients with breast cancer have been of great interest. Several studies have demonstrated the clinical validity of determining the presence or absence and relative quantification of MDD; however, the clinical utility remains elusive for most intended uses. Perhaps the only acceptable use of CTCs is to monitor patients with established metastatic disease to determine whether they are doing well on a given therapeutic approach; or, if CTCs are rising, whether they should have staging imaging performed to evaluate for progression.

However, prospective randomized trials in the adjuvant and metastatic settings are addressing further clinical utilities in other intended uses, such as consideration of an early change in a metastatic regimen. Perhaps more importantly, molecular characterization of DTCs and CTCs might serve as a "liquid biopsy," with exciting implications for treatment based on the real-time biologic and clinically relevant biomarker status of the CTCs. Future trials designed to address clinical utility of DTCs and CTCs are needed to have an impact on patient care.

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SECTION VII

Management of Primary Invasive Breast Cancer

CHAPTER 31

Evaluation of Patients for Metastasis Prior to Primary Therapy

Polly Niravath and C. Kent Osborne

CHAPTER CONTENTS

After the diagnosis of breast cancer is established, subsequent evaluation for metastatic disease prior to initiation of primary therapy is a somewhat controversial topic. High-quality evidence in this regard is unfortunately lacking; therefore, there is not a common, standardized approach to staging among practitioners in the United States. However, staging clearly does have important implications on both prognosis and treatment. This chapter aims to shed light on the available evidence to support staging for newly diagnosed breast cancer.

The danger of an overly aggressive staging approach is likely greater than the risks of a more judicious staging philosophy. Increased staging examinations impose unnecessary financial expense on the health care system. Especially when considering the sheer number of breast cancer patients, the societal and economic cost of "overstaging" is quite considerable; worldwide, approximately 1.15 million new cases of breast cancer occur each year (1). Furthermore, many staging modalities are likely to lead to "false positives" that result in needless biopsies that pose potential danger to the patient's health, invoke patient anxiety, increase health care costs, and delay essential treatments.

Currently, in the United States, staging with advanced imaging modalities is becoming more common for early stage breast cancer patients. A review of Medicare records shows that 18.8% of women with stage I or II breast cancer had CT scans, PET scans, and/or brain MRI as part of a staging workup. The use of preoperative staging CT scan increased from 5.7% to 12.4% between 1992 and 2005, and the use of PET scans increased from 0.8% to 3.4% in the same time period. Brain MRI increased from 0.2% to 1.1%, but bone scans actually declined from 20.1% to 10.7% (2). Although the data do not necessarily support staging asymptomatic patients with early stage breast cancer, this practice is clearly increasing in the United States, which leads to increased medical costs and procedures. Also, the use of preoperative CT scans and bone scans have been shown to significantly delay the time from initial breast complaint to the time of breast surgery (3). If the imaging uncovers false positives, delays will, of course, be even longer because biopsies or confirmatory imaging is often ordered as a result of an abnormal staging examination. These delays in the time to surgery represent a needless decrease in the quality of breast cancer care.

INITIAL EVALUATION

After a patient has had a breast biopsy that establishes the diagnosis of breast cancer, the physician should perform a thorough history and physical exam, including complete review of systems. Routine blood tests, including complete blood count and comprehensive metabolic panel, should also be done at this time. If the patient appears to have early stage disease and the evaluation discussed does not indicate distant metastatic disease, then there is no need for preoperative advanced staging modalities. However, if a patient does have signs or symptoms of possible metastatic disease, such as weight loss, bone pain, persistent cough, or elevated alkaline phosphatase, appropriate staging studies should be done at the physician's discretion (see Fig. 31-1).

In the case of patients with locally advanced disease at the time of diagnosis (T2 or larger lesions or palpable lymphadenopathy), neoadjuvant therapy may be an appropriate approach for them. In this case, it would be prudent to obtain staging prior to starting neoadjuvant therapy with CT scan with contrast of the chest, abdomen, and pelvis as well as bone scan.

For those patients who are not receiving neoadjuvant therapy, however, the risk of distant metastasis is better evaluated based on surgical pathologic criteria, such as tumor size and degree of lymph node involvement. Thus, in cases of small breast cancers that are not amenable to neoadjuvant therapy, decisions regarding staging evaluations are best made after surgery because the pathologic stage of the cancer should inform the choice of staging modalities. In this way, many patients with earlier stage disease can be spared unnecessary imaging procedures, and only those with highest risk of disease will receive advanced staging evaluation. Although it is true that some patients with occult metastatic disease may undergo breast surgery prior to discovering the

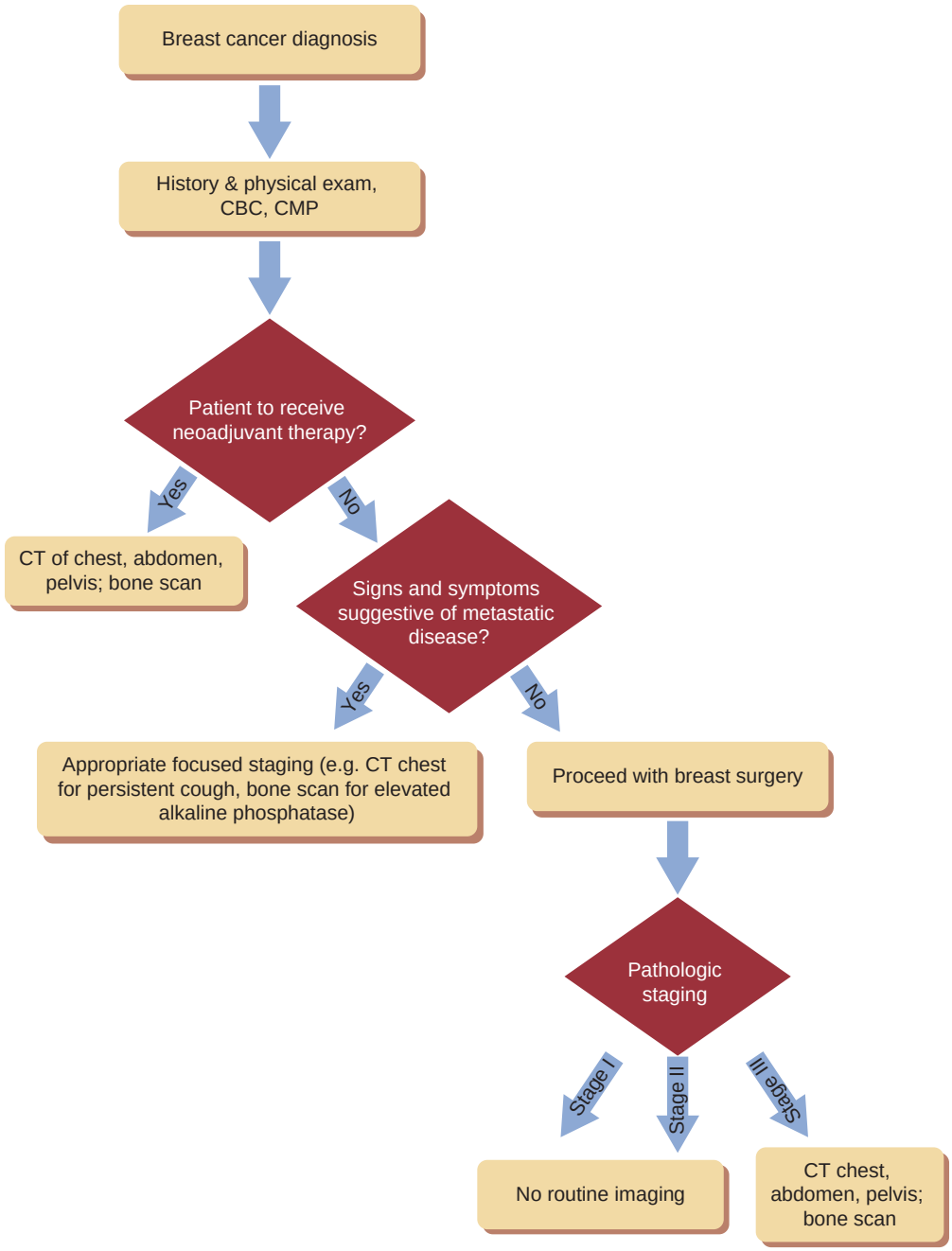

FIGURE 31-1 Proposed staging algorithm.

metastases, there may be some benefit from breast surgery for these patients because retrospective studies have shown increased overall survival in those metastatic patients who have had mastectomy with negative margins at the time of diagnosis (4,5). However, preliminary data from two randomized trials in Turkey and India suggest that there is no overall survival advantage to mastectomy for metastatic patients (6,7), but definitive conclusions about the role of surgery in this setting await additional data. In the meantime, surgery to control local disease is also an important endpoint.

EVALUATION OF THE IPSILATERAL AND CONTRALATERAL BREASTS

At the time of breast cancer diagnosis and prior to breast surgery, each woman should have a bilateral breast exam and mammogram to exclude multicentric disease within the same breast as well as contralateral breast cancer. Depending on the density of the woman's breast and the discretion of the radiologist, breast ultrasound may also be pursued. Ultrasound also affords the possibility to look at the axillary lymph nodes in greater detail than the mammogram does. Please refer to Chapter 12 for more information regarding the use of breast ultrasound in the diagnosis of breast cancer.

Breast MRI is likely the most sensitive imaging modality for comprehensively evaluating the breasts prior to surgery. A large meta-analysis of more than 2,600 newly diagnosed breast cancer patients discovered that 16% of them were found to have additional foci of malignancy in the affected breast. Furthermore, 11.3% converted from wide local excision (WLE) to more extensive surgery, which may have been wider excision or mastectomy. Specifically, 8.1% of the total

group converted from WLE to mastectomy. Conversely, surgery was changed from WLE to mastectomy because of a false positive in 1.1% of women, and surgery was changed from WLE to more extensive excision in 5.5% of patients for a false-positive finding. In this study, for every three women who were found to have additional lesions on MRI, one of the three proved to be a false positive (8).

These risks and benefits are perhaps better weighed when one takes into account the histology of the tumor. It is well known that lobular cancers tend to be more often multicentric and mammographically occult (9). Theoretically, when isolating a high-risk population such as this, the potential benefits of breast MRI may be greater. One retrospective study of 267 breast cancer patients found that 25.5% of patients had more extensive surgery because of preoperative MRI findings. Among these patients, 29% turned out to have had no pathologic verification on surgical specimen to justify the additional surgery. However, when the small subset of lobular carcinoma was studied, 11 of 24 (46%) patients with lobular carcinoma had a change in management because of MRI findings. Furthermore, 9 of these 11 patients had pathologic verification of additional malignancy at the time of surgery, yielding an 82% sensitivity (10). However, it must be noted that ultrasound was not evaluated in this study. In practice, ultrasound is commonly used in conjunction with mammogram to define the extent of disease. Future prospective studies are needed to compare the sensitivity and specificity of combined mammogram and ultrasound to that of breast MRI. Also, it is unknown whether the wider excisions and mastectomies that were prompted by MRI findings would have proven to be clinically relevant. Because almost all women who have lumpectomies will receive adjuvant radiation, it is not known whether the additional surgery truly does lower local recurrence rate as compared to adjuvant radiation. Nonetheless, women with lobular carcinoma may be more likely to have other areas of disease uncovered by MRI, and they are less likely to have false-positive MRI results. Based on the available evidence, breast MRI may be pursued at the physician's discretion in cases of lobular cancer, particularly in the case of a woman with dense breasts on mammogram or high probability of breast cancer. Please refer to Chapter 13 for more information on breast MRI.

BASIC STAGING FOR SYSTEMIC DISEASE (BONE SCAN, LIVER ULTRASOUND, AND CHEST X-RAY)

The scarce data available regarding staging practices in the Unites States reveal that approximately 88% of physicians routinely order staging chest x-rays for all newly diagnosed breast cancer patients, and 39% routinely order bone scans (11). However, the evidence does not support this approach. A systematic review examined the utility of chest x-rays, bone scans, and liver ultrasounds in staging asymptomatic breast cancer patients who have just undergone breast surgery for clinical stage I–III disease (12). The results, among others, are summarized in Table 31-1 (12–16). Clearly, the yield of these staging procedures in uncovering metastatic disease is quite low, particularly in stage I and II disease, and especially when weighed against the risk of false positives, which often necessitate biopsies and provoke anxiety. In fact, when reported, the rate of false positives was far higher than the rate of true positives for all three staging examinations in stage I and II patients.

Based on the available data, routine staging for breast cancer patients with stage I and II disease with bone scan, chest x-ray, and liver ultrasound is not necessary, and it is more likely to lead to false positives than true positives.

CT SCAN

Although chest x-rays, bone scans, and liver ultrasounds clearly have limited utility in evaluation for metastatic disease in early stage patients, many practitioners more commonly use computed tomography (CT) scans of the chest

TABLE 31-1

Metastases Discovered from Staging Studies

		Bone Scan	*Liver Ultrasound*	*Chest X-Ray*
Myers et al. (10)	Stage I	0.5%	0%	0.1%
	Stage II	2.4%	0.4%	0.2%
	Stage III	8.3%	2.0%	1.7%
	False positives	10–22%	33–66%	0–23%
Puglisi et al. (11)	Stage I	5.1%	0%	0%
	Stage II	5.6%	0%	0%
	Stage III	14%	5.7%	7.3%
	False positives	6.1%	6.3%	3.0%
Koizumi et al. (12)	Stage I	0.08%	N/A	N/A
	Stage II	1.09%	N/A	N/A
	Stage III	9.96%	N/A	N/A
Lee et al. (13)	Stage I	0.7%	N/A	N/A
	Stage II	0.6%	N/A	N/A
	Stage IIIA	4.6%	N/A	N/A
Kasem et al. (14)	Stage I	0%	1.6%	N/A
	Stage II	4.1%	1.4%	N/A
	Stage III	0%	0%	N/A
	False positives	11.8%	2.7%	N/A

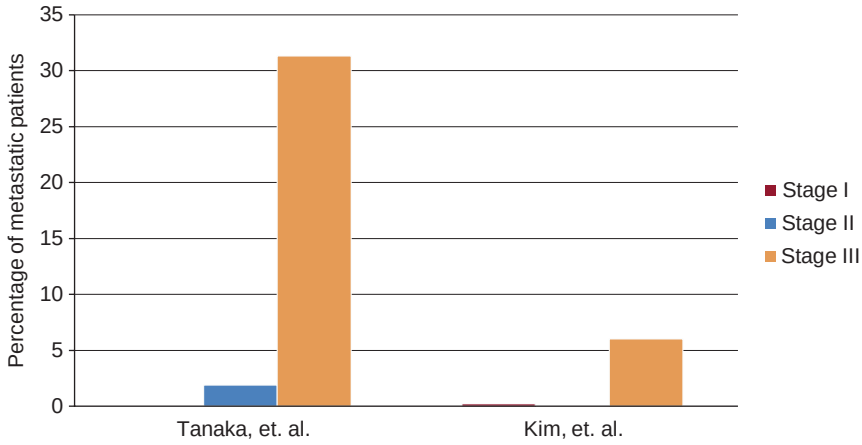

FIGURE 31-2 Metastatic discovery rate as discovered by CT scan. (Data from Tanaka S, Sato N, Fujioka H, et al. Use of contrast-enhanced computed tomography in clinical staging of asymptomatic breast cancer patients to detect asymptomatic distant metastases. *Oncology Letters*. (2012;3(4):772–776; Kim H, Han W, Moon H, et al. The value of preoperative staging chest computed tomography to detect asymptomatic lung and liver metastasis in patients with primary breast carcinoma. *Breast Cancer Res Treat*. 2011;126(3): 637–641.)

and abdomen to stage newly diagnosed breast cancer patients. Within a single institution, retrospective analysis of staging CTs among asymptomatic, newly diagnosed patients yielded newly discovered metastatic disease in 0% of stage I, 1.9% of stage II, and 31.3% of stage III breast cancer patients (17). Another single institution retrospective analysis revealed similar results. Among 1,703 asymptomatic, newly diagnosed breast cancer patients who had preoperative chest CTs that included the liver, 15.6% had an abnormality discovered in the lungs or liver although only 1.5% of the total patients had true metastases. The study did not state how many biopsies were performed for false-positive findings. True metastases were found in 0.2% of stage I patients, 0% of stage II patients; and 6% of stage III patients (18). Thus, there is utility in performing CT scan for stage III patients; however, the risks, including increased medical costs, radiation exposure, and potential for needless biopsies, likely outweigh the benefits in stage I and II patients (see Fig. 31-2). Special caution should be taken in appropriately staging new breast cancer patients.

PET SCAN AND PET/CT

2-18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scans are a somewhat controversial topic within breast cancer staging with new evidence still emerging. A recent prospective Canadian trial of 325 breast cancer patients evaluated PET scan for uncovering axillary lymph node metastases as well as distant metastases. Although PET scans had high specificity for axillary metastasis, the sensitivity was only 23.7%. Furthermore, PET scan uncovered 0.9% of patients with distant metastases and identified 3% of patients with false positives (19). Similarly, another prospective study showed that PET scan had only 61% sensitivity and 80% specificity for detecting axillary lymph node metastases (20). Clearly, current data suggest that PET scan does not have the necessary sensitivity in the axilla, or the specificity in the rest of the body, to be used as a reliable staging tool.

However, PET scan continues to be studied, and it may play a role in the future in a select subset of patients. For example, those with a higher pretest probability of having metastatic disease are more likely to have metastatic disease uncovered through PET scanning. One prospective study examined 48 women with locally advanced breast cancer (tumors greater than 5 cm, fixed axillary lymph nodes, or inflammatory breast cancer) who had been conventionally staged with chest x-ray, bone scan, and liver ultrasound, or CT scan of the chest and abdomen. Researchers discovered that among patients who had no evidence of metastatic disease on these examinations, 14 of 48 had abnormal FDG uptake, and metastases were suspected in 12 patients, or 25% of the study population. Of these, four patients (8.3%) were found to harbor true metastatic lesions (21). In this particular subset, there may be an advantage of PET scan in detecting occult metastatic disease, but this must be weighed against the risk of false positives that often provoke anxiety and prompt invasive biopsies.

Currently, however, PET/CT scanning is used much more commonly than routine PET scan. PET/CT scan combines PET scan and noncontrast CT scan, allowing for more precise correlation of increased metabolic activity with anatomic imaging. One recent study prospectively examined 103 women with newly diagnosed breast cancer with tumors ≥2 cm. All patients had routine examinations (physical examination, mammography, ultrasound of breast and axilla, chest x-ray, and blood parameters) as well as PET/CT prior to operation. PET/CT displayed a 63% sensitivity and a 97% specificity for axillary lymph node detection, and it was not able to detect any micrometastases. Perhaps most importantly, however, none of the axillary lymph node metastases were discovered only on PET/CT; routine staging examination uncovered all lymph node involvement prior to the surgery. However, PET/CT did identify six cases (5.8%) of distant metastatic cancer that would not have been discovered otherwise, and this information did prompt a change in management from adjuvant to metastatic approach. All six cases that proved to be metastatic on PET/CT scan initially had stage II disease. The PET/CT scan also uncovered two new primary malignancies (ovarian cancer and lung cancer) and seven patients who were found to have supraclavicular or internal mammary lymph nodes; however, management and staging of the breast cancer did not change for these nine patients. Essentially, in terms of breast cancer treatment, PET/CT prompted an important change in management in 5.8% of cases (22). However, it is unclear whether PET/CT scan was truly necessary to uncover these metastatic sites because CT scan may have potentially made the same discoveries, but none of the patients had CT scan prior to PET/CT in this study.

Based on a meta-analysis of five studies investigating both conventional imaging (chest x-ray, bone scan, ultrasound, and CT scans) and PET scans or PET/CT scans, the latter was found to have higher median sensitivity for axillary lymph node involvement and distant metastases at 98.7% as compared to conventional imaging sensitivity of 70%. However, specificity data were more variable for PET scanning (23). Consequently, the NCCN Task Force Report

on the use of PET/CT in cancer states that there is no role for PET/CT scan in detection of primary breast cancer, staging of the axilla, searching for distant metastatic disease, or performing posttreatment surveillance (24). Although further research is ongoing at this point, the authors also believe that PET and PET/CT scans should not routinely be used for staging newly diagnosed breast cancer patients at this point.

TUMOR MARKERS

Tumor markers that are sometimes elevated in breast cancer include CA 15-3, CA 27.29, and CEA. Although elevated levels of these markers at the time of breast cancer diagnosis have been shown to correlate with early relapse and death from disease, results have been somewhat conflicting (25–27). Thus, their use as a prognostic marker in the newly diagnosed breast cancer patient is debatable. More importantly, however, these markers have never been proven to be predictive of benefit from treatment. Because they are not likely to change treatment and their interpretation in the setting of early stage disease is unclear, serum breast cancer tumor markers are not recommended as part of routine staging for patients with stage I to III breast cancer (28).

CIRCULATING TUMOR CELLS

Circulating tumor cells (CTCs) may be found in the blood of some breast cancer patients at the time of diagnosis or at any point afterward. These CTCs are believed to represent very early hematogenous dissemination of cells from the breast cancer into the blood. Several methods may be used to enumerate CTCs, although one of the most commonly used methods, which the Food and Drug Administration has also approved, is the CellSearch method. In this method, 7.5 mL of blood is enriched for cells containing the epithelial cell adhesion molecule (CAM)® by using antibody-coated magnetic beads. Then the cells are selected for the ones that are nucleated and stain positive for cytokeratin but negative for CD45 (29). In this way, CTCs can be quantitated per 7.5 mL blood sample. Although baseline levels of circulating tumor cells have been proven to be prognostic for progression-free and overall survival in patients with metastatic breast cancer (30), their significance in early stage breast cancer is less clear. Approximately 10% to 24% of patients with nonmetastatic breast cancer have one or more circulating tumor cells in their blood prior to beginning systemic therapy (29,31). One prospective, single institution study examined 302 patients with stage I to III breast cancer at the time of definitive breast surgery. They found that 24% of patients had at least one circulating tumor cell per 7.5 mL of blood, and at a median follow-up of 35 months, which was associated with poorer progression-free survival (HR 4.62, 95% CI 1.79–11.9) and overall survival (HR 4.04, 95% CI 1.28–12.8) (29). Interestingly, no primary tumor characteristic, including tumor size or pathologic lymph node status, accurately correlated with presence of 1 or more circulating tumor cells. More CTCs had stronger correlation with poor prognosis. Three CTCs as compared to none yielded the sharpest difference in 3-year overall survival with 81% versus 99%. Only 5% of the patients in this study had ≥3 involved lymph nodes (29). Similarly, the SUCCESS trial showed poor prognosis for patients with the presence of circulating tumor cells in the blood at the time of surgery (33). Although CTC quantitation may offer prognostic information at the time of staging, the evidence does not support changing management as a result of baseline circulating tumor cells. In fact, an analysis of the GeparQuattro trial suggested that CTC decline from the time of diagnosis to the completion of neoadjuvant chemotherapy did not correlate with response (32). Thus, it is not recommended as part of routine staging for nonmetastatic breast cancer, and whether it can be used in the adjuvant or neoadjuvant settings to assess response to chemotherapy is not yet clear. See Chapter 30 for more details.

DISSEMINATED TUMOR CELLS

Disseminated tumor cells (DTCs) are cells that are genotypically and phenotypically similar to breast cancer stem cells; these cells are also sometimes called bone marrow micro-metastases. These DTCs are found in the bone marrow of 31% of stage I to III breast cancer patients, and it is associated with poorer overall survival and distant disease-free survival. Those who have DTCs are more likely to have tumors of larger size and higher grade as well as lymph node positivity. However, in multivariable analysis, the presence of DTCs was found to independently be a poor prognostic factor, which is associated with an increase by a factor of 1.93 (95% CI, 1.58–2.36, p value <.001) in death from breast cancer (34). When weighing the issues of cost as well as patient pain and inconvenience from bone marrow biopsy against the relative lack of predictive information provided by DTC enumeration, the procedure is not believed to be warranted in the routine staging of newly diagnosed breast cancer patients at this point.

A SPECIAL WORD ON HIGH-RISK POPULATIONS

Some populations may benefit from more aggressive staging because their pretest probability of metastatic disease is far higher than that of the average breast cancer patient. Patients with inflammatory breast cancer, for example, may be more likely to have metastatic disease discovered on PET scan. One retrospective study that investigated 40 women with unilateral inflammatory breast cancer found that 20 patients had metastatic disease discovered on PET/CT scan, and 7 of these were not known to have had metastatic disease prior to the PET/CT scan. However, of the 20 patients with metastatic disease uncovered on the PET/CT scan, only seven had biopsy confirmation of metastatic disease (35). In a prospective study, 59 women with inflammatory breast cancer were staged with PET/CT scan, and 18 of them (31%) were found to have distant metastatic disease although these metastases were not confirmed by tissue biopsy. Twelve of the patients had metastatic disease *confirmed* by conventional imaging (CT scan and bone scan) (36). Nonetheless, future study in this area may be interesting because women with inflammatory breast cancer tend to have FDG-avid disease, and they have a high probability of metastatic disease.

Similarly, women with four or more positive lymph nodes are much more likely than those with N0 or N1 disease to have distant metastatic disease (37). Staging procedures on these patients is more likely to produce true positives.

SOCIETAL RECOMMENDATIONS

The Cancer Care Ontario Practice Guidelines recommend no routine staging for stage I breast cancers; bone scan only for stage II breast cancer (chest x-ray and liver ultrasound may

be considered for patients with four or more positive lymph nodes); and bone scan, liver ultrasound, and chest x-ray for stage III patients (10). Likewise, the European Society of Medical Oncology (ESMO) recommends staging only with chest x-ray, bone scan, and abdominal ultrasound or CT if the patient has clinically positive axillary lymph nodes, tumor size >5 cm, or clinical signs suggestive of metastatic disease. The National Comprehensive Cancer Network (NCCN) guidelines for breast cancer state that routine baseline staging should be considered for stage IIIA (T3 N1 M0) disease. They recommend a chest CT, abdominal CT (or MRI with or without the pelvis included), and bone scan or fluoride PET/CT. FDG PET/CT is considered optional and is generally used as an adjunct when standard studies are ambiguous; this carries a level 2B recommendation. Furthermore, the NCCN recommends against the use of PET/CT scan for stage I to II patients (38).

MANAGEMENT SUMMARY

- All patient evaluations for breast cancer should begin with a thorough history and physical exam, including a complete review of systems as well as basic laboratory data.
- If the workup does not indicate possible metastatic disease, then surgery should be pursued.
- Those patients who are found to have stage I disease do not need staging examinations.
- Patients with pathologic stage II disease do not routinely need staging examinations. Those patients with multiple positive nodes and unfavorable tumor features may be considered for staging.
- Patients with stage III breast cancer do have a fairly high probability of metastatic disease, warranting the use of routine staging to include bone scan and CT of the chest, abdomen, and pelvis.
- Certain patients with high-risk tumors, such as those with inflammatory breast cancer, may benefit from aggressive preoperative staging, including PET/CT scan.
- PET/CT scans are still being studied for breast cancer staging and should not be routinely used at this point.
- Tumor markers, circulating tumor cells, and disseminated tumor cells should not be used in the staging of newly diagnosed, nonmetastatic breast cancer patients.

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CHAPTER 32

Staging of Breast Cancer

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CHAPTER CONTENTS

Staging refers to the grouping of patients according to the extent of their disease. Staging is useful in (a) estimating prognosis for an individual patient, (b) comparing the results of different treatment programs, and (c) it may help in selecting treatment for an individual patient. Staging can be based on either clinical or pathologic findings. The staging of cancer is determined by the American Joint Committee on Cancer (AJCC). The AJCC comprises six founding organizations, four sponsoring organizations, and seven liaison organizations. Membership is reserved for those organizations whose missions or goals are consistent with, or complementary to, those of the AJCC. The founding organizations include the American Cancer Society, the American College of Surgeons, the American Society of Clinical Oncology, Centers for Disease Control and Prevention, National Cancer Institute, and the College of American Pathologists.

The AJCC staging system provides a strategy for grouping patients with respect to prognosis. The AJCC system uses the TNM classification where **T** describes the size of the primary and whether it has invaded nearby tissue, **N** describes the nearby (regional) that are involved, and **M** describes distant metastases. However, TNM staging, while still important, has been superseded by rapidly evolving molecular characterizations of breast cancers, which more precisely define subgroups with different outcomes, both in terms of prognosis and response to specific treatments. Therapeutic decisions are now formulated in part according to staging categories, but primarily according to tumor size and grade, lymph node status, estrogen-receptor and progesterone-receptor levels in the tumor tissue, human epidermal growth factor receptor 2 (*HER2/neu*) status, menopausal status, and the general health of the patient. Since the last edition, the development and use of multi-gene diagnostic tests, such as Oncotype Dx® and MammaPrint®, have increased substantially and it is anticipated that there will be further developments along these lines.

Staging is still important to determine whether the patient is operable. Generally, any patient with Stage 3B (or 4) is not considered operable. Such patients are treated with initial systemic therapy, discussed in the chapter on locally-advanced and inflammatory breast cancer (Chapters 58 and 59).

The AJCC system is both a clinical and pathologic staging system and is based on the TNM system, in which "T" refers to tumor, "N" to nodes, and "M" to metastasis. The current version is the Seventh Edition of the system and is provided later in this chapter (1).

Pathologic staging can be performed in patients treated with initial definitive surgery or in patients treated with initial (pre-operative or neoadjuvant) systemic therapy followed by definitive surgery. The AJCC system details rules for classification, definition of the anatomy, and stage groups. It represents a significant change from the Sixth Edition, published in 2003. A summary of the changes is given below.

SUMMARY OF CHANGES

Tumor (T)

- Identified specific imaging modalities that can be used to estimate clinical tumor size, including mammography, ultrasound, and magnetic resonance imaging (MRI).
- Made specific recommendations that (i) the microscopic measurement is the most accurate and preferred method

to determine pT with a small invasive cancer that can be entirely submitted in one paraffin block, and (ii) the gross measurement is the most accurate and preferred method to determine pT with larger invasive cancers that must be submitted in multiple paraffin blocks.
- Made the specific recommendation to use the clinical measurement thought to be most accurate to determine the clinical T of breast cancers treated with neoadjuvant therapy. Pathologic (posttreatment) size should be estimated based on the best combination of gross and microscopic histological findings.
- Made the specific recommendation to estimate the size of invasive cancers that are unapparent to any clinical modalities or gross pathologic examination by carefully measuring and recording the relative positions of tissue samples submitted for microscopic evaluation and determining which contain tumor.
- Acknowledged "ductal intraepithelial neoplasia" (DIN) as uncommon, and still not widely accepted, terminology encompassing both DCIS and ADH, and clarification that only cases referred to as DIN containing DCIS (±ADH) are classified as Tis (DCIS).
- Acknowledged "lobular intraepithelial neoplasia" (LIN) as uncommon, and still not widely accepted, terminology encompassing both LCIS and ALH, and clarification that only cases referred to as LIN containing LCIS (±ALH) are classified as Tis (LCIS).
- Clarified that only Paget's disease NOT associated with an underlying noninvasive (that is, DCIS and/or LCIS) or invasive breast cancer should be classified as Tis (Paget's) and that Paget's disease associated with an underlying cancer be classified according to the underlying cancer (Tis, T1, and so on).
- Made the recommendation to estimate the size of noninvasive carcinomas (DCIS and LCIS), even though it does not currently change their T classification, because noninvasive cancer size may influence therapeutic decisions, acknowledging that providing a precise size for LCIS may be difficult.
- Acknowledged that the prognosis of microinvasive carcinoma is generally thought to be quite favorable, although the clinical impact of multifocal microinvasive disease is not well understood at this time.
- Acknowledged that it is not necessary for tumors to be in separate quadrants to be classified as multiple, simultaneous, ipsilateral carcinomas, providing that they can be unambiguously demonstrated to be macroscopically distinct and measurable using available clinical and pathologic techniques.
- Maintained that the term "inflammatory carcinoma" be restricted to cases with typical skin changes involving a third or more of the skin of the breast. While the histologic presence of invasive carcinoma invading dermal lymphatics is supportive of the diagnosis, it is not required, nor is dermal lymphatic invasion without typical clinical findings sufficient for a diagnosis of inflammatory breast cancer.
- Recommend that all invasive cancer should be graded using the Nottingham combined histologic grade (Elston-Ellis modification of Scarff–Bloom–Richardson grading system).

Nodes (N)

- Classification of isolated tumor cell clusters and single cells is more stringent. Small clusters of cells not greater than 0.2 mm, or nonconfluent or nearly confluent clusters of cells not exceeding 200 cells in a single histologic lymph node cross section are classified as isolated tumor cells.
- Use of the (sn) modifier for sentinel node has been clarified and restricted. When six or more sentinel nodes are identified on gross examination of pathology specimens the (sn) modifier should be omitted.
- Stage I breast tumors have been subdivided into Stage IA and Stage IB; Stage IB includes small tumors (T1) with exclusively micrometastases in lymph nodes (N1mi).

Metastases (M)

- Created new M0(i+) category, defined by presence of either disseminated tumor cells detectable in bone marrow or circulating tumor cells or found incidentally in other tissues (such as ovaries removed prophylactically) if not exceeding 0.2 mm. However, this category does not change the stage grouping. Assuming that they do not have clinically and/or radiographically detectable metastases, patients with M0(i+) are staged according to T and N.

Postneoadjuvant Therapy (yc or ypTNM)

- In the setting of patients who received neoadjuvant therapy, pretreatment clinical T (cT) should be based on clinical or imaging findings.
- Postneoadjuvant therapy T should be based on clinical or imaging (ycT) or pathologic findings (ypT).
- A subscript will be added to the clinical N for both node negative and node positive patients to indicate whether the N was derived from clinical examination, fine-needle aspiration, core needle biopsy, or sentinel lymph node biopsy.
- The posttreatment ypT will be defined as the largest contiguous focus of invasive cancer as defined histopathologically with a subscript to indicate the presence of multiple tumor foci. *Note:* Definition of posttreatment ypT remains controversial and an area in transition.
- Posttreatment nodal metastases no greater than 0.2 mm are classified as ypN0(i+) in patients who have not received neoadjuvant systemic therapy. However, patients with this finding are not considered to have achieved a pathologic complete response (pCR).
- A description of the degree of response to neoadjuvant therapy (complete, partial, no response) will be collected by the registrar with the posttreatment ypTNM. The registrars are requested to describe how they defined response (by physical examination, imaging techniques [mammogram, ultrasound, magnetic resonance imaging (MRI)] or pathologically).
- Patients will be considered to have M1 (and therefore Stage IV) breast cancer if they have had clinically or radiographically detectable metastases, with or without biopsy, prior to neoadjuvant systemic therapy, regardless of their status after neoadjuvant systemic therapy. (Tables 32-1 through 32-5)

INTRODUCTION TO THE STAGING SYSTEM

This staging system for carcinoma of the breast applies to infiltrating (including microinvasive) and *in situ* carcinomas. Microscopic confirmation of the diagnosis is mandatory, and the histologic type and grade of carcinoma should be recorded.

Anatomy

Primary Site

The mammary gland, situated on the anterior chest wall, is composed of glandular tissue with a dense fibrous stroma. The glandular tissue consists of lobules that group together into 15 to 25 lobes arranged approximately in a spokelike

TABLE 32-1

Primary Tumor (T)[a]	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma *in situ*
Tis (DCIS)	DCIS
Tis (LCIS)	LCIS
Tis (Paget)	Paget's disease of the nipple NOT associated with invasive carcinoma and/or carcinoma *in situ* (DCIS and/or LCIS) in the underlying breast parenchyma. Carcinomas in the breast parenchyma associated with Paget's disease are categorized based on the size and characteristics of the parenchymal disease, although the presence of Paget's disease should still be noted.
T1	Tumor ≤20 mm in greatest dimension
T1mi	Tumor ≤1 mm in greatest dimension
T1a	Tumor >1 mm but ≤5 mm in greatest dimension
T1b	Tumor >5 mm but ≤10 mm in greatest dimension
T1c	Tumor >10 mm but ≤20 mm in greatest dimension
T2	Tumor >20 mm but ≤50 mm in greatest dimension
T3	Tumor >50 mm in greatest dimension
T4	Tumor of any size with direct extension to the chest wall and/or to the skin (ulceration or skin nodules)[b]
T4a	Extension to the chest wall, not including only pectoralis muscle adherence/invasion
T4b	Ulceration and/or ipsilateral satellite nodules and/or edema (including peau d'orange) of the skin, which do not meet the criteria for inflammatory carcinoma
T4c	Both T4a and T4b
T4d	Inflammatory carcinoma

DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.
[a]The T classification of the primary tumor is the same regardless of whether it is based on clinical or pathologic criteria, or both. Size should be measured to the nearest millimeter. If the tumor size is slightly less than or greater than a cutoff for a given T classification, it is recommended that the size be rounded to the millimeter reading that is closest to the cutoff. For example, a reported size of 1.1 mm is reported as 1 mm, or a size of 2.01 cm is reported as 2.0 cm. Designation should be made with the subscript "c" or "p" modifier to indicate whether the T classification was determined by clinical (physical examination or radiologic) or pathologic measurements, respectively. In general, pathologic determination should take precedence over clinical determination of T size.
[b]Invasion of the dermis alone does not qualify as T4.

pattern. Multiple major and minor ducts connect the milk-secreting lobular units to the nipple. Small milk ducts course throughout the breast, converging into larger collecting ducts that open into the lactiferous sinus at the base of the nipple. Most cancers form initially in the terminal duct lobular units of the breast. Glandular tissue is more abundant in the upper, outer portion of the breast; as a result, half of all breast cancers occur in this area.

Chest Wall

The chest wall includes ribs, intercostal muscles, and serratus anterior muscle, but not the pectoral muscles.

Regional Lymph Nodes

The breast lymphatics drain by way of three major routes: axillary, transpectoral, and internal mammary. Intramammary lymph nodes are coded as axillary lymph nodes for staging purposes. Supraclavicular nodes (SCLNs) are classified as regional lymph nodes for staging purposes. Metastasis to any other lymph node, including cervical or contralateral internal mammary lymph nodes, is classified as distant (M1).

The regional lymph nodes are as follows:

1. Axillary (ipsilateral): interpectoral (Rotter's) nodes and lymph nodes along the axillary vein and its tributaries that may be (but are not required to be) divided into the following levels:
   a. Level I (low-axilla): lymph nodes lateral to the lateral border of pectoralis minor muscle.
   b. Level II (mid-axilla): lymph nodes between the medial and lateral borders of the pectoralis minor muscle and the interpectoral (Rotter's) lymph nodes.
   c. Level III (apical axilla): lymph nodes medial to the medial margin of the pectoralis minor muscle, including those designated as apical.
2. Internal mammary (ipsilateral): lymph nodes in the intercostal spaces along the edge of the sternum in the endothoracic fascia.
3. Supraclavicular: lymph nodes in the supraclavicular fossa, a triangle defined by the omohyoid muscle and tendon (lateral and superior border), the internal jugular vein (medial border), and the clavicle and subclavian vein (lower border). Adjacent lymph nodes outside of this triangle are considered to be lower cervical nodes (M1) (1).

Metastatic Sites

Tumor cells may be disseminated by either the lymphatic or the blood vascular system. The four major sites of involvement are bone, lung, brain, and liver, but tumor cells are also capable of metastasizing to many other sites.

Rules for Classification

Clinical Staging

Clinical staging includes physical examination, with careful inspection and palpation of the skin, mammary gland, and lymph nodes (axillary, supraclavicular, and cervical), imaging, and pathologic examination of the breast or other

TABLE 32-2

Regional Lymph Nodes (N)

	Clinical
NX	Regional lymph nodes cannot be assessed (e.g., previously removed)
N0	No regional lymph node metastases
N1	Metastases to movable ipsilateral level I, II axillary lymph node(s)
N2	Metastases in ipsilateral level I, II axillary lymph nodes that are clinically fixed or matted OR Metastases in clinically detected[a] ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastases
N2a	Metastases in ipsilateral level I, II axillary lymph nodes fixed to one another (matted) or to other structures
N2b	Metastases only in clinically detected[a] ipsilateral internal mammary nodes and in the *absence* of clinically evident level I, II axillary lymph node metastases
N3	Metastases in ipsilateral infraclavicular (level III axillary) lymph node(s) with or without level I, II axillary lymph node involvement OR Metastases in clinically detected[a] ipsilateral internal mammary lymph node(s) with clinically evident level I, II axillary lymph node metastases OR Metastases in ipsilateral supraclavicular lymph node(s) with or without axillary or internal mammary lymph node involvement
N3a	Metastases in ipsilateral infraclavicular lymph node(s)
N3b	Metastases in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c	Metastases in ipsilateral supraclavicular lymph node(s)

[a]Clinically detected is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine-needle aspiration biopsy with cytologic examination. Confirmation of clinically detected metastatic disease by fine-needle aspiration without excision biopsy is designated with an (f) suffix, for example, cN3a(f). Excisional biopsy of a lymph node or biopsy of a sentinel node, in the absence of assignment of a pT, is classified as a clinical N, for example, cN1. Information regarding the confirmation of the nodal status will be designated in site-specific factors as clinical, fine-needle aspiration, core biopsy, or sentinel lymph node biopsy. Pathologic classification (pN) is used for excision or sentinel lymph node biopsy only in conjunction with a pathologic T assignment.

TABLE 32-3

Pathologic (pN)[a,b,c]

pNX	Regional lymph nodes cannot be assessed (e.g., previously removed or not removed for pathologic study)
pN0	No regional lymph node metastasis identified histologically
Note: ITCs are defined as small clusters of cells ≤0.2 mm, or single tumor cells, or a cluster of <200 cells in a single histologic cross-section. ITCs may be detected by routine histology or by IHC methods. Nodes containing only ITCs are excluded from the total positive node count for purposes of N classification but should be included in the total number of nodes evaluated.	
pN0(i–)	No regional lymph node metastases histologically, negative IHC
pN0(i+)	Malignant cells in regional lymph node(s) ≤0.2 mm (detected by H&E or IHC including ITC)
pN0(mol–)	No regional lymph node metastases histologically, negative molecular findings (RT-PCR)
pN0(mol+)	Positive molecular findings (RT-PCR), but no regional lymph node metastases detected by histology or IHC
pN1	Micrometastases OR Metastases in 1–3 axillary lymph nodes AND/OR Metastases in internal mammary nodes with metastases detected by sentinel lymph node biopsy but not clinically detected[b]
pN1mi	Micrometastases (>0.2 mm and/or >200 cells but none >2.0 mm)
pN1a	Metastases in 1–3 axillary lymph nodes, at least one metastasis >2.0 mm
pN1b	Metastases in internal mammary nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected[b]
pN1c	Metastases in 1–3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected

TABLE 32-3 *(Continued)*

Pathologic (pN)[a,b,c]	
pN2	Metastases in 4–9 axillary lymph nodes OR Metastases in clinically detected[b] internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN2a	Metastases in 4–9 axillary lymph nodes (at least 1 tumor deposit >2 mm)
pN2b	Metastases in clinically detected[c] internal mammary lymph nodes in the *absence* of axillary lymph node metastases
pN3	Metastases in ≥10 axillary lymph nodes OR Metastases in infraclavicular (level III axillary) lymph nodes OR Metastases in clinically detected[c] ipsilateral internal mammary lymph nodes in the *presence* of one or more positive level I, II axillary lymph nodes OR Metastases in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected[b] OR Metastases in ipsilateral supraclavicular lymph nodes
pN3a	Metastases in ≥10 axillary lymph nodes (at least 1 tumor deposit >2.0 mm) OR Metastases to the infraclavicular (level III axillary lymph) nodes
pN3b	Metastases in clinically detected[c] ipsilateral internal mammary lymph nodes in the *presence* of one or more positive axillary lymph nodes OR Metastases in >3 axillary lymph nodes and in internal mammary lymph nodes with micrometastases or macrometastases detected by sentinel lymph node biopsy but not clinically detected[b]
pN3c	Metastases in ipsilateral supraclavicular lymph nodes

Posttreatment ypN

–Posttreatment yp "N" should be evaluated as for clinical (pretreatment) "N" methods above. The modifier "sn" is used only if a sentinel node evaluation was performed after treatment. If no subscript is attached, it is assumed that the axillary nodal evaluation was by AND.
–The X classification will be used (ypNX) if no yp posttreatment sn or AND was performed.
–N categories are the same as those used for pN.

AND, axillary node dissection; H&E, hematoxylin and eosin stain; IHC, immunohistochemical; ITC, isolated tumor cells; RT-PCR, reverse transcriptase/polymerase chain reaction.
[a]Classification is based on axillary lymph node dissection with or without sentinel lymph node biopsy. Classification based solely on sentinel lymph node biopsy without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," for example, pN0(sn).
[b]"Not clinically detected" is defined as not detected by imaging studies (excluding lymphoscintigraphy) or not detected by clinical examination.
[c]"Clinically detected" is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination and having characteristics highly suspicious for malignancy or a presumed pathologic macrometastasis based on fine-needle aspiration biopsy with cytologic examination.

TABLE 32-4

Distant Metastases (M)	
M0	No clinical or radiographic evidence of distant metastases
cM0(i+)	No clinical or radiographic evidence of distant metastases, but deposits of molecularly or microscopically detected tumor cells in circulating blood, bone marrow, or other nonregional nodal tissue that are ≤0.2 mm in a patient without symptoms or signs of metastases
M1	Distant detectable metastases as determined by classic clinical and radiographic means and/or histologically proven >0.2 mm

Posttreatment yp M classification. The M category for patients treated with neoadjuvant therapy is the category assigned in the clinical stage, prior to initiation of neoadjuvant therapy. Identification of distant metastases after the start of therapy in cases where pretherapy evaluation showed no metastases is considered progression of disease. If a patient was designated to have detectable distant metastases (M1) before chemotherapy, the patient will be designated as M1 throughout.

TABLE 32-5

Anatomic Stage/Prognostic Groups[a,b]

Stage	*T*	*N*	*M*
0	Tis	N0	M0
IA	T1[a]	N0	M0
IB	T0	N1mi	M0
	T1[b]	N1mi	M0
IIA	T0	N1[b]	M0
	T1[a]	N1[b]	M0
	T2	N0	M0
IIB	T2	N1	M0
	T3	N0	M0
IIIA	T0	N2	M0
	T1[a]	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
IIIC	Any T	N3	M0
IV	Any T	Any N	M1

[a]T1 includes T1mi.
[b]T0 and T1 tumors with nodal micrometastases only are excluded from Stage IIA and are classified Stage IB.
–M0 includes M0(i+).
–The designation pM0 is not valid; any M0 should be clinical.
–If a patient presents with M1 prior to neoadjuvant systemic therapy, the stage is considered Stage IV and remains Stage IV regardless of response to neoadjuvant therapy.
–Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.
–Postneoadjuvant therapy is designated with "yc" or "yp" prefix. Of note, no stage group is assigned if there is a complete pathologic response (CR) to neoadjuvant therapy, for example, ypT0ypN0cM0.

tissues as appropriate to establish the diagnosis of breast carcinoma. The extent of tissue examined pathologically for clinical staging is not so great as that required for pathologic staging (see next section, Pathologic Staging). Imaging findings are considered elements of staging if they are collected within 4 months of diagnosis in the absence of disease progression or through completion of surgery(ies), whichever is longer. Such imaging findings would include the size of the primary tumor and of chest wall invasion, and the presence or absence of regional or distant metastasis. Imaging findings and surgical findings obtained after a patient has been treated with neoadjuvant chemotherapy, hormonal therapy, immunotherapy, or radiation therapy are not considered elements of initial staging.

Pathologic Staging

Pathologic staging includes all data used for clinical staging, plus data from surgical exploration and resection as well as pathologic examination of the primary carcinoma, regional lymph nodes, and metastatic sites (if applicable), including not less than excision of the primary carcinoma with no macroscopic tumor in any margin of resection by pathologic examination. A cancer can be classified pT for pathologic stage grouping if there is only microscopic, but not macroscopic, involvement at the margin. If there is tumor in the margin of resection by macroscopic examination, the cancer is coded pTX because the total extent of the primary tumor cannot be assessed. If the primary tumor is invasive and not only microinvasive, resection of at least the low axillary lymph nodes (Level I)—that is, those lymph nodes located lateral to the lateral border of the pectoralis minor muscle—should be performed for pathologic (pN) classification. Such a resection ordinarily includes six or more lymph nodes. Alternatively, one or more sentinel lymph nodes may be resected and examined for pathologic classification. Certain histologic tumor types (pure tubular carcinoma <1 cm, pure mucinous carcinoma <1 cm, and microinvasive carcinoma) have a very low incidence of axillary lymph node metastasis and do not usually require an axillary lymph node dissection. Cancerous nodules in the axillary fat adjacent to the breast, without histologic evidence of residual lymph node tissue, are classified as regional lymph node metastases (N). Pathologic stage grouping includes any of the following combinations of pathologic and clinical classifications: pT pN pM, or pT pN cM, or cT cN pM. If surgery occurs after the patient has received neoadjuvant chemotherapy, hormonal therapy, immunotherapy, or radiation therapy, the prefix "y" should be used with the TNM classification (e.g., ypTNM).

TNM CLASSIFICATION

Primary Tumor (T)

Determining Tumor Size

The clinical measurement used for classifying the primary tumor (T) is the one judged to be most accurate for that particular case (i.e., physical examination or imaging such as mammography or ultrasonography). The pathologic tumor size for the T classification is a measurement of *the invasive component only*. For example, if there is a 4.0-cm intraductal component and a 0.3-cm invasive component, the tumor is classified T1a. The size of the primary tumor is measured for T classification before any tissue is removed for special studies, such as for estrogen receptors. In patients who have received multiple core biopsies, measuring only the residual lesion may result in significantly underclassifying the T component and thus understaging the tumor. In such cases, original tumor size should be reconstructed on the basis of a combination of imaging and all histologic findings.

Tis Classification

Carcinoma *in situ,* with no evidence of an invasive component, is classified as Tis, with a subclassification indicating type. Cases of ductal carcinoma *in situ* and cases with both ductal carcinoma *in situ* (DCIS) and lobular carcinoma *in situ* (LCIS) are classified Tis. LCIS is increasingly defined as a risk factor for subsequent breast cancer, although there is some evidence that it may occasionally be a precursor of invasive lobular carcinoma. For example, this may be the case with LCIS with more atypical cytology (pleomorphic), as well as more extensive and locally distorting examples of well-developed LCIS. Regardless of this controversy, LCIS is reported as a malignancy by national database registrars and should be designated as such in this classification system (e.g., Tis [LCIS]). Paget's disease of the nipple without an associated tumor mass (clinical) or invasive carcinoma (pathologic) is classified Tis (Paget's). Paget's disease with a demonstrable mass (clinical) anywhere in that breast or an invasive component (pathologic) is classified according to the size of the tumor mass or invasive component.

Microinvasion of Breast Carcinoma

Microinvasion is the extension of cancer cells beyond the basement membrane into the adjacent tissues with no focus more than 0.1 cm in greatest dimension. When there are multiple foci of microinvasion, the size of only the largest focus is used to classify the microinvasion. (Do not use the sum of all the individual foci.) The presence of multiple foci of microinvasion should be noted or quantified, as it is with multiple larger invasive carcinomas.

Multiple Simultaneous Ipsilateral Primary Carcinomas

The following guidelines are used in classifying multiple simultaneous ipsilateral primary (infiltrating, macroscopically measurable) carcinomas. These criteria do not apply to one macroscopic carcinoma associated with multiple separate microscopic foci. Most conservatively, tumors are defined as arising independently only if they occur in different quadrants of the breast.

1. Use the largest primary carcinoma to designate T classification. Do not assign a separate T classification for the smaller tumor(s).
2. Enter into the record that this is a case of multiple simultaneous ipsilateral primary carcinomas. The outcome of such cases should be analyzed separately.

Simultaneous Bilateral Breast Carcinomas

Each carcinoma is staged as a separate primary carcinoma in a separate organ.

Inflammatory Carcinoma

Inflammatory carcinoma is a clinicopathologic entity characterized by diffuse erythema and edema (*peau d'orange*) of the breast, often without an underlying palpable mass. These clinical findings should involve most of the skin of the breast. Classically, the skin changes arise quickly in the affected breast. Thus, the term *inflammatory carcinoma* should not be applied to a patient with neglected locally advanced cancer of the breast presenting late in the course of her disease. On imaging, there may be a detectable mass and characteristic thickening of the skin over the breast. This clinical presentation is due to tumor emboli in dermal lymphatics, which may or may not be apparent on skin biopsy. The tumor of inflammatory carcinoma is classified T4d. It is important to remember that inflammatory carcinoma is primarily a clinical diagnosis. Involvement of the dermal lymphatics alone does not indicate inflammatory carcinoma in the absence of clinical findings. In addition to the clinical picture, however, a biopsy is still necessary to demonstrate cancer either in the dermal lymphatics or in the breast parenchyma itself.

Skin of Breast

Dimpling of the skin, nipple retraction, or any other skin change except those described under T4b and T4d may occur in T1, T2, or T3 without changing the classification.

Regional Lymph Nodes (N)

Macrometastasis

Cases in which regional lymph nodes cannot be assessed (previously removed or not removed for pathologic examination) are designated NX or pNX. Cases in which no regional lymph node metastasis is detected are designated N0 or pN0.

In patients who are clinically node positive, N1 designates metastasis to one or more movable ipsilateral axillary lymph nodes, N2a designates metastasis to axillary lymph nodes that are fixed to each other (matted) or to other structures, and N3a indicates metastasis to ipsilateral infraclavicular lymph nodes. Metastases to the ipsilateral internal mammary nodes are designated as N2b when they are detected by imaging studies (including computed tomography [CT] scan and ultrasonography, but excluding lymphoscintigraphy) or by clinical examination and when they do not occur in conjunction with metastasis to the axillary lymph nodes. Metastases to the ipsilateral internal mammary nodes are designated as N3b when they are detected by imaging studies or by clinical examination and when they occur in conjunction with metastasis to the axillary lymph nodes. Metastases to the ipsilateral SCLNs are designated as N3c regardless of the presence or absence of axillary or internal mammary nodal involvement.

In patients who are pathologically node positive with one or more tumor deposits greater than 2 mm, cases with 1 to 3 positive axillary lymph nodes are classified pN1a, cases with 4 to 9 positive axillary lymph nodes are classified pN2a, and cases with 10 or more positive axillary lymph nodes are classified pN3a. Cases with histologically confirmed metastasis to the internal mammary nodes, detected by sentinel lymph node dissection but not by imaging studies (excluding lymphoscintigraphy) or clinical examination, are classified as pN1b if occurring in the *absence* of metastasis to the axillary lymph nodes and as pN1c if occurring in the *presence* of metastases to one to three axillary lymph nodes. (If four or more axillary lymph nodes are involved, the classification pN3b is used.) Clinical involvement with histologic confirmation of the internal mammary nodes by imaging studies (excluding lymphoscintigraphy) in the absence or presence of axillary nodal metastases are classified as pN2b and pN3b, respectively. Histologic evidence of metastasis in ipsilateral SCLNs is classified as pN3c. A classification of pN3, regardless of primary tumor size or grade, is classified as stage IIIc. A case in which the classification is based only on sentinel lymph node dissection is given the additional designation (sn) for "sentinel node"—for example, pN1(sn). For a case in which an initial classification is based on a sentinel lymph node dissection but a standard axillary lymph node dissection is subsequently performed, the classification is based on the total results of the axillary lymph node dissection (i.e., including the sentinel node).

Isolated Tumor Cells and Micrometastases

Isolated tumor cells (ITCs) are defined as single cells or small clusters of cells not greater than 0.2 mm in largest dimension, usually with no histologic evidence of malignant activity (such as proliferation or stromal reaction). If an additional immunohistochemistry (IHC) examination was made for ITCs in a patient with histologically negative lymph nodes, the regional lymph nodes should be designated as pN0(i–) or pN0(i+), as appropriate.

Micrometastases are defined as tumor deposits greater than 0.2 mm but not greater than 2.0 mm in largest dimension that may have histologic evidence of malignant activity (such as proliferation or stromal reaction). Cases in which only micrometastases are detected (none greater than 2 mm) are classified pN1mi. The classification is designated as (i+) for "immunohistochemical" if micrometastasis was detected only by IHC (e.g., pN1mi (i+)).

If histologically and immunohistochemically negative lymph nodes are examined for evidence of metastasis using molecular methods (reverse transcriptase polymerase chain reaction [RT-PCR]), the regional lymph nodes are classified as pN0(mol–) or pN0(mol+), as appropriate.

Distant Metastasis (M)

Cases in which distant metastasis cannot be assessed are designated MX, cases in which there is no distant metastasis are designated M0, and cases in which one or more distant metastases are identified are designated M1. A negative clinical history and examination are sufficient to designate a case as M0; extensive imaging or other testing is not required. Note that positive SCLNs are now classified as N3 rather than M1.

DEFINITION OF TNM

Primary Tumor (T)

Definitions for classifying the primary tumor (T) are the same for clinical and for pathologic classification. If the measurement is made by physical examination, the examiner will use the major headings (T1, T2, or T3). If other measurements, such as mammographic or pathologic measurements, are used, the subsets of T1 can be used. Tumors should be measured to the nearest 0.1-cm increment.

TX Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma *in situ*
Tis (DCIS) Ductal carcinoma *in situ*
Tis (LCIS) Lobular carcinoma *in situ*
Tis (Paget's) Paget's disease of the nipple with no tumor

Note: Paget's disease associated with a tumor is classified according to the size of the tumor.

T1 Tumor 2 cm or less in greatest dimension
T1mic Microinvasion 0.1 cm or less in greatest dimension
T1a Tumor more than 0.1 cm but not more than 0.5 cm in greatest dimension
T1b Tumor more than 0.5 cm but not more than 1 cm in greatest dimension
T1c Tumor more than 1 cm but not more than 2 cm in greatest dimension
T2 Tumor more than 2 cm but not more than 5 cm in greatest dimension
T3 Tumor more than 5 cm in greatest dimension
T4 Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below
T4a Extension to chest wall, not including pectoralis muscle
T4b Edema (including *peau d'orange*) or ulceration of the skin of the breast, or satellite skin nodules confined to the same breast
T4c Both T4a and T4b
T4d Inflammatory carcinoma

Regional Lymph Nodes (N)

Clinical

NX Regional lymph nodes cannot be assessed (e.g., previously removed)
N0 No regional lymph node metastasis
N1 Metastasis to movable ipsilateral axillary lymph node(s)
N2 Metastases in ipsilateral axillary lymph nodes fixed or matted, or in clinically apparent ipsilateral internal mammary nodes in the *absence* of clinically evident axillary lymph node metastasis
N2a Metastasis in ipsilateral axillary lymph nodes fixed to one another (matted) or to other structures
N2b Metastasis only in clinically apparent* ipsilateral internal mammary nodes and in the *absence* of clinically evident axillary lymph node metastasis
N3 Metastasis in ipsilateral infraclavicular lymph node(s) with or without axillary lymph node involvement, or in clinically apparent* ipsilateral internal mammary lymph node(s) and in the *presence* of clinically evident axillary lymph node metastasis; or metastasis in ipsilateral SCLNs with or without axillary or internal mammary lymph node involvement
N3a Metastasis in ipsilateral infraclavicular lymph node(s)
N3b Metastasis in ipsilateral internal mammary lymph node(s) and axillary lymph node(s)
N3c Metastasis in ipsilateral SCLNs

Pathologic (pN)†

pNX Regional lymph nodes cannot be assessed (e.g., previously removed, or not removed for pathologic study)
pN0 No regional lymph node metastasis histologically, no additional examination for ITC

Note: ITC are defined as single tumor cells or small cell clusters not greater than 0.2 mm, usually detected only by IHC or molecular methods but which may be verified on H&E stains. ITCs do not usually show evidence of malignant activity (e.g., proliferation or stromal reaction).

PN0(i–) No regional lymph node metastasis histologically, negative IHC
PN0(i+) No regional lymph node metastasis histologically, positive IHC, no IHC cluster greater than 0.2 mm
PN0(mol–) No regional lymph node metastasis histologically, negative molecular findings (RT-PCR)‡
PN0(mol+) No regional lymph node metastasis histologically, positive molecular findings (RT-PCR)‡
PN1 Metastasis in one to three axillary lymph nodes, or in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent
PN1mi Micrometastasis (greater than 0.2 mm, none greater than 2.0 mm)
PN1a Metastasis in one to three axillary lymph nodes
PN1b Metastasis in internal mammary nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent*
PN1c Metastasis in one to three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent.* (If associated with greater than three positive axillary lymph nodes, the internal mammary nodes are classified as pN3b to reflect increased tumor burden.)
pN2 Metastasis in four to nine axillary lymph nodes, or in clinically apparent internal mammary lymph nodes in the *absence* of axillary lymph node metastasis
pN2a Metastasis in four to nine axillary lymph nodes (at least one tumor deposit greater than 2.0 mm)
pN2b Metastasis in clinically apparent† internal mammary lymph nodes in the absence of axillary lymph node metastasis

*_Clinically apparent_ is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination or grossly visible pathologically.
†Classification is based on axillary lymph node dissection with or without sentinel lymph node dissection. Classification based solely on sentinel lymph node dissection without subsequent axillary lymph node dissection is designated (sn) for "sentinel node," e.g., pN0(i+)(sn).
‡RT-PCR, reverse transcriptase/polymerase chain reaction.

pN3 Metastasis in 10 or more axillary lymph nodes, or in infraclavicular lymph nodes, or in clinically apparent† ipsilateral internal mammary lymph nodes in the *presence* of 1 or more positive axillary lymph nodes; or in more than 3 axillary lymph nodes with clinically negative microscopic metastasis in internal mammary lymph nodes; or in ipsilateral SCLNs

pN3a Metastasis in 10 or more axillary lymph nodes (at least one tumor deposit greater than 2.0 mm), or metastasis to the infraclavicular lymph nodes

pN3b Metastasis in clinically apparent† ipsilateral internal mammary lymph nodes in the presence of one or more positive axillary lymph nodes; or in more than three axillary lymph nodes and in internal mammary lymph nodes with microscopic disease detected by sentinel lymph node dissection but not clinically apparent*

pN3c Metastasis in ipsilateral SCLNs

Distant Metastasis (M)

MX Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis

STAGE GROUPING

Stage 0	Tis	N0	M0
Stage I	T1†	N0	M0
Stage IIA	T0	N1	M0
	T1†	N1	M0
	T2	N0	M0
Stage IIB	T2	N1	M0
	T3	N0	M0
Stage IIIA	T0	N2	M0
	T1†	N2	M0
	T2	N2	M0
	T3	N1	M0
	T3	N2	M0
Stage IIIB	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IIIC	Any T	N3	M0
Stage IV	Any T	Any N	M1

Note: Stage designation may be changed if postsurgical imaging studies reveal the presence of distant metastases, provided that the studies are carried out within 4 months of diagnosis in the absence of disease progression and provided that the patient has not received neoadjuvant therapy.

Clinically apparent is defined as detected by imaging studies (excluding lymphoscintigraphy) or by clinical examination.
†T1 includes T1mic

HISTOPATHOLOGIC TYPE

The histopathologic types are the following:

In Situ Carcinomas

NOS (not otherwise specified)
Intraductal
Paget's disease and intraductal

Invasive Carcinomas

NOS
Ductal
Inflammatory
Medullary, NOS
Medullary with lymphoid stroma
Mucinous
Papillary (predominantly micropapillary pattern)
Tubular
Lobular
Paget's disease and infiltrating
Undifferentiated
Squamous cell
Adenoid cystic
Secretory
Cribriform

HISTOLOGIC GRADE (G) (NOTTINGHAM COMBINED HISTOLOGIC GRADE IS RECOMMENDED)

All invasive breast carcinomas with the exception of medullary carcinoma should be graded. The Nottingham combined histologic grade (Elston-Ellis modification of Scarff-Bloom-Richardson grading system) is recommended. The grade for a tumor is determined by assessing morphologic features (tubule formation, nuclear pleomorphism, and mitotic count), assigning a value of 1 (favorable) to 3 (unfavorable) for each feature, and adding together the scores for all three categories. A combined score of 3 to 5 points is designated as grade 1; a combined score of 6 or 7 points is grade 2; a combined score of 8 or 9 points is grade 3.

GX Grade cannot be assessed
G1 Low combined histologic grade (favorable)
G2 Intermediate combined histologic grade (moderately favorable)
G3 High combined histologic grade (unfavorable)

These tentative observations, coupled with the overall sparseness and variability of the information, strongly suggest that the available data are not yet mature enough to offer guidance in incorporating histologic grade into the staging system for breast cancer. Because the evidence indicating that histologic grade is an important prognostic factor in breast cancer is so robust, it seems certain that emerging data will support the incorporation of grade into the AJCC staging system in the near future.

REFERENCE

1. Edge SB, Byrd DR, Compton CC, eds. *AJCC cancer staging manual*. 7th ed. New York: Springer; 2010.

CHAPTER 33

Mastectomy

Monica Morrow and Mehra Golshan

CHAPTER CONTENTS

HISTORY OF MASTECTOMY

The origin of the word *mastectomy* is the Greek term *mastos*, meaning the breast. Over the past century, the procedure has evolved considerably from the initial descriptions by Halsted and Meyer in the mid-1890s. In 1894, William Stewart Halsted published the Johns Hopkins Hospital experience with radical mastectomy, reporting a remarkable local regional control rate of 73% with no operative mortality (1). The actuarial survival rate was double that of untreated patients, with a 5-year survival rate of 40%, despite the advanced stage of many of the tumors and the lack of any adjuvant therapy. At that time, the success of the procedure was attributed to the en bloc removal of the breast and its draining lymphatics, and, after this report, the radical mastectomy remained the standard of care until the 1970s.

It eventually became apparent that the radical mastectomy failed to cure many women with breast cancer, and this was attributed by some to its failure to include all of the draining lymphatics of the breast in the en bloc resection. The extended radical mastectomy, which included the en bloc resection of the internal mammary nodes and the medial ribs, was developed to address this issue. After a randomized trial failed to demonstrate a survival benefit for this more morbid procedure (2), it was abandoned. The adoption of the modified radical mastectomy, a term used to describe a variety of surgical procedures that included removal of the entire breast and the axillary nodes but not the pectoralis major muscle, represented a major departure from the Halstedian principles of en bloc cancer surgery. Only 2 relatively small randomized trials directly compared radical and modified radical mastectomy, and neither found a survival difference. The major impetus for abandoning radical mastectomy was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 trial. This study randomized clinical node negative women to radical mastectomy, simple mastectomy with node field irradiation, or simple mastectomy with no axillary surgery and delayed axillary dissection if clinical axillary metastases developed. After 25 years of follow-up, no survival differences have ever been apparent between treatments (3). Remarkably, in this trial done prior to the use of any adjuvant systemic therapy, although 40% of patients in the radical mastectomy group had axillary nodal metastases, only 18.5% of those randomized to the simple mastectomy and axillary observation group developed axillary first failure. This trial was a watershed in our understanding of the biology of breast cancer and paved the way for trials of breast-conserving therapy (Chapter 35), the use of immediate breast reconstruction (Chapter 36), and, ultimately, abandonment of axillary dissection in patients with a positive sentinel node undergoing breast-conservation therapy (Chapter 37).

PATIENT SELECTION AND CRITERIA FOR INOPERABILITY

Patient evaluation and relative and absolute contraindications to breast-conserving therapy necessitating mastectomy are discussed in detail in Chapter 35. Briefly, contraindications result from the inability to reduce the tumor burden to a microscopic level, where it is likely to be controlled by radiotherapy, and the inability to safely deliver radiotherapy. Thus, multicentric disease, extensive malignant-appearing microcalcifications, and inability to obtain negative margins are contraindications related to disease burden, while a history of prior irradiation to the breast region and early pregnancy are contraindications related to the inability to safely irradiate the patient. Most women with stage 1 and 2 breast cancer are candidates for breast conservation. In a population-based study of 1,984 women treated in 2005–2006, 13% were felt to have contraindications to breast conservation, and 9% attempted lumpectomy but were converted to mastectomy. Additionally, 9% of women opted to undergo mastectomy in the absence of contraindications to breast conservation (4). Mastectomy today refers to total or complete mastectomy, with axillary staging with sentinel node biopsy in the clinically node-negative patient, or needle biopsy in the patient with clinically suspicious nodes. Mastectomy with axillary dissection is termed modified radical mastectomy. There are virtually no indications for radical mastectomy as an initial management approach to breast cancer at this time. However, there are some patients whose disease is too advanced to be approached with any

type of mastectomy as initial therapy, and would be treated with drug therapy and/or radiation first.

Criteria for inoperability were described by Haagensen in 1943 based on outcomes of patients treated between 1915 and 1935 (5) and remain surprisingly relevant today. They include inflammatory carcinoma, satellite skin nodules, extensive edema of the skin of the breast, ulceration, and fixation of the tumor to the boney chest wall. Edema of the ipsilateral arm, fixed axillary nodes, and supraclavicular metastases are all indications of inoperable nodal disease. Inoperability is readily apparent based on a physical examination. Patients with small areas of skin ulceration due to very superficial tumors are not uniformly inoperable. Involvement of the pectoralis major by tumor is not an indication of inoperability, nor is it incorporated in the TNM staging system. In practice, there is no indication today for resection of the pectoralis major (radical mastectomy) as a primary surgical approach. Patients with large tumors involving a substantial amount of the pectoral muscle should be treated with neoadjuvant therapy, as should patients with classic signs of inoperability (see Chapter 58, Locally Advanced Breast Cancer). In contrast, patients with T1 and T2 tumors located posteriorly in the breast do not a priori require neoadjuvant therapy because they appear to abut the pectoral muscle and may be treated with mastectomy or breast conservation. If a tumor involves the pectoral muscle at surgery, a piece of the muscle can be removed to obtain an adequate margin. Patients presenting with distant metastases and an intact primary tumor are not offered initial local therapy, but may be treated surgically if they have a limited number of metastatic sites and a good response to systemic therapy. This controversial area is discussed in detail in Chapter 68.

Current Technique

Approaches to mastectomy currently in use include total or simple mastectomy, skin-sparing total mastectomy to facilitate immediate breast reconstruction, and nipple sparing mastectomy. The approach to the axilla is independent of the type of mastectomy performed and is discussed in detail in Chapters 37 and 38. The total mastectomy procedure includes the removal of the entire mammary gland, with dissection extending superiorly to the clavicle, inferiorly to the rectus sheath insertion, medially to the sternal border, and laterally to the latissimus dorsi muscle. When axillary dissection is not performed, care must be taken to remove the entire axillary tail of the breast by extending the dissection superiorly along both the pectoralis minor and the latissimus dorsi muscles until the axillary investing fascia is entered or the sentinel node biopsy cavity is encountered. The posterior boundary of the dissection is the pectoralis major fascia. This fascia was initially thought to be an anatomic barrier to the lymphatic spread of cancer, a concept now recognized to be invalid since lymphatics penetrate the fascia, but the fascia may be preserved to facilitate expander/implant reconstruction. The flap thickness should result in removal of all of the breast parenchyma while leaving a layer of subcutaneous fat and superficial vasculature to minimize the risk of necrosis (Fig. 33-1). The flap thickness will vary with the amount of subcutaneous fat and surgical technique; however, flaps thicker than 5 mm are associated with significant residual glandular breast tissue (6).

Unfortunately, no reliable technique allows for intraoperative assessment of flap thickness. Flaps can be raised with the knife, scissor, or electrocautery, and there is no evidence of superiority of one technique. Some groups advocate the use of breast tumescence (a combination of lactated ringers and lidocaine/marcaine with epinephrine) to minimize

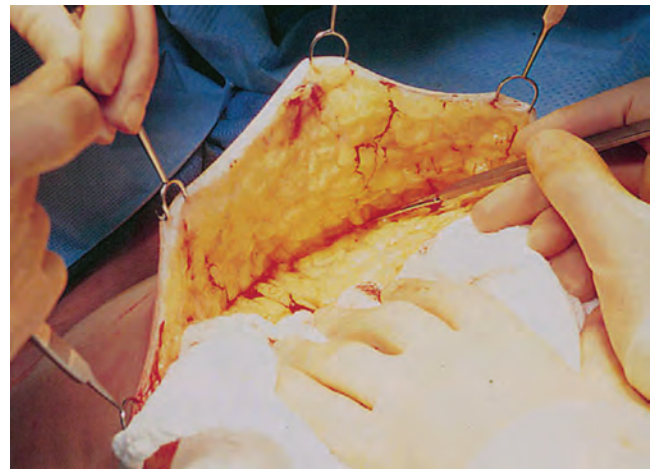

FIGURE 33-1 Flap thickness at the time of a modified radical mastectomy.

the blood loss seen with sharp dissection. Advocates of this approach believe it minimizes thermal damage to the flap, although data on its benefits and complications are sparse (Fig. 33-2). When immediate reconstruction is not performed, the goal is to remove the breast and its excess skin so the chest wall is flat without redundant skin. A smooth chest wall surface helps to facilitate an appropriate fit for a breast prosthesis. In addition, redundant skin is difficult to care for and becomes scarred to the chest wall, so it is not useful for delayed reconstruction. Incision placement should be determined by the shape of the breast, and extending incisions medially to where they are visible in clothing is unnecessary. Transverse incisions are associated with a lower rate of skin necrosis than vertical ones. In general, the pectoralis minor muscle should be preserved. Division of its tendon facilitates access to level III lymph nodes when there is extensive axillary disease, and the muscle may be resected in the case of a bulky adherent tumor, although in the era of neoadjuvant therapy, this scenario is uncommon.

Mastectomy is an extremely safe operation that can be performed on women of all ages and on those with significant co-morbidities with a low risk of operative mortality. In a United States Department of Veterans Affairs study of 408 patients undergoing mastectomy, 73% of whom were age 50 years or older, the 30-day operative mortality rate and rate

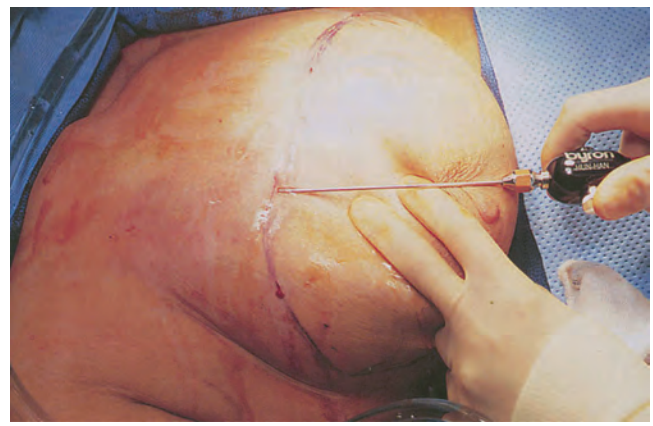

FIGURE 33-2 Tumescent injection to reduce bleeding and facilitate knife dissection.

of operation-related readmissions were both less than 1% (7). The most common complications perioperatively were superficial wound infections, seen in 6% of patients. The National Surgical Quality Improvement Program's (NSQIP) Patient Safety in Surgery study collected data on breast surgery from 14 universities and 4 community centers. The mastectomy mortality rate was 0.24%, and the 30-day morbidity rate was 5.7% with a 3.6% incidence of wound complications (8). Factors that predispose to infection include the use of a two-step procedure (i.e., initial surgical biopsy or attempted lumpectomy) and prolonged suction catheter drainage. Early infections present as cellulitis, whereas those occurring later present as abscess. *Streptococcus* and *staphylococcus aureus* are the most common etiologic organisms. Because the incidence of infection after mastectomy is so low, the cost effectiveness of routine prophylactic antibiotic use is uncertain, although Platt et al. (9) did demonstrate that a single dose of preoperative cephalosporin reduced the incidence of infection by 38%. Antibiotics are routinely given to patients having immediate reconstruction and those who have had prior open surgery. Seroma formation is a universal occurrence after mastectomy and should not be considered a complication; drains are routinely placed to allow fusion of the dermal layer to the chest wall. Flap necrosis has become less common as abandonment of the Halstedian concepts of breast cancer surgery meant that extremely thin skin flaps and removal of large amounts of skin were no longer felt to be important to cure of breast cancer. Most flap necrosis is partial thickness and occurs adjacent to the incision line (Fig. 33-3). Skin necrosis can be minimized by avoiding removal of the subcutaneous fat layer from the flaps, closure under tension, and pressure dressings, all of which decrease the already compromised blood supply to the skin. Postoperative phantom breast syndrome is well described and occurs in approximately 25% of women after mastectomy (10). Chronic pain was previously thought to be an uncommon sequelae of mastectomy, but prospective cohort studies suggest that this syndrome is seen in 40–50% of women (11,12). In one study, half of women who had postmastectomy pain in the early postop period had persistent pain a mean of 9 years after surgery (12). Young age is associated with a higher risk of postmastectomy pain syndrome in most studies. The pain is thought to be neuropathic in etiology, and the outcome of physical therapy and pharmacologic intervention has varied. Patients should be advised preoperatively that they will experience a loss of chest wall sensation with mastectomy, with return of a variable degree of feeling beginning about 1 year postoperatively.

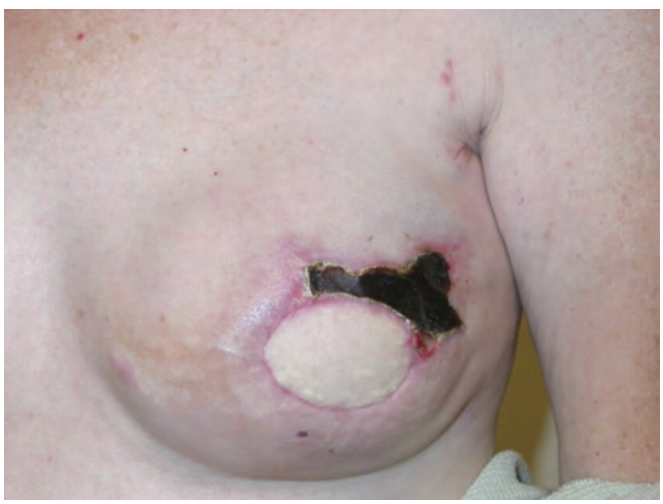

FIGURE 33-3 Partial thickness flap necrosis adjacent to the incision line in a skin-sparing mastectomy. The eschar is beginning to separate.

Skin-Sparing Mastectomy

When immediate reconstruction is planned, a skin-sparing approach is preferred. First described by Toth and Lappert (13) in 1991, this procedure removes the nipple, areola, and the breast parenchyma, while maintaining the overlying breast skin as an envelope for the reconstruction. Traditionally, surgical biopsy scars have been removed because they are potentially contaminated with cancer cells. Whether this is necessary is uncertain. Since DCIS and stage 1 and 2 breast cancer are not diseases of the skin, skin-sparing mastectomy should not increase the rate of chest wall recurrence. However, it is technically more difficult to perform a mastectomy through a small skin-sparing incision, and care must be taken to ensure that tissue is removed to the standard anatomic limits of a mastectomy. Adequate exposure is gained through incision, rather than excision, of the skin. A 2012 meta-analysis compared rates of local recurrence after mastectomy and immediate reconstruction to rates of local recurrence after mastectomy alone in 3,710 patients, all from retrospective cohort studies. The odds ratio for local recurrence was 0.98 (95% CI, 0.62–1.54) (14). In studies specifically examining skin-sparing mastectomy for DCIS, reported rates of local recurrence range from 0 to 3.8% (15), similar to the 1.4% incidence reported for conventional mastectomy (16). Initial concerns that immediate breast reconstruction might impede the detection of local recurrence have not been proven to be true. The majority of local recurrences occur in the skin or subcutaneous fat, and their detection is not affected by the presence of an underlying reconstruction.

Nipple- or Areolar-Sparing Mastectomy

Nipple- and areolar-sparing mastectomy (NSM), also known as total skin-sparing mastectomy, has become increasingly popular due to the excellent cosmetic results that can be achieved in properly selected patients. The oncologic concerns raised by NSM include the possibility that occult cancer will be left behind in the nipple-areolar complex (NAC) and the need to leave behind some breast tissue beneath the NAC to provide a blood supply, raising the possibility that new cancers could develop in this tissue in the future. The reported rates of occult nipple involvement with cancer vary from 5% to 58% (17). This wide variation is secondary to differences in both patient populations studied and the extent of histologic evaluation of the NAC. Brachtel et al. performed a prospective study of 316 consecutive mastectomy specimens, 232 in patients with cancer with grossly normal nipples (18); although the median distance from the primary tumor to the nipple was 4 cm, 21% of cases had tumor involving the nipple. The NAC involvement was DCIS in 62% of cases and invasive in the remainder. On multivariate analysis, tumor size, the distance from the tumor to the nipple, and HER2 amplification were significant predictors of nipple involvement. Intraoperative frozen section is commonly used to identify unsuspected involvement of the NAC, with reported false-negative rates ranging from 1% to 3% in small studies. However, in a study of 1,001 NSMs, Petit et al. found a false-negative rate of 8.6% for frozen section (19). The frozen section is performed on the subareolar breast tissue. Brachtel et al. reported that of 45 patients with histologic involvement of the nipple in their series, 36 had involvement of the subareolar tissue, and in 9, tumor was

present only in the nipple, resulting in a sensitivity of 80% for frozen section of the subareolar tissue and a negative predictive value of 96% (18). Efforts to detect NAC involvement with preoperative imaging have not proven to be particularly successful to date. Sacchini examined the use of magnetic resonance imaging in 125 patients, 41 with DCIS, and the remainder with invasive carcinoma, and found a sensitivity of 57% and a specificity of 85.5% for the detection of tumor in the NAC. Sensitivity was 75% for invasive cancer and 33% for DCIS. The risk of future cancer in the retained NAC is related to the amount of underlying breast tissue. Even when very thin nipple flaps are created, this remains a potential problem. In a study of 62 BRCA mutation carriers, 15 (24%) were found to have terminal duct lobular units (TDLU) in the NAC. Some have advocated nipple removal with preservation of the areola to avoid this problem, but in this study, only 3 of the 15 cases had TDLUs confined to the nipple papilla (20). In addition to concerns about recurrence in the retained NAC, the decreased exposure from the limited incisions used for NSM (discussed below) raises the possibility of an increased risk of recurrence elsewhere on the chest wall due to retained breast tissue (Fig. 33-4). In spite of these theoretical concerns, initial reports of outcomes of NSM have been largely favorable. In a 2013 review of oncologic outcomes in 10 studies including 1,148 mastectomies, the locoregional recurrence rate was 2.8% (21). However, the median follow-up was only 2 years. A definite note of caution regarding the safety of NSM was sounded by the report from Petit et al. describing the vast experience of the European Institute of Oncology with NSM (22). They reported 772 patients with invasive cancer and 162 with DCIS, and all received intraoperative radiotherapy to the NAC at a dose of 16 Gy. With a median follow-up of 50 months, the 5-year local recurrence rate for the invasive cancer patients was 4.4%, and the recurrence rate was 7.8% for those with DCIS. As illustrated in Table 33-1, the majority of these recurrences did not occur in the NAC but elsewhere on the chest wall. When this study was initially reported at 20 months follow-up, there were no recurrences in the NAC, and the overall rate of local recurrence was only 1.4% (19), illustrating the need for adequate follow-up to determine the safety of this operative approach. In this series, recurrence in the NAC presented as Paget's disease in 20% of cases (23), and this type of recurrence was associated with DCIS or an invasive carcinoma with an extensive intraductal component at initial presentation as well as HER2 overexpression.

TABLE 33-1

Local Recurrence After Nipple-Sparing Mastectomy

5-Year Rate of Local Recurrence	*Invasive Cancer*	*DCIS*
	n = 772	**n = 162**
Nipple areolar complex	0.8%	2.9%
Chest wall	3.6%	4.9%

Median follow-up: 50 months. All patients received 16 Gy to the nipple areolar complex.
DCIS, ductal carcinoma in situ.
Data from Petit JY, Veronesi U, Orecchia R, et al. Nipple-sparing mastectomy with nipple areola intraoperative radiotherapy: one thousand and one cases of a five years experience at the European Institute of Oncology in Milan (EIO). *Breast Cancer Res Treat* 2009;117(2):333–338.

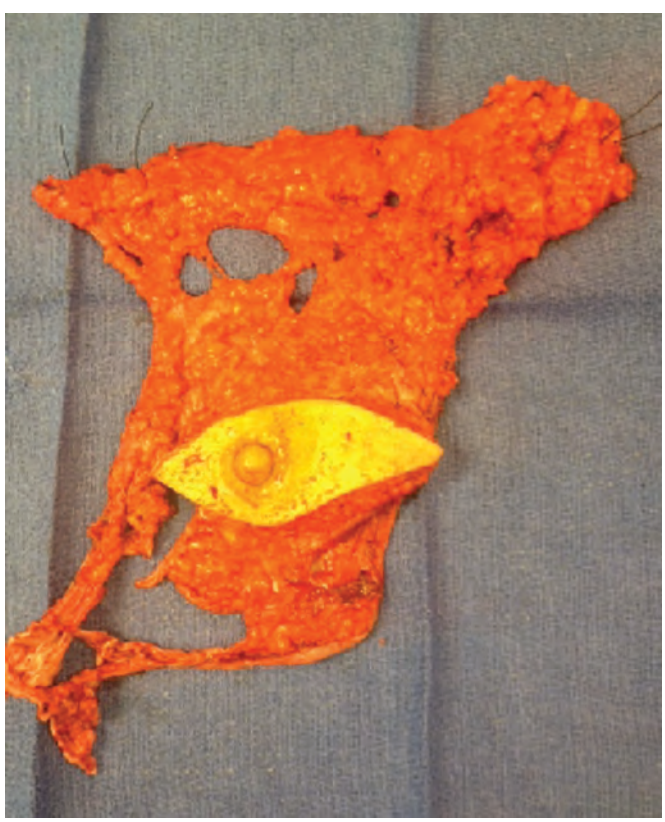

FIGURE 33-4 Retained breast tissue after nipple-sparing mastectomy in a patient who developed recurrent DCIS at a distance from the nipple.

Non-Oncologic Outcomes of NSM

The non-oncologic outcomes of interest after NSM are the incidence of nipple necrosis, retention of sensation in the nipple, and the overall cosmetic result. In a review of 3,091 mastectomies, some degree of nipple necrosis was reported in 9.1% of cases, with complete necrosis in 2%. Additionally, some degree of skin flap necrosis was seen in 9.5% of cases, with a 3.4% incidence of expander-implant loss (21). Factors associated with nipple necrosis include smoking, thin areolar flaps, circumareolar incisions, and flap reconstruction or placement of permanent implants (as opposed to tissue expanders) (17). Sensation after NSM has not been systematically evaluated in a prospective fashion. Petit et al. reported that nipple sensation was generally lost, with a rating of 2/10 to light touch; some recovery was seen in 15% of 1,001 patients at 1 year (19). In this study, both patients and surgeons evaluated the overall cosmetic outcome as 8/10. In contrast, in a series of 54 NSMs from the University of Texas MD Anderson Cancer Center, the cosmetic appearance of the NAC was rated by surgeons as poor or unacceptable in 44% of cases (24). Studies comparing cosmetic outcomes after NSM (Fig. 33-5A) and skin-sparing mastectomy with nipple reconstruction (Fig. 33-5B) were not identified during literature review for this chapter.

Patient Selection and Technique

Clinical evidence of NAC involvement is an absolute contraindication to NSM, as are T3 and T4 cancers and tumors within 1 cm of the nipple. The procedure should be used with caution in patients with cancers larger than 3 cm, particularly larger cancers in small breasts, and those with DCIS extensive enough to necessitate mastectomy. The ideal candidate for NSM is the patient with a small peripheral tumor who is a

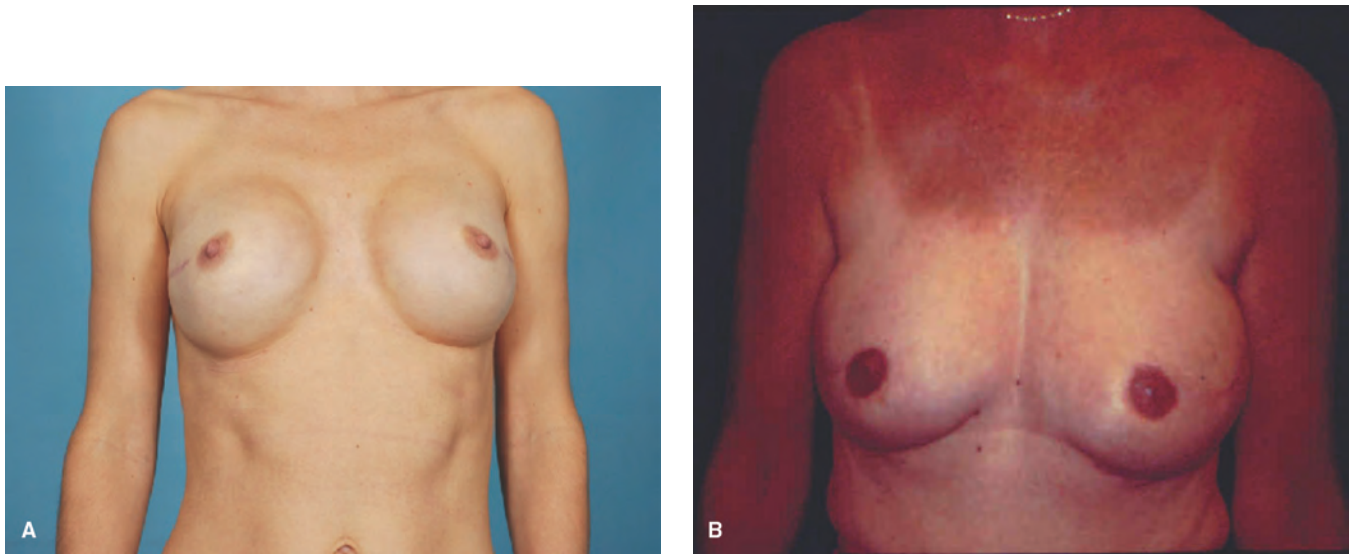

FIGURE 33-5 **(A)** Breast appearance after bilateral nipple-sparing mastectomy. **(B)** Breast appearance after bilateral skin-sparing mastectomy and nipple reconstruction.

candidate for breast conservation, but who wishes to undergo a mastectomy. Women undergoing prophylactic mastectomy are also appropriate candidates, although the impact of leaving behind breast tissue on the risk of subsequent cancer development in BRCA mutation carriers is unknown at this time. Circumareolar incisions should be avoided. Lateral incisions or inframammary incisions are preferable for preserving the blood supply to the NAC, with the choice depending upon breast size and the distance from the inframammary fold to the clavicle. The use of intraoperative frozen section and marking the subareolar region of the mastectomy specimen facilitate evaluation of the adequacy of the procedure. At present, patients should be counseled that in the absence of high-quality prospective studies and long-term follow-up, NSM cannot be considered the standard approach to mastectomy but is an option for selected patients with favorable cancers. Patient education about the risks, uncertainties, and alterations in nipple sensation is essential.

Intramammary Lymph Node Metastases

Intramammary lymph nodes are usually incidental findings, and the reported incidence varies from 1% to 48% (25). In the 7th Edition of the American Joint Committee on Cancer staging system, there is no distinction made between intramammary nodes and axillary nodes, with metastases to either group classifying the patient as at least N1. Metastases to the intramammary nodes are highly correlated with axillary nodal metastases, and approximately 60–80% of patients with intramammary metastases have concurrent axillary disease (26,27). In the era of sentinel lymph node biopsy, the clinical question of whether the presence of an intramammary node metastasis in conjunction with a negative axillary sentinel node biopsy is an indication for axillary dissection has arisen. A literature review identified only 28 reported cases with a positive intramammary node and a negative axillary sentinel node out of a pool of 27,238 patients. A completion axillary dissection was performed in 14 of the 28 cases, and no axillary nodal disease was identified (26). Although the evidence is limited, intramammary node metastasis alone should not be considered an indication for axillary dissection. Prognostically, they have the same impact as axillary nodal metastases.

Margin Status and Local Recurrence

Axillary nodal status is the most important predictor of local-regional recurrence (LRR) after mastectomy. Other factors, including molecular subtype (as approximated by immunohistochemical markers), tumor size and grade, and age, have also been associated with LRR. The diagnosis, management, and prognosis of LRR after mastectomy are discussed in detail in Chapter 69. The impact of mastectomy margin status on recurrence is controversial and will be reviewed here. The literature on this subject is extremely variable, in part because margins were not routinely assessed in many studies, techniques of pathologic processing varied, and, as is the case with margins in breast-conserving therapy, no standard definition of a close margin was employed. Most studies examining margins have considered only the posterior margin. Assessment of anterior margins, particularly in skin-sparing mastectomy, is difficult because ink frequently leaks into the crevices of the fatty, irregular breast tissue, resulting in false-positive readings of close or positive margins. Additionally, studies do not always distinguish between invasive and in situ cancer in proximity to the margin, and it is not clear that DCIS close to a margin is important when there is no residual breast tissue. Positive margins are uncommon, seen in only 2.5% of 12,552 mastectomies reviewed by Rowell (28). Close margins, defined as anywhere from <2 mm to 1 cm, were present in 8% of 8,964 patients. In five studies in which radiotherapy was not given, the relative risk of LRR was 2.6 (95% CI, 1.8–3.8; $p < .00001$) for those with close or positive margins (28); however, in individual studies in which multivariate analysis was used to control for other factors known to influence LRR, margin status was a significant predictor in two studies and not significant in two others. In two additional studies in which all patients received radiotherapy, margin status was not a predictor of LRR. In a more recent study, Childs et al. assessed the impact of both anterior and posterior margin status on recurrence in a group of 397 women undergoing mastectomy but not radiotherapy between 1998 and 2005 (29). Positive superficial margins were present in 10% of patients, and positive posterior margins were present in 6%. Close margins, defined as <2 mm, were seen in 14% and 9%, respectively. At a median follow-up of 6.7 years, the 5-year rate of LRR was 6.2% for those with positive margins

compared to 1.8% for those with close or negative margins (p = .013). The type of tumor at the margin (invasive vs. DCIS) and which margin was involved were not significant predictors of recurrence. On multivariate analysis, only positive margins and triple-negative subtype were predictors for isolated LRR. Ideally, positive margins are avoided by removing a piece of the pectoral muscle when a tumor is in close proximity to the posterior margin and creating thin skin flaps anteriorly. When margins are truly positive, the use of postmastectomy radiotherapy seems prudent, although communication between the surgeon and the radiation oncologist regarding the intraoperative findings is helpful in making this decision. Given the uncertainty regarding the impact of close margins on LRR, using this as the sole indication for postmastectomy radiotherapy is not advisable. Rather, close margins should be considered in the context of other factors that influence local recurrence when making a decision about the benefits of postmastectomy radiotherapy.

MANAGEMENT SUMMARY

- Mastectomy historically was the primary mode of local therapy for breast cancer. Despite the increased use of breast-conserving therapy, mastectomy remains an option for women diagnosed with breast cancer.
- Criteria of inoperability include inflammatory cancer, skin satellites, ulcerated tumors, and tumors fixed to the bony chest wall. Preoperative chemotherapy or endocrine therapy will render the majority of these cases operable.
- The use of skin-sparing mastectomy to facilitate immediate reconstruction does not increase the risk of local recurrence.
- Nipple-sparing mastectomy leaves behind residual breast tissue, and surgical exposure is more challenging than in a skin-sparing mastectomy. The long-term oncologic results of this procedure are uncertain. Patients with cancers in proximity to the nipple, locally advanced disease, and extensive DCIS are not candidates for this approach.
- Involvement of intramammary lymph nodes has a prognosis similar to axillary node involvement and is associated with axillary metastases. In the uncommon setting of a positive intramammary node and a negative axillary sentinel node, axillary dissection is not indicated.
- Positive mastectomy margins are usually an indication for radiotherapy. The significance of close margins is uncertain, and they should be considered in the context of other factors influencing the risk of local recurrence when making decisions about radiotherapy. Close margins alone do not indicate the need for irradiation.

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CHAPTER 34

Contralateral Prophylactic Mastectomy

Todd M. Tuttle

CHAPTER CONTENTS

INTRODUCTION

Patients with unilateral breast cancer are at increased risk for developing cancer in the contralateral breast. As a result, some patients choose contralateral prophylactic mastectomy (CPM) to prevent cancer in the contralateral breast. Several studies have reported that the CPM rates have markedly increased in recent years in the United States. In this chapter, we will discuss recent CPM trends, potential reasons patients choose CPM, outcomes after CPM, and alternative strategies for managing the increased risk of contralateral breast cancer among survivors of unilateral breast cancer.

CPM TRENDS

Contralateral prophylactic mastectomy is the removal of the normal intact breast among women with unilateral breast cancer. The Surveillance Epidemiology and End Results (SEER) registry began coding CPM in 1998. At that time, the proportion of patients who underwent CPM in the United States was very low (1). However, the CPM rate among all surgically treated patients with invasive breast cancer increased 150% from 1998 to 2003 in the United States (Fig. 34-1). Among mastectomy patients, the CPM rate increased 162% from 1998 to 2003 (Fig. 34-2). These trends were observed for all cancer stages and continued to increase at the end of the study period with no plateau. Among the SEER registries, Atlanta had the highest CPM rates, while Connecticut had the lowest rates. Although significant geographic variations were observed between different SEER registries, no general geographic trends were identified. Similar findings were observed in the SEER database among patients with ductal carcinoma *in situ* (DCIS) (2).

Other studies using different databases have confirmed these findings. Using the American College of Surgeons' National Cancer Data Base (NCDB), Yao et al. reported similar increases in CPM rates from 1998 to 2007; by 2007, the rates were still increasing with no plateau effect (3). In a study using the New York State Cancer Registry, McLaughlin et al. reported that CPM use more than doubled from 1995 to 2005 (4). Single-institutional studies have also demonstrated marked increases in CPM rates (5–7).

In contrast, similar trends have not been observed in Europe. In a single-center study from Switzerland, Güth et al. reported that the CPM rates at an academic surgery center did not increase from 1995 to 2009 (8). The authors concluded that the increased use of CPM was a "trend made in the USA." Another study supports this viewpoint. In an international registry of women with unilateral breast cancer and BRCA mutation, Metcalfe et al. reported that 49% of women in the United States underwent CPM (9). In contrast, the CPM rates for Europe and Israel were only about 10% or less.

Various patient, tumor, and treatment factors are significantly associated with CPM rates (see Table 34-1). Younger women are much more likely to receive CPM (1,3). White race, higher education level, private health insurance, and family history of breast cancer have also been associated with higher CPM rates (1,3,5,7). In the SEER study, the presence of infiltrating lobular histology was one of the strongest predictors of CPM (1). Yet, population-based studies indicate that the risk of contralateral breast cancer is not significantly increased for infiltrating lobular histology as compared with infiltrating ductal histology (10). Multicentric breast cancer has also been associated with higher CPM rates (11). BRCA testing is significantly associated with CPM, even among patients who do not have BRCA mutations. In one single-center study, the CPM rate was 40% among those patients who tested negative for mutations (12). Several studies have reported that preoperative MRI is associated with CPM (5,7,11). Patients treated at comprehensive cancer programs or teaching facilities are more likely to receive CPM (3).

REASONS FOR INCREASED CPM RATES

This trend towards more aggressive breast cancer surgery is curious and counterintuitive in the modern era of minimally invasive surgery. The following section of this chapter is largely speculative because the exact reasons for increased CPM rates in the United States are unknown. However, many factors probably contribute to increased CPM use. Public awareness of genetic breast cancer and increased BRCA testing may partially explain these observations. Improvements in mastectomy (including skin-sparing and nipple-sparing mastectomy) and reconstruction techniques and access to breast reconstruction probably contribute to increased CPM rates.

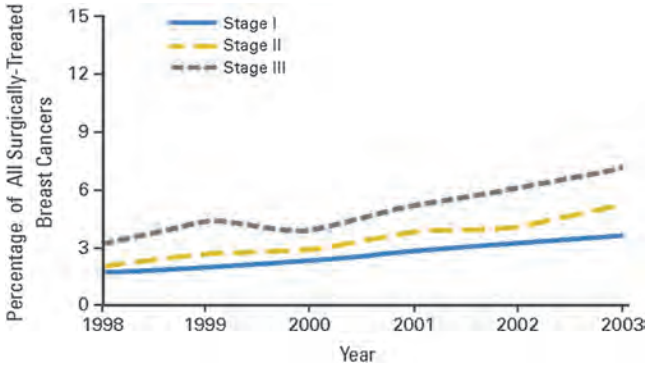

FIGURE 34-1 Overall CPM rates in the United States according to cancer stage. (From Tuttle TM, Habermann EB, Grund EH, et al. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. *JCO* 2007;25:5203–5209.)

Moreover, symmetric reconstruction is often easier to achieve after bilateral mastectomy as compared to unilateral mastectomy. Additionally, the native and reconstructed breast age differently, so symmetric outcomes may diminish over time.

Several studies have reported that preoperative breast MRI is associated with higher CPM rates (5,7). The proposed explanation is that MRI findings introduce concern about the opposite breast. For example, a patient is diagnosed with a unilateral breast cancer, and clinical breast examination and mammography of the contralateral breast are normal. The patient is an ideal candidate for breast-conserving treatment. However, an MRI is obtained which demonstrates an occult indeterminate lesion in the contralateral breast. Next, the patient undergoes a second-look (targeted) ultrasound to characterize this MRI finding. The ultrasound imaging is normal, so she gets called back again for an MRI-guided biopsy, which is negative for cancer. However, the patient decides to have bilateral mastectomy to avoid this stressful scenario again. Preoperative breast MRI probably contributes to increased CPM rates, but the initial observed CPM trends in the United States preceded the widespread use of breast MRI (1,3).

Obesity rates in the United States have markedly increased over the past two decades. An obese woman with large breasts may encounter asymmetry and balance problems after unilateral mastectomy without reconstruction. Also, a plastic surgeon may have technical challenges in achieving a symmetric reconstruction after unilateral mastectomy for an obese woman with large breasts. For some women, bilateral mastectomy with or without reconstruction may provide effective local breast cancer treatment, avoid future radiographic surveillance, and may relieve symptoms from macromastia. Nevertheless, it is not known whether increasing obesity rates are contributing to current CPM trends.

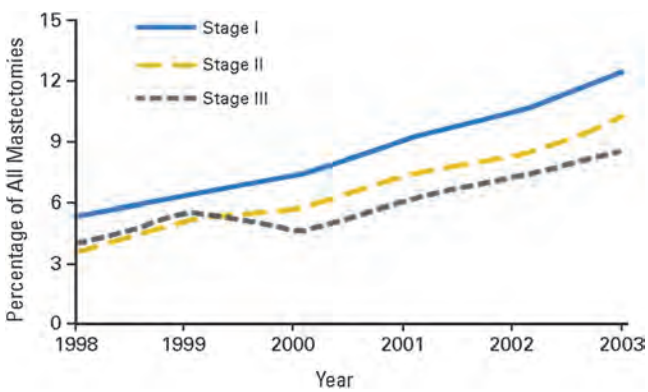

FIGURE 34-2 CPM rates among mastectomy patients according to cancer stage. (From Tuttle TM, Habermann EB, Grund EH, et al. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: a trend toward more aggressive surgical treatment. *JCO* 2007;25:5203–5209.)

TABLE 34-1

Factors Associated with Contralateral Prophylactic Mastectomy Use

Patient
Young age
White race
Private insurance
Family history of breast cancer
Tumor
Infiltrating lobular histology
Multicentric disease
Tumor size
Treatment
BRCA testing
MRI
Breast reconstruction
Facility type

Another possible explanation for the increased CPM rates is that some patients may considerably overestimate their risk of contralateral breast cancer. Previous studies have reported that women with early breast cancer markedly overestimate their risk of recurrence (13). In a recent survey of 350 mastectomy patients, Han et al. reported that the most common reason for CPM was worry about contralateral breast cancer (14).

The annual rates of metachronous contralateral breast cancer for women with unilateral breast cancer are fairly constant (10). In an analysis of the SEER database, Gao et al. reported that medullary carcinoma, black race, and age >55 years were associated with significantly higher rates of contralateral breast cancer (10). The incidence of contralateral breast cancer was not significantly different for DCIS or infiltrating lobular as compared with infiltrating ductal carcinoma. The Early Breast Cancer Trialists' Collaborative Group recently updated their meta-analyses and reported that the annual rate of contralateral breast cancer was about 0.4% for patients with estrogen receptor-positive breast cancer treated with tamoxifen; the annual rate of contralateral breast cancer was about 0.5% for patients with estrogen receptor-negative breast cancer (15). All age, tumor, and treatment subgroups had rates less than 0.7%/year. Thus, the 10-year cumulative risk of contralateral breast cancer is about 4% to 5%. In fact, the risk of contralateral breast cancer may be even lower for patients diagnosed today. Nichols et al. reported that the rates of metachronous contralateral breast cancer have significantly decreased since 1985 largely because of adjuvant systemic therapies (16).

Abbott et al. recently published the results of a prospective single-center study designed to determine patients' perceived risk of contralateral breast cancer (17). Patients completed a standardized survey prior to surgical

consultation and were asked to estimate their risk of contralateral breast cancer. Patients substantially overestimated their 10-year cumulative risk of contralateral breast cancer, with a mean perceived risk of 31.4%. Also, an increased perceived risk of contralateral breast cancer was significantly associated with measurements of psychological distress.

Moreover, some patients may overestimate the oncologic benefits of CPM. In a review of open-ended comments from women who underwent CPM, Altschuler et al. recorded comments such as "I do not worry about recurrence," and I am "free of worries about breast cancer" (18). Such comments suggest a lack of understanding of the benefits of CPM, as removal of the normal contralateral breast does not treat systemic metastases from the known ipsilateral breast cancer.

OUTCOMES AFTER CPM

Several studies have demonstrated that CPM is effective in reducing the risk of contralateral breast cancer. In a study of 745 breast cancer patients with a family history of breast cancer, McDonnell et al. reported that CPM reduced the incidence of contralateral breast cancer by more than 90% (19). In a retrospective study of 239 patients, Goldflam et al. reported that only 1 contralateral breast cancer (0.4%) developed after CPM (20). Depending upon the statistical methods used, CPM reduces the risk of contralateral breast cancer by about 90%.

However, the effectiveness of CPM in reducing breast cancer mortality is not as clear. The only plausible way that CPM improves breast cancer survival is by reducing the risk of a potentially fatal contralateral breast cancer. A recent survival analysis of the SEER database included patients with unilateral breast cancer diagnosed between 1998 and 2003 (21). The authors concluded that CPM is associated with a small improvement (4.8%) in 5-year breast cancer specific survival rates for young women with early-stage estrogen receptor-negative breast cancer. However, the cumulative incidence of contralateral breast cancer was less than 1% in this study; so, the apparent survival benefit is most likely due to selection bias. In a retrospective single-center study, Boughey et al. reported that CPM was associated with improved overall survival and disease free survival rates (22). However, a recent Cochrane review of published CPM studies concluded that "there is insufficient evidence that CPM improves survival" (23).

Despite the results of retrospective or cancer registry studies, CPM is not likely to improve breast cancer survival rates for patients who do not have BRCA mutations. For these patients, the 10-year cumulative risk of contralateral breast cancer is about 4% to 5%; most metachronous contralateral breast cancers are stage I or IIA with a 10-year mortality rate of about 10% to 20%. Thus, the 20-year mortality rate from a contralateral breast cancer is about 1% or less. In addition, many patients die from systemic metastases from their known ipsilateral breast cancer or from other causes during 20-year follow-up. Finally, CPM does not prevent all contralateral breast cancers. Thus, CPM will not decrease breast cancer mortality rates for most breast cancer patients without BRCA mutations.

On the other hand, for patients with BRCA-associated unilateral breast cancer, the annual risk of contralateral breast cancer is about 4% per year with a cumulative 10-year risk of contralateral breast cancer of about 40% (24). Thus, the possibility of developing a potentially fatal contralateral breast cancer is substantially higher among breast cancer patients with a BRCA mutation. The relative risk reduction of CPM is similar for patients with and without BRCA mutations. Using Markov modeling, Schrag et al. estimated that CPM would increase life expectancy by 0.6 to 2.1 years for a 30-year old patient with a BRCA mutation (25). Patients with unilateral breast cancer who have received supradia-phragmatic radiotherapy for Hodgkin's lymphoma may also potentially benefit from CPM because the annual risk of contralateral breast cancer is about 3% to 4% per year (26). Clearly, randomized trials comparing CPM with no CPM for either selected (BRCA mutations) or heterogeneous patients are not feasible.

Contralateral prophylactic mastectomy is an irreversible procedure and is not risk free. Severe complications after CPM may potentially delay recommended adjuvant therapy and may require additional surgical procedures and subsequent loss of reconstruction. The overall complication rate after bilateral mastectomy and reconstruction is about 15% to 20% (20). About half of the complications are secondary to the prophylactic mastectomy. Even without complications, these operations are long (often 5 to 6 hours) and require 2 to 3 days of inpatient hospital care, drainage catheters, and 3- to 4-week overall recovery.

Despite potential risks and complications, most patients are satisfied with their decision to undergo CPM. The greatest reported benefit contributing to patient satisfaction is a reduction in breast cancer related concerns. Frost et al. reported that 83% of patients were either satisfied or very satisfied with their decision to undergo CPM at a mean of 10 years after surgery (27). Some women have negative psychosocial outcomes following CPM, most often related to high levels of psychological distress, sexual function, and body image or poor cosmetic outcome (18). Montgomery et al. reported that the most common reasons for regret after CPM were a poor cosmetic outcome and diminished sense of sexuality (28).

ALTERNATIVES TO CPM

Patients with unilateral breast cancer have options that are less drastic than CPM. Surveillance with clinical breast examination, mammography, and potentially breast MRI may detect cancers at earlier stages. Several prospective randomized trials have demonstrated that tamoxifen, given as adjuvant therapy for estrogen receptor-positive breast cancer, significantly reduces the rate of contralateral breast cancer. In the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-14 study, 2,892 women with node-negative, estrogen receptor–positive breast tumors were randomly assigned to either tamoxifen (20 mg/d) or placebo for at least 5 years (29). After an average follow-up of 53 months, 55 contralateral breast cancers developed in placebo-treated women and 28 developed in the tamoxifen-treated women (p = .001).

Aromatase inhibitors may reduce the risk of contralateral breast cancer as much as, or even more than, tamoxifen (30). The ATAC (Arimidex, Tamoxifen Alone or in Combination) Trial demonstrated that anastrozole was superior to tamoxifen in preventing contralateral breast cancer in postmenopausal women. Ovarian ablation and cytotoxic chemotherapy also reduce the risk of contralateral breast cancer (31).

CONCLUSIONS

Increasingly more patients in the United States with invasive breast cancer and DCIS undergo CPM to prevent contralateral breast cancer. Patient, tumor, and treatment factors are

associated with increased use. Indeed, CPM does reduce the risk of contralateral breast cancer, but does not impact breast cancer survival rates. Controversy exists about whether the physician or patient should initiate the discussion of CPM. If a patient appropriately chooses breast-conserving surgery, then CPM is not a relevant treatment. For patients who undergo mastectomy, CPM may be a reasonable option, particularly if a patient has a BRCA mutation, strong family history, is obese, or if imaging of the contralateral breast is difficult. Recent studies have demonstrated that many patients are not well informed about the risk of contralateral breast cancer or the benefits of CPM. Physicians need to provide breast cancer patients with accurate information on the risk of contralateral breast cancer and on the risks and benefits of CPM. In addition, physicians should encourage appropriate patients to consider less drastic options (e.g., endocrine therapy) to reduce the risk of contralateral breast cancer.

Presently, no study has prospectively evaluated the complex decision-making processes that lead to CPM. Future research should include development of models and instruments to elucidate these processes. Also, the surgeon's role and influence in choice of breast cancer surgery should be evaluated. Finally, decision aids should be developed for breast cancer patients and physicians.

MANAGEMENT SUMMARY

- The annual risk of developing contralateral breast cancer is about 0.5% per year among patients without BRCA mutations.
- The annual risk is about 4% per year among patients with BRCA mutations.
- Many patients substantially overestimate their risk of contralateral breast cancer.
- Contralateral prophylactic mastectomy reduces the risk of contralateral breast by 90% or more.
- Contralateral prophylactic mastectomy does not improve breast cancer mortality rates.
- The rates of contralateral prophylactic mastectomy have markedly increased in the United States in recent years.
- Physicians should discuss alternative approaches to contralateral prophylactic mastectomy including surveillance and endocrine therapy.

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CHAPTER 35

Breast-Conserving Therapy

Jay R. Harris and Monica Morrow

CHAPTER CONTENTS

Breast-conserving therapy (BCT), a combination of breast-conserving surgery (BCS) followed by whole breast irradiation, is an established standard of care for local-regional treatment for early-stage breast cancer. The first clinical trials investigating BCT began more than three decades ago. The outcome data from these trials, including a meta-analysis of all of the trials (1), provided clear evidence that breast-conserving surgery followed by whole breast radiation achieved long-term survival equivalent to mastectomy.

Currently, most patients with newly diagnosed breast cancer are candidates for BCT. The increased use of mammographic screening, and improved public education about breast cancer, have dramatically increased the percentage of cases that present with early-stage disease. Studies have demonstrated that BCT positively impacts patient well-being and quality of life. Over time, as experience has been gained with BCT and the use of adjuvant systemic therapy has become routine even for patients with stage 1 breast cancer, rates of local recurrence (LR) after BCT have declined to less than 0.5% per year (2). Despite the established efficacy and excellent outcomes of BCT, recent data show an increase in the utilization of therapeutic mastectomy and prophylactic contralateral mastectomy, particularly among younger patients (3).

This chapter will review the progress that has been made in BCT, including the current selection criteria for BCT, the importance of radiation therapy (RT) as a component of BCT, comparing the approaches of conventional whole breast irradiation versus accelerated whole breast irradiation versus accelerated partial breast irradiation, the patient-, treatment-, and tumor-related factors that influence outcome, and the technical details of optimizing both surgical and radiation treatment of early-stage breast cancer.

SELECTION CRITERIA FOR BREAST-CONSERVING THERAPY

BCT is generally reserved for patients with tumors smaller than 5 cm. However, more important than absolute tumor size is the relationship between tumor size and breast size. The tumor must be small enough, in relation to the size of the breast, to permit the tumor to be resected with clear margins and an acceptable cosmetic result. In patients with invasive breast cancer in which the tumor-to-breast size ratio is unfavorable, preoperative chemotherapy or endocrine therapy can be used to decrease the tumor size sufficiently to permit BCT (see Chapters 54 and 55).

The 2012 National Comprehensive Cancer Network (NCCN) guidelines to contraindications for BCT requiring RT include:

Absolute Contraindications

- Prior RT to the breast or chest wall
- Breast cancer early in a pregnancy that would necessitate RT during pregnancy
- Diffuse suspicious, malignant-appearing microcalcifications
- Widespread disease that cannot be incorporated by excision through a single incision that achieves negative margins with a satisfactory cosmetic result

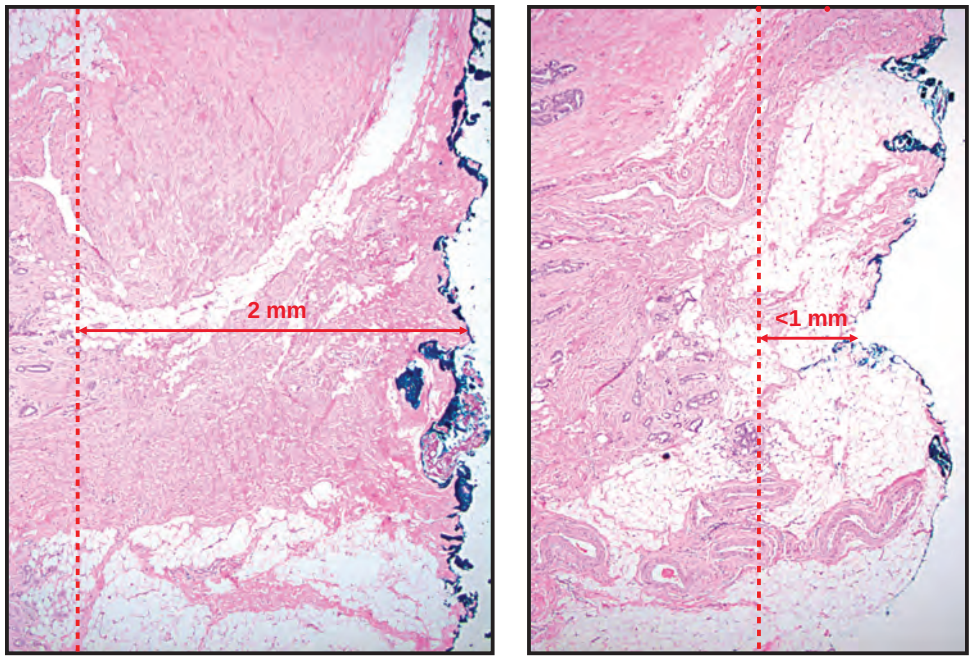

FIGURE 35-1 **Sampling error and margin assessment.** On the left is an initial section with a margin width of 2 mm. A slightly deeper section, shown on the right, was taken for special studies and showed a margin width of less than 1 mm.

Relative Contraindications

- Active connective tissue disease involving the skin (especially scleroderma and lupus, but not rheumatoid arthritis)
- Focally positive margin in the absence of an extensive intraductal component (see below)
- Women with a known or suspected genetic predisposition to breast cancer

The evaluation for BCT includes a history, physical exam, and diagnostic mammography. Using this approach, patients suitable for BCT can be identified with a high degree of success as illustrated by a population-based study of 800 women attempting BCT in which surgery was successful in 88%. Of the 12% who were converted to mastectomy, re-excision was attempted in only one-third, suggesting that the 88% is a minimum estimate (4). There is controversy regarding the role of additional imaging studies, particularly magnetic resonance imaging (MRI) of the breast, in selecting patients for BCT. A meta-analysis of 3,112 patients in 9 studies with comparison cohorts treated with and without MRI found no difference in the need for re-excision or unexpected conversion to mastectomy, after age adjustment, in patients managed with and without MRI (5). The lack of impact of MRI on LR rates is discussed in the following section in the context of margins.

MARGINS AND LOCAL RECURRENCE

Margin width is assessed by applying ink (ideally colored to reflect the individual margins) to the surface of the specimen. Margin width is the distance between tumor cells and inked surface. A *negative margin* is defined by "no ink on any cancer cells." Despite the NCCN guidelines, what constitutes an adequate margin is controversial (6). In surveys, no single margin width is endorsed by more than 50% of respondents (7,8). Many practitioners favor a margin of 2 mm or even greater. As a result, re-excision is commonly used, even with a negative margin. Part of this is due to difficulties in margin assessment. Specimen processing is not standardized and varies between institutions. Sampling error is another difficulty. Even with fastidious assessment of margins, however, only a very small percentage of the entire margin is assessed. This is illustrated in Figure 35-1. On the left is an initial section with a margin width of 2 mm. A slightly deeper section, shown on the right, was taken for special studies and showed a margin width of less than 1 mm. A meta-analysis of 21 studies reporting LR relative to margin width showed that LR was significantly greater with a positive margin than a negative margin, but increasing margin width did not significantly decrease LR (9).

It is becoming increasingly clear that factors other than margin width are the primary determinants of local control. In more recent studies, which include the routine use of adjuvant systemic therapy, substantially reduced rates of LR have been seen. This is illustrated in the 10-year rates of LR in successive National Surgical Adjuvant Breast and Bowel Project (NSABP) trials in node-negative patients treated with BCT (2). In NSABP B-13, which randomized patients with estrogen receptor (ER) negative cancer to adjuvant chemotherapy or not, 10-year LR was 15.3% without chemotherapy and only 2.6% in patients with chemotherapy. Similarly, in NSABP B-14, which randomized patients with ER positive cancer to adjuvant tamoxifen or placebo, 10-year LR was 11.0% with placebo and only 3.6% in patients treated with tamoxifen. During these trials, the NSABP used "no ink on tumor" as the definition of a negative margin. Studies examining the impact of adding trastuzumab to adjuvant chemotherapy in women with HER2-overexpressing tumors demonstrate an additional 40% reduction in the risk of LR, with a median follow-up of 1.5 to 2.0 years (10). In a retrospective study from Memorial Sloan-Kettering Cancer Center, 3-year rates of LR decreased from 7% to 1% in patients with HER2-overexpressing tumors after the addition of trastuzumab to chemotherapy (11). Updated results from Dana-Farber Cancer Institute/Brigham and Women's Hospital, and Massachusetts General Hospital included 1,434 patients; 91% were treated with adjuvant systemic therapy (not including trastuzumab), and with a median follow-up time of 85 months, the 5-year rate of LR was 1.6% and the overall crude rate of LR was 3.1% (12). (These rates are expected

to double at a median follow-up of 10 years.) In this study, as well as several others, the main prognostic factor for LR was biologic subtype approximated by hormonal receptors, HER2 status, and histologic grade, with Luminal A = HR+, HER2-, Gr 1-2; Luminal B = HR+, HER2-, Gr 3; Luminal-HER = HR+, HER2+; HER2 = HR-, HER2+; and triple negative = HR-, HER2-. The crude rate of LR by subtype was 1.5% for Luminal A, 4.0% for Luminal B, 1.0% for Luminal-HER, 10.9% for HER2+, and 8.8% for triple-negative cancers. Age was also in the final model, but the magnitude of the effect was much smaller, with a crude rate of LR of 6.5% for the patients in the lowest age quartile (ages 23 to 46) compared with only 0.9% for patients in the highest age quartile (ages 64 to 88). Margin status was not in the final model of prognostic factors for LR. These and other data indicate that the biological features of the tumor are most important in determining the risk of LR. Studies examining the relationship between molecular subtype, as approximated by receptor status, and LR are summarized in Table 35-1 (12–14). Although definitions of the Luminal B subtype have varied over time, the lowest rates of LR are consistently seen in patients with Luminal A cancers and the highest rates in those with triple-negative cancers (12–14), and this relationship persists even for T1a, b and microinvasive cancers (15) and in patients receiving neoadjuvant chemotherapy (16). The higher rates of LR in patients with triple-negative cancers have raised concern that these patients might benefit from treatment with mastectomy. However, patients with triple-negative cancers have the highest LR risk after both BCT and mastectomy, and retrospective studies do not demonstrate an improvement in local control after mastectomy compared to lumpectomy and radiation, even in this more aggressive tumor subset (17–19). In multivariable analyses controlling for both conventional prognostic factors and biologic subtype, type of surgical procedure (mastectomy vs. BCT) is not a clinically significant predictor of LR for neither high-risk triple negative patients (18) nor the lower-risk ER positive subset (20).

There are additional lines of evidence that widely negative margins are not required (in the large majority of patients) for successful BCT when routine adjuvant systemic therapy is employed. Multiple studies have demonstrated that breast MRI in patients with a known primary identifies multifocal and multicentric cancers (located at a considerable distance from the known primary) in about 11% of patients (21) and triples the age-adjusted odds ratio of an initial mastectomy rather than BCT (5); however, the available studies do not demonstrate lower rate of LR with BCT in patients receiving MRI compared to those who have not (22,23). Additional evidence for the concept that minimizing the subclinical tumor burden is not critical for reducing LR in the current era of multimodality treatment comes from the results of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial. In that study, women undergoing breast-conserving surgery, sentinel node biopsy, and whole breast irradiation, who had metastases in one or two sentinel lymph nodes, were randomized to axillary dissection or no further axillary treatment. All patients received adjuvant systemic therapy. In spite of the finding of additional nodal metastases in 27% of the axillary dissection group, only 0.9% of patients in the sentinel node-only group experienced a first recurrence in the axilla (24).

In considering the use of margins in BCT, it is useful to note that breast cancers are very often multifocal, with at least 40% of cases having microscopic foci greater than 2 cm from the edge of the cancer. This frequency is not influenced by tumor size, and these microscopic foci are more often ductal carcinoma *in situ* (DCIS) than invasive cancer. *A key concept in the practice of BCT is that margin evaluation (and mammography) are used to insure that there is only limited residual cancer capable of being eradicated with conventional doses of RT, but not to insure there is no cancer remaining.*

Thus, the current evidence indicates that in the context of highly effective systemic therapy, no ink on tumor is a sufficient margin for the large majority of patients. However, there are some exceptions, and these include cancers with an extensive intraductal component (EIC), patients receiving preoperative chemotherapy, and pure DCIS. EIC is defined by prominent DCIS within the tumor (~25%) and present in adjacent tissue. The presence of an EIC predicted for LR in patients treated with BCT without margin evaluation; however, EIC ceased to be a prognostic factor for LR with the routine use of margin evaluation. The presence of an EIC also predicts for patients with prominent residual disease after a gross excision of the tumor. Similar considerations exist for patients with pure DCIS, and this is supported by clinical data (25). In both situations, obtaining clearly negative margins is prudent. Finally, since tumors typically respond to preoperative chemotherapy in a honeycomb pattern rather than a concentric pattern, obtaining clearly negative margins is also prudent in the setting of preoperative chemotherapy.

ROLE OF RADIATION THERAPY IN BREAST-CONSERVING THERAPY

Radiation treatments play an important role in successful BCT for patients with invasive breast cancer. It has been clearly demonstrated that radiation treatment of the ipsilateral breast reduces the probability of LR after lumpectomy. More importantly, meta-analyses from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) of all the randomized prospective trials comparing BCS or mastectomy with or without postoperative RT indicate that by eradicating persistent local disease after surgery, RT use reduced the risk of

TABLE 35-1

Local Recurrence after Breast-Conserving Therapy and Molecular Subtype

			Local Recurrence (%)			
Author	*No. of Patients*	*Follow-Up*	*Luminal A*	*Luminal B*	*HER2*[a]	*Triple Negative*
Millar et al. (13)	498	5 yr	1.0	4.3	7.7	9.6
Arvold et al. (12)	1,434	5 yr	0.8	2.3	10.9	8.8
Voduc et al. (14)	1,461	10 yr	8.0	10.0	21.0	14.0

[a]No adjuvant trastuzumab.

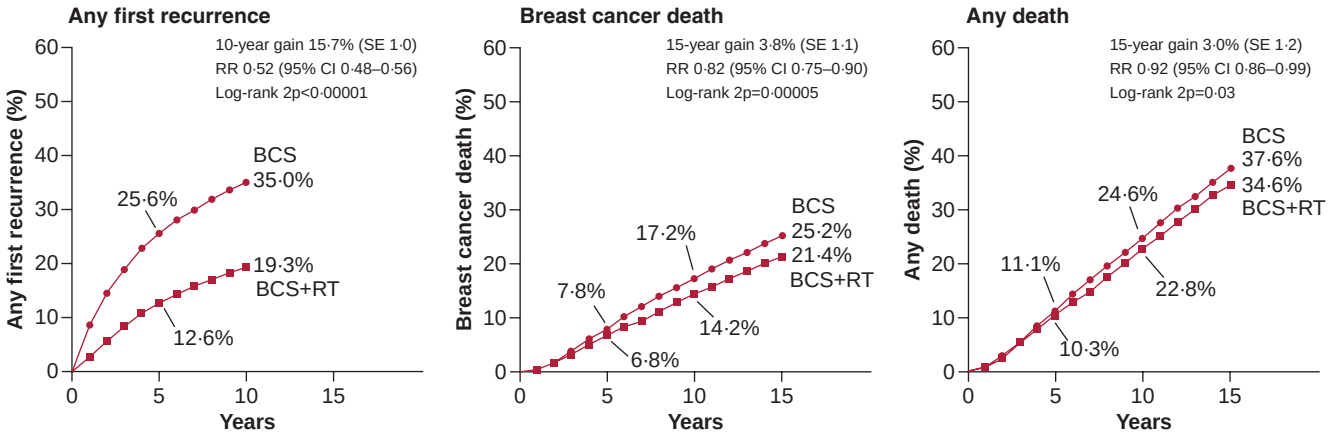

FIGURE 35-2 The data from the EBCTCG meta-analysis of trials investigating breast-conserving surgery with or without breast radiation. Effect of RT after BCS on 10-year risk of any (local-regional or distant) first recurrence and on 15-year risks of breast cancer death and death from any cause in 10,801 women (67% with pathologically node-negative disease) in 17 trials. (From Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. *Lancet* 2011;378:1707–16, with permission.)

subsequent death from breast cancer. The first analysis was published in 2005 and described a 4 to 1 ratio between avoiding LR at 5 years and improving survival at 15 years. After either BCS or mastectomy, RT proportionally reduced LR by 70%. An updated analysis was published in 2011 restricted to patients treated with BCS (26). In this updated analysis, 7 trials of BCS in low-risk patients, most treated with adjuvant hormonal therapy and randomized to breast RT or not, were added to the original 10 trials in the 2005 publication for a total of 10,801 women, 3,143 deaths, and a median woman–years at risk of 9.5. Importantly, the EBCTCG moved from assessing the effect of RT on LR to its effect on first failure (or first recurrence, either LR or distant metastasis). Although commonly employed in studies on the local treatment of breast cancer, actuarial calculation of time to LR is, strictly, not statistically valid. As shown in Figure 35-2, RT proportionally reduced the annual rate of any failure (LR or distant metastases) over the first 10 years by about half (relative risk [RR] = 0.52) and proportionally reduced the annual rate of breast cancer death by about one-sixth. The absolute benefit of RT was greater in patients with the greater risk of recurrence. In node-negative patients, the absolute benefit was strongly correlated with age (inversely), tumor grade and size, and ER status, with very small absolute benefit seen in some subgroups. The updated EBCTCG analysis still demonstrates that local treatment is linked to improved long-term survival; however, the new 4:1 ratio is between the reduction in first failure at 10 years (not the reduction in LR at 5 years) and the reduction in mortality at 15 years.

Do All Patients Treated with Breast-Conserving Therapy Require Radiation?

The initial trials that demonstrated a clear benefit for radiation in BCT included populations that were heterogeneous with respect to risk factors associated with LR. Therefore, the second generation of clinical trials studying BCT investigated whether radiation could be safely omitted in favorable subgroups. Unfortunately, most of these studies were unsuccessful in positively answering the question. For example, a single-arm, 82-patient prospective trial conducted at Harvard Medical School investigated whether breast radiation could be omitted in patients with pT1N0 breast cancer without an extensive intraductal component or lymphovascular space invasion that was excised with 1 cm or greater margins. Despite these favorable features, the trial was closed early after the breast recurrence rate exceeded the predefined stopping rules. The LR rate after a median follow-up of 86 months was 23% (27). These recurrence rates were similar to those seen in a trial from the Milan Cancer Institute that randomized women with tumors 2.5 cm or smaller to a quadrantectomy and axillary dissection without radiation or this same surgery followed by breast irradiation. Despite a more extensive surgical procedure than what is routinely utilized in most North American trials, the 10-year risk of in-breast recurrence was markedly higher in the absence of RT (24%) compared with patients who received RT (6%) ($p < .001$) (28). Randomized trials from Sweden and Finland have also attempted to specifically address whether patients with stage I disease require RT after BCT, and in both of these studies, the use of radiation led to a highly significant improvement in local outcomes (29,30). Finally, it is also clear from several trials that the use of adjuvant chemotherapy does not obviate the need for breast irradiation. For example, in the NSABP B-06 trial, chemotherapy was used for patients with lymph node-positive disease, and these patients had a 44% 20-year risk of in-breast recurrence without radiation compared to a rate of only 9% for those treated with lumpectomy, radiation, and chemotherapy (31).

The most recent randomized trials attempting to identify a favorable cohort with a low risk of in-breast recurrence without radiation have focused on postmenopausal women with hormone receptor positive stage I disease treated with breast-conserving surgery and hormonal therapy. The data from these trials are shown in Table 35-2 (32–37) and demonstrate that the combined modality treatment of breast-conserving surgery, radiation, and adjuvant hormonal therapy is associated with a very low 5-year risk of in-breast or local-regional recurrence.

TABLE 35-2

Randomized Studies Comparing Radiation Use after Breast-Conserving Surgery in Patients with Stage I Disease Treated with Hormonal Therapy

Trial (Reference)	*No. of Patients: Selection*	*Follow-Up (Median months)*	*Hormonal Therapy (%)*	*Hormonal Therapy + Radiation (%)*	*5-Yr End Point*
NSABP B-21 (32)	1,009: ≤1 cm, pN0	87	8.4	1.1	LR
Scottish (33)	427: <70, T1,2, pN0	67	25.0	3.1	L-RR
Austrian (37)	869: ≤3 cm, grade 1, 2, pN0	54	5.1	0.4	LR
Canadian (34)	769: >50, T1/2, pN0	67	7.7	0.6	LR
			13.2	1.1	L-RR
CALGB (35, 36)	636: >70, T1, c, pN0	95	7	1	Crude L-RR

LR, local recurrence; L-RR, local-regional recurrence; CALGB, Cancer and Leukemia Group-B.

In contrast, data from the Scottish trial and the NSABP B-21 trial suggest that the risk of in-breast recurrence remains clinically relevant with BCS and hormonal therapy alone. The one cohort of patients for whom BCS without radiation might be considered as an appropriate option are elderly females with an ER positive stage I breast cancer who are treated with hormonal therapy. The Cancer and Leukemia Group-B (CALGB) Intergroup trial randomized women 70 years of age and older with these disease characteristics to breast-conserving surgery plus tamoxifen or BCS, tamoxifen, and breast irradiation (35). With a median follow-up of 95 months, radiation reduced the local-regional recurrence from 7% to 1% (36). It should be noted that approximately 1 of 6 of these patients enrolled in this study died of intercurrent disease by 5 years. Therefore, how these data should be applied to women over 70 years of age who have a longer life expectancy is less clear. To further study this question, investigators from Yale University reviewed the Surveillance, Epidemiology and End Results (SEER)-Medicare Database and identified 8,724 patients who met the eligibility criteria for this trial. They found similar 5-year outcome rates as those reported in the Intergroup trial (38). However, these investigators also were able to analyze patient subsets and found that the benefits of RT were of a clinically relevant magnitude for patients aged 70 to 79 who had no comorbidities. In contrast, those patients 80 years or older and those with multiple comorbidities had a higher risk of dying from non-breast-cancer–related causes within 5 years and therefore were not at high risk of developing an in-breast recurrence.

In conclusion, all of the clinical studies to date have indicated that without breast irradiation, the risk of LRs after breast-conserving surgery alone is too high and, therefore, breast irradiation should be considered a standard component of treatment for all women with early-stage invasive disease. This has become more feasible with the development of hypofractionated (shorter-course) approaches discussed later. Thus far, the attempts to define subsets of breast cancer patients with favorable early-stage disease that may not require RT by using standard clinical and pathologic criteria have been unsuccessful, with the possible exception of women over 70 years of age with stage I, ER positive disease who are willing to be treated with hormonal therapy. Studies are underway to find molecular markers that can reliably identify patients who may be adequately treated with breast-conserving surgery alone without the need for radiation.

Patient-Related, Disease-Related, and Treatment-Related Factors Associated with Local Outcome after Breast-Conserving Therapy

Patients treated with BCT have excellent rates of local control. The EBCTCG meta-analysis of the first generation of clinical trials investigating breast conservation reported a 5-year in-breast recurrence rate of 6.7% for patients with node-negative disease and 11% for those with node-positive disease (1). The respective 10-year in-breast recurrence rates for these cohorts were 10% and 13.1%, respectively. As previously indicated, there have been a number of changes that occurred over the past few decades that have favorably affected these rates. In part, these changes have come from a greater understanding of patient, disease, and treatment factors that are associated with LRs, and this has helped to refine the selection criteria for breast conservation and has led to changes in treatment techniques to improve outcomes.

Patient-Related Factors. An important patient-related factor that affects in-breast recurrence rates is patient age. Several single-institution studies have reported that young patient age, usually defined as age less than 30 to 40 years, is associated with an increased risk of local recurrence (LR), distant metastases (DM), and reduced disease-specific survival (39–42). This finding was also noted in an European Organisation for Research and Treatment of Cancer (EORTC) randomized trial that investigated the use of a tumor bed boost after whole breast irradiation. Overall, when patients from both arms of the study were evaluated, the 5-year in-breast recurrence rate for patients 40 years of age or less was 15%, compared to rates of 7% for patients aged 41 to 50 years, 4% for patients aged 51 to 60 years, and 3% for patients older than 60 years of age (39). Younger age has also been shown in some studies to adversely affect LR rates after mastectomy. A study from investigators at the University of Texas MD Anderson Cancer Center retrospectively evaluated the local-regional treatment outcome of 668 breast cancers in patients 35 years of age or less (40). In this series, patients with stage I disease who were treated with chemotherapy had acceptable local-regional treatment outcomes with either BCT or mastectomy. However, the patients with stage II disease treated with BCT (18%) or mastectomy without radiation (23%) had higher 10-year local-regional recurrence rates than those treated with mastectomy and postmastectomy radiation (6%). There is some evidence that the impact of young age on the risk of LR has decreased

over time. In a population-based registry study, Van der Sangen et al. reported that the 5-year risk of LR in women less than 40 years of age undergoing BCT decreased from 11% for those treated from 1993 to 1998, to 3.8% for those treated between 2000 to 2005 (43). How much of the age-related risk of LR is due to a higher proportion of unfavorable cancer subtypes, such as triple-negative disease, is unclear. Cancello et al. retrospectively examined patients enrolled in International Breast Cancer Study Group trials to determine the impact of age within breast cancer subtypes. In patients with Luminal A type tumors, no increase in LR was seen in those under 35 years of age compared to patients aged 35 to 50 years, but for other subtypes, there was a trend for very young age to be associated with an increased risk of LR, although this did not reach statistical significance in some groups due to sample size (44). As noted above in a recent series from the Dana-Farber Cancer Institute/Brigham and Women's Hospital, and Massachusetts General Hospital in Boston, age was also in the final model along with subtype, but the magnitude of the effect was much smaller than for subtype, with a crude rate of LR of 6.5% for the patients in the lowest age quartile (ages 23 to 46) compared with only 0.9% for patients in the highest age quartile (ages 64 to 88). Additionally, both poor prognosis Amsterdam genetic signatures and high 21 gene recurrence scores (Oncotype Dx) are more frequent in younger women (45,46); as a result, further research evaluating the interaction between molecular subtype and age is needed. At present, young age alone should not be considered a contraindication to BCT.

A second, important patient-related factor that can influence rates of LR is the presence of a germline mutation in *BRCA1* or *BRCA2*. Investigators from Yale University determined *BRCA* gene status in 127 patients, 42 years of age or less, who were treated with lumpectomy and radiation, and found 22 with deleterious mutations. After 12 years, the rates of ipsilateral breast recurrence (49% vs. 21%; $p = .007$) and contralateral cancer (42% vs. 9%; $p = .001$) were both significantly higher in the patients with *BRCA* mutations (47). Many of these ipsilateral breast recurrences may actually be second breast cancers. Also, these high rates of in-breast recurrence may be significantly less in carriers who have undergone a bilateral oophorectomy. This finding was noted in a multicenter retrospective study that did not find an overall difference in the 10-year rate of in-breast recurrence in mutation carriers (12%) versus matched controls (9%). However, mutation carriers who had not had a bilateral oophorectomy experienced increased rates of in-breast recurrence compared to controls (hazard ratio [HR] 1.99; $p = .04$) (48). Age at initial cancer diagnosis also impacts the risk of subsequent cancers in the ipsilateral breast. Table 35-3 (47–50) displays published studies that have evaluated the rates of ipsilateral tumor recurrences and of contralateral breast cancer in *BRCA* mutation carriers. The choice of mastectomy versus BCT is influenced by patient preference, age, stage, and whether the mutation is in *BRCA1* or *BRCA2*. Younger patients with early-stage breast cancer are encouraged to have mastectomy. Older patients can be considered for BCT, particularly if the breast cancer is more advanced and/or *BRCA2* associated (see Chapter 17).

Disease-Related Factors. One of the most important pathologic factors that affects rates of local control after BCT is surgical margins. When BCT was first introduced, the importance of achieving histologically negative margins was not recognized, and a number of patients in early BCT publications had either unknown margin status or positive surgical margins. Retrospective analyses indicated that such patients had higher rates of LR, particularly if the disease had an extensive intraductal component (defined as tumors that are predominantly non-invasive or tumors with a DCIS component comprising at least 25% and with DCIS present in surrounding normal breast tissue) (51). The fact that biologic factors are increasingly recognized as determinants of LR after both mastectomy and BCT has been discussed in detail, as has the role of systemic therapy in reducing LR and the lack of evidence that margins more widely clear than tumor not touching ink are necessary for the majority of breast cancer patients. The presence of ink on tumor remains an indication for re-excision, but when re-excision carries a significant aesthetic consequence, the degree of margin involvement should be considered. Specifically, some retrospective series have found that patients with a focally positive margin have better outcomes that those with margin involvement over a wider area. In one study, Vicini et al. (52) retrospectively reassessed margin status in 607 cases treated with BCT and reported a 12-year in-breast recurrence rate of 9% in patients with negative margins, 6% when a small amount of disease was close to the margin, 18% for those with an intermediate degree of disease close to the margin, 24% for those with a large volume of disease close to margin, and 30% for those with a positive margin. It is also useful to note that margins at the skin anteriorly or at the pectoral fascia posteriorly are not of concern since breast tissue does not extend beyond those margins. Good communication between the surgical and radiation oncologists is important in this regard.

Not surprisingly, the importance of margin status on LR is also affected by other factors, such as age, use of systemic therapy, and timing of radiation delivery. Park et al. (53) reported that the use of systemic treatments reduced the in-breast recurrence rates for patients with focally positive margins (8-year rate of 7%), whereas higher rates were seen in those with focally positive margins who did not receive systemic therapy and in all patients with more diffusely positive margins. Jobsen et al. (54) showed that

TABLE 35-3

Rates of Ipsilateral Tumor Recurrences and Development of Contralateral Breast Cancer in *BRCA* Carriers Treated with Breast-Conserving Therapy

Study (Reference)	*No. of Patients*	*Follow-Up (Years)*	*Ipsilateral Breast Recurrence (%)*	*Contralateral Breast Cancer Development (%)*
Pierce et al. (48)	160	15	24	39
Haffty et al. (47)	23	12	46	42
Robson et al. (49)	87	10	14	38
Seynaeve et al. (50)	87	10	30	14

TABLE 35-4

Effect of Systemic Therapy on In-Breast Recurrence Rates in Patients Treated with Breast-Conserving Surgery and Radiation Therapy

Study (Reference)	*No. of Patients: Selection, Type of Systemic Treatment*	*Follow-Up (Years)*	*Radiation (%)*	*Systemic Therapy + Radiation (%)*
NSABP B-21 (32)	673: ≤1 cm, pN0, tamoxifen	8	9.3	2.8
NSABP B-13 (62)	760: pN0, chemotherapy	10	15.3	2.6
University of Texas MD Anderson Cancer Center (61)	484: pN0, chemotherapy or tamoxifen	8	14.8	4.4
Yale (63)	548: chemotherapy or tamoxifen	7	12	6

margin status was of particular importance in women 40 years of age or less. In this younger cohort, the risk of in-breast recurrence according to margin status was 37% in those with positive margins compared with only 8% in those with negative margins. Finally, in a randomized prospective trial, investigators from Harvard Medical School found that patients with close or positive margins had a high rate of LR if radiation was delayed in order to first deliver adjuvant chemotherapy, but if negative margins were achieved, there was no adverse affect of radiation delay in local control (55).

Taken together, these data suggest that margin status correlates with long-term local control for patients treated with BCT. It is therefore reasonable to recommend re-excision for patients with positive margins and individualize treatment recommendations for patients with close margins. Other disease-related factors that have been correlated with local control rates include the presence of multicentric disease, histology of the tumor, lymphovascular space invasion, and the stage of disease. Limited data suggest that *gross multicentric disease*, defined as separate foci of disease in different quadrants of the breast, adversely affects local outcome (56). However, given the improvement in local control seen since the time that multicentricity was identified as a contraindication to BCT, this issue is being revisited in a prospective trial which should provide more definitive information. Most tumor histologies have similar LR rates when all other factors are equal. For example, Salvadori et al. (57) reported that the in-breast tumor recurrence rate for 286 cases of lobular cancer was 7% and was equivalent to the rate for those patients with infiltrating ductal carcinoma. Similarly, investigators from the University of Texas MD Anderson Cancer Center reported a 7% 10-year recurrence rate for patients with lobular carcinoma versus a 9% rate for those with invasive ductal carcinoma (58). One unusual histology that may be associated with higher rates of LR after BCT and mastectomy is metaplastic carcinoma (59). Lymphovascular space invasion has also been noted by multiple authors to be associated with increased rates of in-breast recurrence after BCT (30,60), but is also associated with increased rates of chest wall recurrence after mastectomy. Finally, stage of disease has a relatively minor influence on the likelihood of LR. In the EBCTCG meta-analysis of data from randomized trials, the 5-year risk of LR was 11% in patients with positive lymph nodes versus 7% for those with negative lymph nodes (1). Investigators from the University of Texas MD Anderson Cancer Center found that stage was an important factor in LR rates for young breast cancer patients. The 10-year rate of LR after BCT, radiation, and chemotherapy for patients 35 years of age or less was 12% for those with stage I disease and 18% for those with stage II disease (40).

Treatment-Related Factors. Systemic treatments reduce the risk of recurrence in the ipsilateral breast in patients who are treated with whole breast irradiation. Table 35-4 (32,61–63) shows data from prospective trials and single-institution studies highlighting this benefit. In the NSABP B-21 trial, which enrolled patients with lymph node-negative breast tumors smaller than 1 cm, the crude rate of LR was only 3% in patients treated with BCT and tamoxifen compared with 7% in women treated with BCT without tamoxifen (32).

A tumor bed boost after whole breast irradiation is another treatment-related factor that can decrease the risk of in-breast recurrence. The first randomized trial investigating the impact of a 10-Gy boost after 50 Gy of breast irradiation was performed in Lyon, France. The use of a boost led to a small but statistically significant reduction in the rate of LR at 5 years (3.6% vs. 4.5%; $p = .04$) (64). The EORTC has subsequently published a much larger trial that randomized patients to receive or not receive a 16 Gy boost after 50 Gy of whole breast radiation treatment. The use of a boost reduced the risk of an in-breast recurrence at 5 years by 40% ($p < .001$, the absolute reduction in risk at 5 years was ~4%) (39,65). Patients of all ages achieved the same proportional benefit from the boost, but the absolute benefit was greatest in the younger patients. At 10-years, the risk of in-breast recurrence was reduced with a tumor bed boost from 10.2% to 6.2% (65). The 10-year results of the EORTC trial for patients divided according to age are shown in Table 35-5 (65).

TABLE 35-5

Ten-Year In-Breast Recurrence Rates of the European Organisation for Research and Treatment of Cancer Boost versus No Boost Trial for Patients Divided According to Age

	Boost (%)	*No Boost (%)*
Overall results	10.2	6.2
Age ≤40 yrs	23.9	13.5
Age 41–50 yrs	12.5	8.7
Age 51–60 yrs	7.8	4.9
Age ≥60 yrs	7.3	3.8

Data from Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol* 2007;25:3259–3265 (65).

INTEGRATION OF RADIATION WITH SYSTEMIC TREATMENT

Most patients with early-stage breast cancer are treated with surgery, systemic therapy, and RT, and therefore the sequencing of RT with systemic treatments remains an important clinical question. To determine the optimal sequencing schedule of chemotherapy and radiation, investigators from the Harvard Medical School/Dana-Farber Cancer Institute conducted a randomized trial that compared four cycles of doxorubicin-based combination chemotherapy followed by RT or RT followed by the same chemotherapy. The updated results showed no statistically significant differences in LR, distant metastasis, or overall survival between the two groups (55). Patients with close surgical margins had an increased risk of LR when sequenced with chemotherapy followed by radiation, suggesting that re-excision should be considered for such patients. A second important study from the CALGB addressed whether a more extended delay in radiation in order to treat with both anthracyclines and taxanes increased LR risk. These investigators reported that those treated with paclitaxel after anthracyclines had lower risks of isolated local-regional recurrence than those treated with just four cycles of anthracyclines (3.7% vs. 9.7%, respectively; $p = .04$) (66). Given this information, it has become standard that patients receive initial chemotherapy followed by RT.

There are no randomized trials that directly compared concurrent tamoxifen and radiation versus radiation followed by tamoxifen. However, three recent retrospective reports found no difference in outcome according to the sequencing of radiation and hormonal therapy. Pierce et al. (67) examined this question in 309 patients treated within the Southwest Oncology Group and found 10-year rates of recurrence of 7% with concurrent treatment versus 5% with sequential therapies ($p = .54$). Ahn et al. (68) from Yale University examined this issue in 495 patients treated with breast conservation and also found no difference in local control, development of DM, and overall survival after 10 years. Finally, Harris et al. (69) from the University of Pennsylvania conducted a similar analysis and also found very similar results.

Finally, for patients receiving adjuvant trastuzumab, most have continued this therapy concurrently during the course of radiation, and the data thus far suggest that this combination is not associated with increased complication rates. Data from the NSABP B-31 trial showed a rate of congestive heart failure of 3.2% for patients treated with trastuzumab and left-sided radiation compared to a rate of 4% for those treated with trastuzumab and no left-sided radiation ($p = .80$) (70). These data were supported by the North Central Cancer Treatment Group N9831 trial that compared the rate of cardiac events in patients treated with trastuzumab with (1.5%) or without (6.3%) radiation (71). Furthermore, none of the radiation-associated adverse events were increased in those treated concurrently with trastuzumab versus those who were not.

Treatment Techniques for Breast-Conserving Therapy

Surgical Technique

The surgical incision should be close enough to the primary tumor to allow adequate exposure. Although circumareolar incisions provide the best cosmetic results, the size of the areola and the distance from the tumor to the areola should be considered when selecting an incision. To optimize the cosmetic outcome, biopsy incisions in the upper breast are usually oriented in a curvilinear fashion, and biopsy incisions in the lower breast are oriented in a radial fashion. For all but superficial cancers, preserving the breast tissue anterior to the lesion by incising it, rather than excising it, will help to maintain breast contour. Clips are placed to mark the extent of the resection cavity and are very helpful in planning the radiation boost. Deep parenchymal sutures may be used for closing the defect, especially in patients who undergo large-volume excisions. In patients with prominent calcifications, a postoperative mammogram is obtained before the initiation of RT. (This is particularly true if the specimen mammogram does not provide clear evidence that all suspicious calcifications have been removed.) If the postoperative mammogram reveals residual calcifications at the lumpectomy site, localization and re-excision should be performed to remove all suspicious microcalcifications. With standard resections, patient satisfaction with the cosmetic outcome is high, with 90% rating their cosmetic outcomes as "excellent" or "good."

Recently, there has been great interest in *oncoplastic surgery* defined as the use of plastic surgical techniques of tissue rearrangement and contralateral symmetry procedures to improve the aesthetic outcome of BCT. Much of the impetus for oncoplastic surgery comes from the belief that the removal of large amounts of normal breast tissue to obtain more widely clear margins decreases the risk of LR. As previously discussed, evidence to support this belief is lacking. Neoadjuvant chemotherapy to shrink large tumors prior to surgery is an alternative approach that has been proven to be safe and effective in prospective randomized trials, and, in patients who will need chemotherapy anyway, has the advantage of not requiring a more extensive surgical procedure. Thus, the pool of patients requiring oncoplastic surgery is relatively small. To date, there are very limited data regarding cosmetic outcomes and LR risks with this approach. In one study of 127 patients who were offered both conventional BCT or oncoplastic surgery, patient satisfaction with cosmetic outcome did not differ between groups (72). In addition to the lack of clear evidence of benefit, the tissue rearrangement frequently makes tumor bed localization for radiation boost treatment more difficult and can lead to difficulties with re-excisions should the margins be positive.

Technique of Conventional Radiation Treatments

Conventional radiation treatments have targeted the entire ipsilateral breast and treated this region to a dose of 45 to 50 Gy delivered in 25 to 28 daily fractions. Subsequently, a 1.5 to 2.0 cm volume around the surgical cavity is treated as a tumor bed boost field with an additional 10 to 16 Gy in 5 to 8 daily fractions, typically using electron beam. Treatments are given in an outpatient setting and each daily treatment takes approximately 15 minutes in the treatment room. The entire course of therapy is typically 6 weeks.

Contemporary whole breast irradiation begins with CT-based planning. Patients are typically treated supine with arms above the head. Other positions, such as prone or lateral decubitus, can be useful for patients with large or pendulous breasts. Left-sided tumors can be treated using a heart block, prone technique, or breath-holding techniques to avoid direct heart irradiation, but patient cooperation and special in-room patient position monitoring are required for the breath-holding technique. Contouring breast cancer volumes is important, and the mean heart dose should be determined. An atlas for contouring is available from the RTOG/NRG Group at http://www.rtog.org/corelab/ContouringAtlases/BreastCancerAtlas.aspx. Late cardiac effects of radiation are dependent on the mean

heart dose and influenced by the presence of cardiac risk factors (73).

Whole breast irradiation is usually delivered via tangent fields using high-energy x-rays. Typically, two opposed photon fields that tangentially cover the anterior chest and minimize the intrathoracic normal tissue are used to treat the breast. An example of such fields is shown in Figure 35-3. Forward planning techniques allow addition of sub-fields to optimize dose homogeneity; intensity modulated radiation treatment (IMRT) is typically not required and can be associated with increased low-dose radiation to adjacent normal tissues. An example of treatment fields used to modulate the intensity of the RT is shown in Figure 35-4. In some cases, the use of higher linear accelerator energies, such as 10 MV or a mixture of 15 and 6 MV, is needed to assure adequate dose homogeneity. Adequate dose homogeneity by selection of beam energy and modulation of beams has been shown to minimize acute skin reactions and maximize long-term cosmetic results. Three-dimensional treatment planning of the boost fields helps to select the appropriate energy to ensure optimal efficacy and safety. Figure 35-5 shows an example of a tumor bed boost field.

Standard tangent fields cover a substantial percentage of level I and II axillary nodes. High tangent techniques can be used to treat a greater percentage of the axilla. Provider-assessed rates of fibrosis and telangiectasias were increased

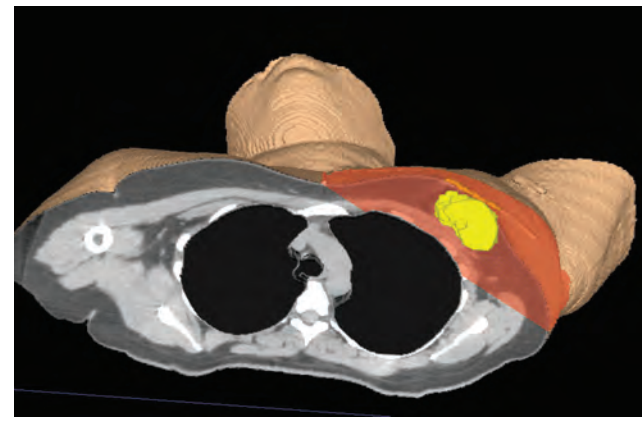

FIGURE 35-3 **A skin rendering and axial image of medial and lateral tangential photon fields typically used to treat the breast.** The two fields are opposed such that the dose fall-off over depth is matched to provide a homogeneous distribution of dose. Angles of beam entrance and exit are selected to minimize dose to intrathoracic structures. In this figure, the tumor bed location within the breast has been contoured on sequential axial slices and reconstructed as a solid yellow contour.

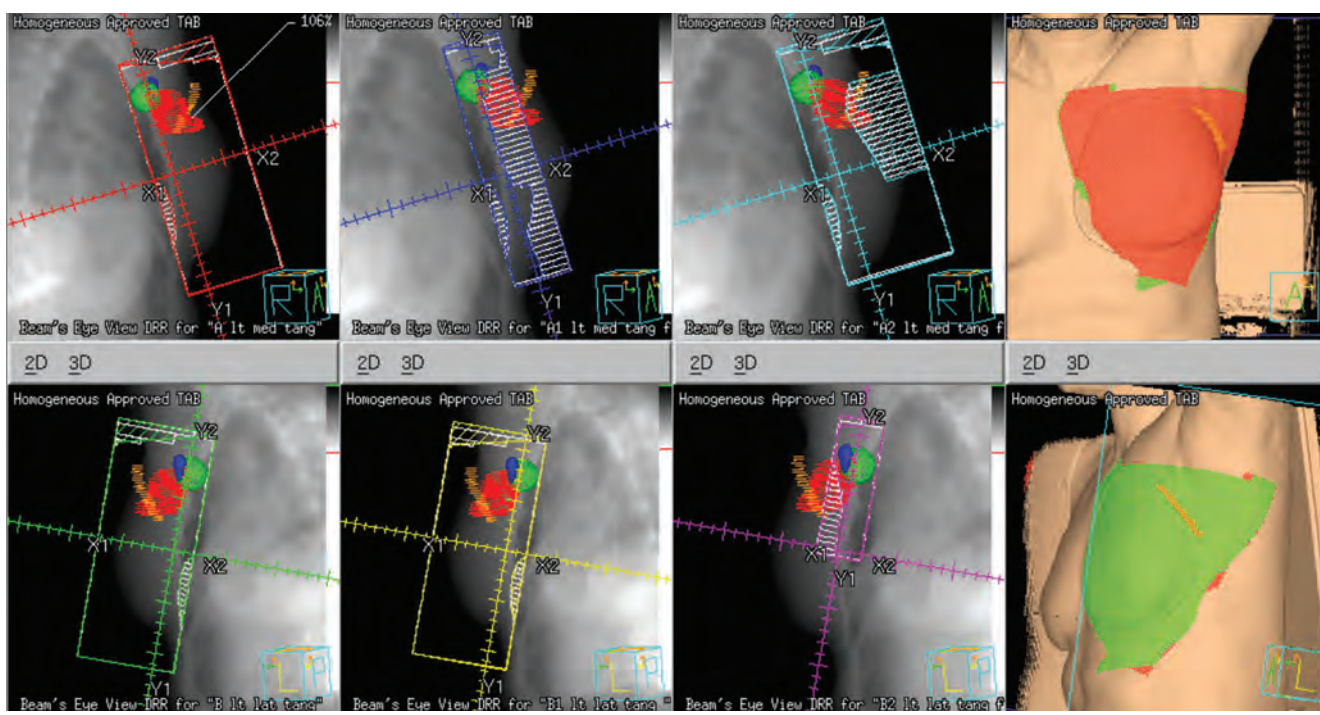

FIGURE 35-4 **An example of modulated radiation treatment fields used to treat the breast.** Two opposed medial and lateral tangent fields generate a dose distribution in the breast that has excess dose in the thinner areas of the breast, such as the apex, where the distance traveled by the beam and resulting dose fall-off is less (relative to the base of the breast). Resulting "hot spots" are subsequently blocked by subfield created by inserting multi-leaf collimators located within the head of the linear accelerator and blocking dose to these regions. A multi-leaf collimator that shielded the heart was also used in the inferior portion of all of the fields in this particular case.

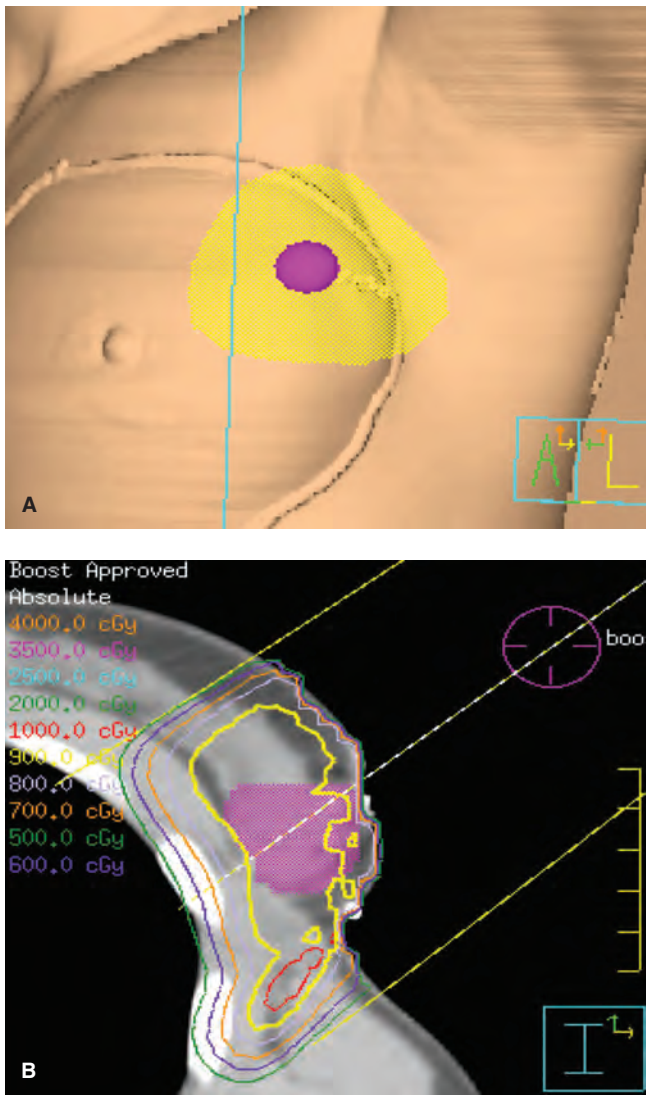

FIGURE 35-5 A skin rendering **(A)** and axial image **(B)** of a boost electron field to supplement the radiation dose to the tumor bed after completion of whole breast radiation treatment. The axial image shows the tumor bed contoured in pink with the isodose curves of the single electron beam. The selection of electron beam energy determines the penetration distance of the electron beam dose and allows the appropriate isodose curve to adequately encompass the target volume.

with addition of a boost, but patient-reported cosmetic outcomes did not differ.

ACCELERATED WHOLE BREAST AND PARTIAL BREAST IRRADIATION

The protracted nature of radiation treatments can place hardships on patients and medical systems. Accordingly, there has been an interest in studying whether the treatment course can be shortened without compromising the efficacy or increasing the toxicity of the therapy. Accelerated (or hypofractionated) whole breast irradiation (AWBI) shortens the length of the treatment course and has become more feasible due to two major developments:

1) technical improvements in the delivery of breast irradiation that result in a much higher level of radiation dose homogeneity; and
2) a better understanding of the biologic equivalence of accelerated and conventional dose schedules.

Several large randomized trials have investigated AWBI in the treatment of early breast cancer (Table 35-6) (74–77). In each of these trials, hypofractionated schedules were compared to conventional whole breast irradiation of 50 Gy in 2 Gy daily fractions. Doses in the experimental arms varied from 39 Gy in 13 fractions in the RMG/GOG and START A trials to 42.5 Gy in 16 fractions in the Canadian trial. No significant differences in overall local control rates between conventional and hypofractionated arms were noted in any of these trials. Given its large size and long follow-up, the Canadian trial, in particular, has been widely considered to be practice changing. In an exploratory subset analysis, women with grade 3 tumors had a 15.6% rate of LR in the hypofractionated arm of the Canadian trial versus 4.7% in the conventional fractionation arm (p = .01). This difference, however, was not seen in other large retrospective patient populations or in the START A and B trials. The 10-year results of the START A and B trials were presented at the 2012 San Antonio Breast Cancer Symposium. Rates of LR were comparable in all treatment arms. These results are confirmatory to the Canadian trial results.

The cosmetic implications of AWBI were also assessed in these trials and were quite favorable. In the START B trial, normal tissue effects were better in patients treated with 40 Gy in 15 fractions compared with 50 Gy in 25 fractions. Comparable cosmetic outcomes and toxicities were seen in the two arms in the Canadian trial. Continued follow-up will be needed to determine how long-term cosmetic effects and toxicity of AWBI compare to conventional whole breast irradiation.

Based on the available data, a task force of the American Society for Radiation Oncology (ASTRO) has developed guidelines for the use of AWBI (78). The task force favored a dose schedule of 42.5 Gy in 16 fractions (Canadian) and its use in patients 50 years of age or older with pT1-2N0 cancer treated with BCS and not treated with adjuvant chemotherapy where the dose homogeneity is within +/-7% and the heart can be excluded from direct irradiation. There was no agreement on the use of a boost. 40 Gy in 15 fractions was adopted as the United Kingdom standard for all patients with invasive breast cancer in 2009.

Additional follow-up is being obtained on the first generation AWBI trials, and multiple second-generation AWBI trials have already been launched. Trial designs vary and it is likely that the results of these trials will expand the accepted indications and dose schedules for AWBI.

Rationale for Accelerated Partial Breast Irradiation

Although whole breast irradiation remains the most common technique for delivery of radiation as part of BCT, APBI has been employed for many years, and there is widespread interest surrounding its use. The rationale for APBI stems from the observation that the majority of in-breast recurrences occur near the primary tumor site. Therefore, confining radiation to the area immediately surrounding the tumor may provide equivalent rates of primary tumor control while sparing radiation to regions that are at low risk of harboring clinically relevant microscopic disease. APBI can also

TABLE 35-6

Randomized Trials Comparing Conventional Whole Breast Irradiation to Accelerated Whole Breast Irradiation

Trial (Reference)	*No. of Patients*	*Median Follow-Up*	*Patient/Tumor Characteristics*	*Surgery*	*Systemic Therapy*	*Dose (Gy)/ No. of Fractions*	*Comments*	*IBTR*	*p-value*	*OS*	*Cosmesis*	*Toxicity*
Canadian (77)	1,234	12.0 y	pT1-2 pN0	Lumpectomy + ALND	HT (41.0%)	50.0/25.0	No boost dose or RNI	6.7%	NS	84.4%	Good or excellent cosmetic outcome 71.3%	Grade 2–3 skin/ subcut tissue toxicity 7.7%/10.4%
				No tumor on ink	CT (11.0%)	42.5/16.0		6.2%		84.6%	69.8%	8.9%/11.9%
START A (74)	2,236	9.3 y	pT1-3a pN0-1 M0	BCT +/- ALND (85%), or mastectomy without immediate reconstruction (15%)	HT (79%)	50.0/25.0	RNI when indicated (14%)	7.4% at 10 y	NS	NA	HR any moderate/marked effect (MD) 1	Fair–poor cosmetic outcome (5 y) 41%
			Age >18 yrs	Clear margins ≥1 mm	CT (36%)	41.6/13.0	10 Gy tumor bed boost (61%)	6.3 % at 10 y		NA	0.94	36%
						39.0/13.0		8.8 % at 10 y		NA	0.80	
START B (75)	2,215	9.9 y	pT1-3a pN0-1 M0	BCT +/- ALND (92%), or mastectomy without immediate reconstruction (8%)	HT (87%)	50.0/25.0	RNI when indicated (7%)	5.5% at 10 y	NS	NA	HR for moderate/ marked effect (MD) 1	Fair-poor cosmetic outcome (5 y) 41%
			Age >18 yrs	clear margins ≥1 mm	CT (22%)	40.0/15.0	10 Gy tumor bed boost (43%)	4.3% at 10 y		NA	0.77	36%
RMH/GOC (76)	1,410	9.7 y	T1-3 N0-1 M0	Lumpectomy +/- ALND	HT alone (65.0%)	50.0/25.0	14 Gy tumor bed boost (75%)	12.1% at 10 y		95% (pooled)	Any change in breast appearance (photo) 35%	Fair–poor cosmetic outcome 61%
			Age <75 yrs	Macroscopically clear margins	CT alone (2.8%)	42.9/13.0	Single anterior field to treat SCV PAB if axilla included	9.6%	p = .027 (42.9 vs. 39.0)		42%	66%
					HT+CT (11.0%)	39.0/13.0		14.8%			27%, p <.001 (comparing all three)	51%

IBTR, ipsilateral breast tumor recurrence; OS, overall survival; ALND, axillary lymph node dissection; HT, hormone therapy; RNI, regional nodal irradiation; NA, not applicable; NS, not significant; CT, chemotherapy; START, United Kingdom Standardisation of Breast Radiotherapy; BCS, breast-conserving surgery; RMH, Royal Marsden Hospital, Scotland, United Kingdom; GOC, Gloucestershire Oncology Centre, Cheltenham, United Kingdom; HR, hazard ratio; SCV, supraclavicular; PAB, posterior axillary boost.

potentially minimize dose to adjacent normal structures, including the heart, lungs, ribs, and soft tissues, which could reduce the risk of radiation-induced late complications.

Because less total tissue is irradiated, higher daily doses can be delivered over fewer fractions, making treatment more convenient for patients. Shorter courses could also improve compliance with radiation in the elderly and geographically isolated populations, both of which have been shown to have lower compliance with radiation following BCS. Finally, some forms of APBI could improve efficiency and decrease cost of treatment.

Accelerated Partial Breast Irradiation Techniques and Non-randomized Experiences

Several techniques have been developed to deliver APBI. Although the modalities vary significantly, all are designed to deliver therapeutic doses to the tissue near the surgical cavity that is felt to be at highest risk of recurrence.

External beam radiation techniques similar to those used for whole breast irradiation have been adapted to deliver APBI. These techniques have the advantage of being noninvasive and can utilize many of the same treatment planning and delivery tools as whole breast irradiation. Typical doses are 36 to 38.5 Gy in 10 fractions delivered twice daily over 5 days. Conformal 3D-RT or IMRT planning can be used, and a variety of beam arrangements have been described. Early results from a number of institutional reports look favorable. Efficacy data from RTOG 0319, a Phase I/II trial with 58 patients, showed an LR rate of 6% (4% within the treatment field), and 2 patients with a grade III skin toxicity at 4.5 years. No clear dose-toxicity relationship has been identified—although initial results are promising— but long-term follow-up is lacking (79). Whelan et al. reported at the October 2012 ASTRO meeting that the cosmetic results in the recently closed Canadian Randomized Trial of Accelerated Partial Breast Irradiation (RAPID) trial (discussed below) for patients on the APBI arm were significantly worse than for patients treated on the conventional whole breast irradiation arm. In the Canadian RAPID trial, the doses and techniques used were similar to the external beam treatment for APBI in the NSABP B-39/RTOG 0413 trial, and the cosmetic results were assessed by the use of photographs, a nurse, the patient, and a panel of blinded physicians.

Interstitial brachytherapy using multiple catheters and high-dose rate (HDR) or low-dose rate (LDR) sources was originally developed to deliver a boost dose to the surgical cavity following whole breast irradiation, but was adapted to deliver APBI. The number and position of catheters is determined by the size and shape of the surgical cavity. Once inserted, the catheters are after-loaded at predetermined locations in order to deliver the target dose to the breast tissue immediately surrounding the surgical cavity. Iodine-125 sources are typically used for LDR delivery and are prescribed to 45–50 Gy. Iridium-192 is the most common HDR source and is prescribed to 34 Gy, typically given over 10 fractions (twice daily for 5 days). Due to the steep dose falloff, interstitial brachytherapy allows for rapid delivery of high radiation doses to target tissues with nearly complete sparing of surrounding normal structures. However, due to the invasive nature of the procedure, infection, fat necrosis, or scarring can occur.

Several interstitial brachytherapy experiences for early-stage breast cancer have been published. RTOG 95-17 enrolled 100 stage I/II breast cancer patients who were treated with catheter-based HDR or LDR brachytherapy. LR rates for HDR and LDR techniques were 3% and 6%, respectively. A separate toxicity analysis revealed 2 grade 3–4 toxicities with HDR and 3 grade 3–4 toxicities with LDR. The 10-year cumulative incidence of LR in a series of patients treated with interstitial brachytherapy at William Beaumont Hospital was 5%, with a matched-pair analysis showing similar outcomes to patients treated with whole breast irradiation (80). The 5-year rate of fat necrosis in these patients was 11%, but 95% to 99% of cosmetic outcomes were reported as good to excellent. However, 12-year updated results from a series of 50 patients treated with LDR interstitial brachytherapy from Massachusetts General Hospital showed 6 cases of LR (12%), lower rates of acceptable cosmetic results (67% good-excellent, 54% moderate-severe fibrosis), and more treatment-related toxicity with longer follow-up (81). While in retrospect, the technique of interstitial implant in this trial was not ideal, the results illustrate the need for very long follow-up to adequately assess both local tumor control and toxicity with unconventional fractionation.

Intracavitary brachytherapy is an alternative brachytherapy technique that can be used to deliver APBI. The most commonly used intracavitary device is the MammoSite® applicator (Hologic, Bedford, MA), which has been United States Food and Drug Administration (FDA)-approved since 2002. The device is inserted into the lumpectomy cavity during surgery or several days following surgery (after pathologic confirmation of margin status) and inflated. A computed tomography (CT) is obtained for treatment planning, and Iridium-192 is afterloaded into a single lumen in the center of the balloon to deliver the prescribed dose at the surface of the lumpectomy cavity surrounding the balloon. Alternate devices with multiple lumens are also available and allow for greater flexibility in treatment planning. A dose of 34 Gy is delivered in 3.4 Gy fractions given twice daily over 5 days. Following treatment, the balloon is deflated and removed. Advantages of intracavitary brachytherapy include its ease of use compared to interstitial techniques and its reproducibility in delivery of radiation dose to the balloon surface. However, problems with dose homogeneity can occur when the surgical cavity is irregularly shaped, and treatment of superficial cavities can lead to a high skin dose and increased toxicity. The 5-year rate of LR in over 1,400 patients enrolled on the MammoSite registry is 3.8%, with good-to-excellent cosmetic results reported in 90.4%. Two-year data from a multi-institutional series of 483 patients treated using the MammoSite applicator show a 1.6% LR rate and 90% good-to-excellent cosmetic outcomes. A recent population-based retrospective analysis of 92,735 older women treated with brachytherapy-based APBI showed a significantly increased incidence of subsequent mastectomy as well as higher rates of postoperative complications, breast pain, fat necrosis, and rib fracture with brachytherapy compared to whole breast irradiation (82).

Intraoperative radiation is another technique for delivery of APBI and is administered in a single fraction to the lumpectomy cavity immediately following tumor removal. One technique, targeted intraoperative radiotherapy (TARGIT), employs low-energy x-rays emitted from a source located at the center of a spherical applicator placed within the surgical cavity. The prescription dose of 20 Gy at 0.2 cm depth and 5 Gy at 1.0 cm depth is delivered over several minutes, after which the applicator is removed and the surgical incision closed. The technique has been criticized for not delivering adequate dose to a sufficient margin around the cavity. Another technique, intraoperative electron beam radiotherapy (ELIOT), employs a dedicated linear accelerator in the operating room to deliver electron beam radiation. Although not widely practiced in the United States,

intraoperative radiation has the advantage of being completed in a single day and treats the operative bed in its native state prior to surgical closure. In a series of more than 1,800 women treated with quadrantectomy followed by intraoperative radiation with electrons, the rates of LR and new primary ipsilateral cancers at 36 months were 2.3% and 1.3%, respectively, while rates of fat necrosis and fibrosis were 4.2% and 1.8%, respectively (83). Another disadvantage of intraoperative radiation is that pathologic information regarding margin status and lymph node involvement are not available at the time of treatment. If unfavorable pathologic features are found, subsequent whole breast irradiation can be administered. When used as a boost prior to planned postoperative whole breast irradiation, intraoperative delivery of 20 Gy to the surgical cavity was associated with a 5-year LR rate of 1.7%.

Randomized Trials Comparing Accelerated Partial Breast Irradiation to Whole Breast Irradiation

Four randomized trials have been published that compared conventional whole breast irradiation to APBI (Table 35-7) (84). The first published trial was conducted at Christie Hospital in Manchester, United Kingdom, and randomized over 700 women to receive external beam APBI to the surgical cavity or an accelerated course of whole breast irradiation. With follow-up of 8 years, there was no difference in overall or disease-specific survival, but LR was significantly higher in the APBI arm compared to the whole breast irradiation arm (25% vs. 13%; p = .00008). The LR rate was 22% in the APBI arm versus 12% in the whole breast irradiation arm for women with invasive ductal carcinoma, and 43% in the APBI arm versus 17% in the whole breast irradiation arm for patients with invasive lobular carcinoma. The results of the trial suggest superior local control with whole breast irradiation, but several factors limit its applicability. Microscopic margin status was not evaluated in these patients, and axillary lymph node staging was not performed. The doses used for whole breast irradiation are significantly lower than typically used today, and no boost was given. Many patients had poor prognostic factors, including large tumor size, non-ductal histology, high grade, and the presence of lymphovascular invasion that today would prompt more aggressive therapy.

The second published, randomized APBI experience is from Leeds Hospital, United Kingdom. Women were also randomized to external beam APBI or an accelerated course of whole breast irradiation. At 8 years median follow-up, there were 4 LRs in the whole breast irradiation arm compared to 10 in the APBI arm (p = .07), and 4 isolated axillary recurrences in the whole breast irradiation arm compared to 10 in the APBI arm (p = .05). Once again, the lack of microscopic margin status severely limits the findings of this trial.

A randomized trial comparing conventional whole breast irradiation to APBI was also conducted in Hungary. The majority of APBI patients underwent multi-catheter Iridium-192 brachytherapy, while a smaller percentage who were technically unsuited for brachytherapy were treated using external beam APBI. At a median follow-up of 66 months, LR as a first event occurred in 6 patients (4.7%) in the APBI arm and 4 patients (3.1%) in the whole breast irradiation arm. In the APBI arm, 2 of the 6 IBTR's were in the treated volume or its margin. The rate of excellent-to-good cosmetic results was 77.6% in the APBI arm and 62.9% in the whole breast irradiation arm (p = .009). In a separate publication, the reported rates of asymptomatic or symptomatic fat necrosis at 4 years did not differ between whole breast irradiation and APBI patients (84). The trial is limited by the relatively small number of patients, short follow-up, and variability in treatment within each arm across institutions.

The most recent published trial comparing conventional whole breast irradiation to APBI is the TARGIT-A trial. APBI patients underwent wide-local excision plus sentinel lymph node biopsy or axillary dissection followed by TARGIT to a prescribed surface dose of 20 Gy. Fourteen percent of patients treated with TARGIT had adverse pathologic features on final pathology and subsequently underwent whole breast irradiation. With 4 years of median follow-up, there were 6 LR's in the TARGIT arm versus 5 in the whole breast irradiation arm, and 4 axillary recurrences in the TARGIT arm versus 3 in the whole breast irradiation arm. The number of patients with major toxicity was similar between arms; however, the type of complications varied. Seroma requiring 3 or more aspirations occurred more frequently in the TARGIT arm (2.1% vs. 0.8%; p = .012), while RTOG grade 3 toxicity was more common in the whole breast irradiation arm (2.1% vs. 0.5%; p = .002).

The results of 3 of these APBI trials have been analyzed in a meta-analysis. Although enrollment criteria and APBI techniques vary widely across studies, no difference in survival was noted in patients treated with APBI versus whole breast irradiation (p = .55). APBI was associated with a higher risk of IBTR (odds ratio [OR] 2.15; 95% confidence interval [CI] 1.40–3.31) and axillary (OR 3.43; 95% CI, 2.06–5.72) recurrence.

Consensus Guidelines and Usage for Accelerated Partial Breast Irradiation

Given the expanding use of APBI in the treatment of early-stage breast cancer, task forces representing several professional societies have published consensus statements regarding its usage. ASTRO defined categories of patients for whom APBI is deemed *suitable, cautionary*, or *unsuitable* (85).

- Suitable patients are those ≥60 years of age with small, unifocal tumors of ductal or other favorable histologic subtype without nodal involvement who have undergone complete surgical excision with negative margins and had not received neoadjuvant chemotherapy. Only patients in the suitable category are recommended to undergo APBI outside of a clinical trial.
- Cautionary patients are those with larger tumors, less-favorable histology, an EIC, pure DCIS, or close surgical margins.
- Young patients or patients with large tumors, positive margins, unfavorable pathologic features, or involved lymph nodes are considered unsuitable candidates for APBI.

There is ongoing debate about whether more groups of patients should be considered suitable. Due to the variability of technical factors and the short available follow-up, recommendations regarding APBI technique and treatment planning were not addressed. Support for these guidelines is seen in a retrospective study of 1,822 patients with ELIOT as the sole radiation modality. The 5-year rate of LR for suitable, cautionary, and unsuitable patients were 1.5%, 4.4%, and 8.8%, respectively (p = .0003).

The American Brachytherapy Society (ABS) Breast Brachytherapy Task Group recommends limiting APBI with interstitial or intracavitary brachytherapy to patients ≥50 years of age with invasive ductal tumors measuring ≤3 cm and with no nodal involvement (86). Multifocal disease and EIC are considered relative contraindications.

Despite the recommendations of such task forces, APBI usage and techniques vary widely. A 2011 analysis of Medicare data suggests that the use of brachytherapy following breast-conserving surgery has increased from <1% of new breast cancer cases in 2001 to 10% of cases in 2006. This increase has correlated with FDA approval of MammoSite and its reimbursement by Medicare. A similar analysis of the SEER database shows the percentage of women receiving brachytherapy-based APBI increased from 0.4% in 2000 to 6.6% in 2007. In the study, 65.8% of treated patients were classified as cautionary or unsuitable based on ASTRO criteria.

Although its use is increasing, the growth in APBI is variable across patient demographics and regions. Brachytherapy-based APBI was more common among Caucasian patients and those with non-HMO insurance. Metropolitan regions, regions with higher median incomes, and regions with lower densities of radiation oncologists were also more likely to have higher rates of APBI.

Ongoing or Recently Closed Studies

Several randomized trials comparing APBI to WBI are ongoing (Table 35-8). The NSABP B-39/RTOG 0413 trial is the largest of these trials, and as of November 2012 has nearly completed randomization of 4,300 post-lumpectomy patients to conventional whole breast irradiation or APBI using multi-catheter brachytherapy, balloon catheter brachytherapy, or external beam radiation. Randomized trials are also underway in other countries and compare APBI to conventional whole breast irradiation or AWBI. Although many of these trials are accruing briskly and early toxicity results may be available in the next several years, many more years will be required before data regarding long-term efficacy and safety are available. In total, over 14,000 patients have been accrued in randomized phase III trials of APBI (compared to less than 4,100 patients in the trials that established the equivalence of BCT to mastectomy), so definitive results should become available with time. In May 2012, the first results of the ELIOT trial were presented at the Groupe Européen de Curiethérapie-European Society for Radiotherapy and Oncology (GEC-ESTRO) meeting showing a 5-year IBTR rate of 0.7% for conventional whole breast irradiation and 5.3% for patients treated with ELIOT.

In the current situation, where definitive results from trials comparing conventional whole breast irradiation, AWBI, and APBI are not available, there will inevitably be controversy where experts will differ in their opinions. It should also be noted that the time course to assess efficacy and safety in local treatment of the breast is protracted, and many of the early assessments of the results of BCS and whole breast irradiation underestimated late LRs and side effects. Long-term follow-up provided information and refinements in techniques that helped to insure that current BCS and whole breast irradiation would be safer and more effective. It is likely that there will be similar evolutions in the techniques of these various newer approaches and that there will be roles for conventional whole breast irradiation, AWBI, and APBI in the future.

Indications for Targeting Lymph Nodes in the Radiation Treatment Volume

In addition to treatment of the breast, radiation treatments are highly effective in eradicating microscopic disease within regional lymph nodes. Accordingly, treatment of lymph node regions is indicated for appropriately selected patients. Patients with a negative sentinel lymph node biopsy are at very low risk for residual nodal disease; and therefore, radiation of lymphatics is generally not indicated. Breast irradiation incidentally includes irradiation of most level I axillary nodes, and it has been shown that axillary recurrence is lower in BCT sentinel-node negative patients than in sentinel-node negative mastectomy patients. However, radiation of the lymphatics is indicated for selected patients with stage II disease and patients treated with BCT who are found to have four or more positive lymph nodes. Prospective clinical trials are currently being conducted to further define the risks, benefits, and indications for radiation of regional lymph nodes. The use of regional node irradiation may undergo substantial revision with publication of the results from MA.20 and EORTC 22922/10925, both testing the role of nodal irradiation in low-to-moderate risk BCT patients (87,88). The 5-year results of MA.20 were presented at the 2011 American Society of Clinical Oncology annual meeting by Whelan et al. and demonstrated significantly lower rates of local-regional recurrence and also of DM, and a trend to improved survival with nodal irradiation.

Treatment of the regional nodes requires additional fields. The radiation oncologist needs to decide whether to treat just level III and the supraclavicular nodes, or to also treat the full axilla. This depends on the thoroughness of the level I/II axillary dissection (by review of the operative note and/or discussion with the surgeon), the percentage of nodes that are positive (especially if >50% positive), and the presence or absence of significant (>2 mm) extranodal extension. There are no evidence-based guidelines for making this decision, and the decision needs to consider that the combination of a full level I/II dissection and full axillary irradiation results in a high likelihood (~30%) of lymphedema. When treating just level III and the supraclavicular nodes, the lateral border of the third anterior field is at the coracoid process with the depth measured in the individual patient. When including the full axilla, the lateral border is determined by contouring the axillary nodes/volume and, in nearly all cases, a posterior field is also needed to assure adequate dose homogeneity. When treating the internal mammary nodes, the nodes in the first three interspaces need to be contoured and can either be included in the tangents (partially wide tangents) or by use of a separate e-beam field matched to the tangents. The former is preferred, if possible, to avoid overlap of fields.

Based on the results of ACOSOG Z0011 (24), radiation oncologists are frequently asked to treat BCT patients following sentinel node biopsy with one or two positive sentinel nodes without completion axillary dissection. In the trial, patients were treated with breast tangents without use of a third field; however, patients in the trial were thought to be a particularly favorable subset: 46% of the positive sentinel nodes were micrometastases, and only 27% of patients randomized to completion dissection had additional positive axillary nodes, raising the possibility that axillary irradiation might be beneficial in a more diverse patient population. Results from Memorial Sloan-Kettering Cancer Center of a prospective study of 290 consecutive patients with sentinel node macrometastases meeting ACOSOG Z11 eligibility criteria (clinical T1, 2 and N0, no neoadjuvant therapy undergoing BCT) provide additional information relevant to this discussion. Axillary dissection was indicated in only 16.5% of patients on the basis of 3 or more sentinel nodes with metastases or gross extranodal extension. The median age of patients undergoing sentinel node biopsy alone was 58 years compared to 59 years for those requiring dissection

TABLE 35-7

Randomized Trials Comparing Accelerated Partial Breast Irradiation to Whole Breast Irradiation

Trial (Reference)	*No. of Patients*	*Median Follow-Up*	*Inclusion Criteria*	*Surgery*	*Systemic Therapy*	*Surgical Margins*
Christie Hospital	708	65 mos (update 8 y)	<70 y, tumor <4 cm, clinically negative axilla	Lumpectomy	None	Macroscopically uninvolved
Leeds Hospital, Yorkshire	174	8 y	pT1-2 N0-1	Lumpectomy + ALND	CMF chemo+Tam 5 yrs (all)	Macroscopically uninvolved
Hungary (84)	258	66 mo	pT1 N0-1mi, Gr 1-2, non-lobular histology, no EIC	Lumpectomy + ALND or SLNB	Per institution 68% HT, 2% CT	>2 mm
TARGIT-A (74)	2232	4 y	≥45 y, unifocal IDC amenable to WLE	Lumpectomy + ALND or SLNB	Per institution 66% HT, 12% CT	Microscopically free of tumor

OS, overall survival; IBTR, ipsilateral breast tumor recurrence; LRR, local-regional recurrence; PBI, partial breast irradiation; NS, not significant; DSS, disease-specific survival; SCV, supraclavicular; WBI, whole breast irradiation; ALND, axillary lymph node dissection; CMF, cyclophosphamide, methotrexate, and fluorouracil 5FU; Tam, tamoxifen; NR, not reported; EIC, extensive intraductal component; SLNB, sentinel lymph node biopsy; HT, hormone therapy, CT, chemotherapy; HDR, high dose rate; EB, external beam; TARGIT, targeted intraoperative radiotherapy; IDC, invasive ductal carcinoma; WLE, wide local excision.

Technique	*OS*	*p-value*	*IBTR*	*LRR*	*Cosmetic Outcomes*	
PBI: 8–14MeV en face electron beams 40.0–42.5 Gy, 8 fx, 10 days	OS 72.75 (7 y actuarial) DSS 73% (8 y median)	NS	25% (8 y actuarial)	Axillary 23% (7 y) SCV 5%	Marked fibrosis 14%	Marked telangiectasias 33%
WBI: parallel opposed 4 MV photon beam 40 Gy, 15 fx, 21 days bolus surgical scar, matched nodal field 40 Gy, 15 fx, 21 days	OS 71.2% (7 y actuarial) DSS 72% (8 y median)		13%	Axillary 10% (7 y) SCV 5%	5%	12%
PBI: en face Co, Cs, or electron beam, or tangent pair to tumor bed 55 Gy, 20 fx, 28 days	70% (8 y)	NS	10 patients (8 y)	24%	NR	
WBI: parallel opposed photon beams 40 Gy, 15 fx, 21 days en face boost to tumor bed 15 Gy, 5 fx	73%		4 patients	9%		
PBI: Iridium-192 HDR multicatheter brachytherapy 36.4 Gy, 7 fx, 4 days (100% dose to surgical cavity + 2 cm) performed 4–6 wks after surgery (69%), en face electron beam 50 Gy to tumor bed (31%)	94.6% (5 y)	NS	4.7% (5 y)	6.3%	Excellent-good cosmesis 77.6% (HDR 81.2%, EB 70.0%)	p = .009
WBI: parallel opposed Co or 6–9 MV photon beams 50 Gy, 25 fx, 5 wks	91.8%		3.1%	3.9%	62.9%	
PBI: intraoperative 50 kV x-rays 20 Gy at applicator surface alone (86%), or followed by WBI if unfavorable pathologic features (14%)			6 patients	4 axillary recurrences	Any complication 17.6%	p = .009
WBI: per institution, typically 40–56 Gy in 2 Gy fractions with or without a 10–16 Gy tumor bed boost			5 patients	3 axillary recurrences	15.5%	p = NS

TABLE 35-8

Ongoing Accelerated Partial Breast Irradiation Trials

Trial (Reference)	*Opened*	*Accrual*	*Inclusion Criteria*	*Surgery*	*PBI Technique*	*WBI Technique*	*Primary Endpoint*	*Secondary Endpoints*
NSABP B39/ RTOG 0413	3/2005	4,300 (Goal)	Stage 0, I, II tumor ≤3 cm, ≤3 positive LNs (closed to low risk in 2007)	Lumpectomy to uninvolved margins and ALND or SLNB	3D-CRT 38.5 Gy in 10 fx or multicatheter brachy therapy 34 Gy in 10 fx or intracavity brachytherapy 34 Gy in 10 fx	50 Gy in 2 Gy fx or 50.4 Gy in 1.8 Gy fx ± tumor bed boost to 60.0-66.6 Gy	IBTR	OS, RFS, distant DFS, toxicity, cosmesis, QOL
Canadian RAPID	1/2006	2,135 (Closed)	≥40 y of age, tumor ≤3 cm, pN0	Lumpectomy to uninvolved margins and negative ALND or SLNB	3D-CRT 38.5 Gy in 10 fx	42.5 Gy in 16 fx over 22 days or 50 Gy in 25 fx (if large breasts) ± 10 Gy tumor bed boost	IBTR	OS, DFS, EFS, toxicity, cosmesis, QOL, cost effectiveness
MRC IMPORT-LOW	9/2006	2,100 (Closed)	≥50 y of age, IDC ≤2 cm, grade 1–2, ≤pN1mi	Lumpectomy with ≥2 mm margins and ALND or SLNB	Arm 1: 40 Gy in 15 fx to tumor bed Arm 2; 40 Gy in 15 fx to tumor bed *plus* 36 Gy in 15 fx to remainder of breast	40 Gy in 15 fx		
ELIOT	11/2000	1,300 (Closed)	>48 y of age, tumors ≤2.5 cm, tumor location not amenable to ELIOT (axillary tail, close to skin)	Quadrantectomy and ALND or SLNB	Intraoperative electron beam 21 Gy in 1 fx to applicator surface	50 Gy in Gy fx ± 10Gy boost to tumor bed		
University of Florence	9/2005	520 (Goal)	>40 y of age, tumors ≤2.5 cm	Lumpectomy with ≥5 mm margins	IMRT 30 Gy in 5 fx to tumor bed	50 Gy in 25 fx		Initial toxicity analysis: grade 1 and 2 toxicity 22% and 19% for WBI vs. 5% and 0.8% for PBI
GEC-ESTRO	5/2004	1,195 (Closed)	>40 y of age, stage 0–II, tumors ≤3 cm, no EIC, ≤pN1mi	Lumpectomy with ≥2 mm margins (≥ 5 mm if DCIS or ILC)	HDR 32.0 Gy in 8 fx *or* HDR 30.3 Gy in 7 fx *or* PDR 50 Gy at 0.6-0.8 Gy/hr	50.0-50.4 Gy in 25–28 fx plus 10 Gy tumor bed boost	IBTR	OS, DFS, distant DFS, toxicity, cosmesis, QOL initial toxicity analysis: grade 3 dermatitis 7.1% for WBI versus 0.2% for PBI ($p < .0001$)

PBI, partial breast irradiation; WBI, whole breast irradiation; NSABP, National Surgical Adjuvant Breast and Bowel Project; RTOG, Radiation Therapy Oncology Group; LNs, lymph nodes; ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; 3D-CRT, 3D conformal radiation therapy; IBTR, ipsilateral breast tumor recurrence; OS, overall survival; RFS, recurrence-free survival; DFS, disease-free survival; QOL, quality of life; RAPID, Randomized Trial of Accelerated Partial Breast Irradiation; EFS, event-free survival; IDC, invasive ductal carcinoma; ELIOT, intraoperative electron beam radiotherapy; GEC-ESTRO, Groupe Européen de Curiethérapie—European Society for Radiotherapy and Oncology; ILC, invasive lobular carcinoma.

(p = .54), and 13% of patients in both groups were younger than 45 years of age. ER, PR, and HER2 status did not differ between patients undergoing sentinel node biopsy alone or axillary dissection, and 84% and 83% respectively were ER and/or PR positive and HER2 negative. Nomograms are available from Memorial Sloan-Kettering Cancer Center (www.mskcc.org/cancer-care/adult/breast/prediction-tools) and from The University of Texas MD Anderson Cancer Center (www3.mdanderson.org/app/medcalc/bc_nomogram2/index.cfm?pagename=nsln) to estimate the likelihood of positive nonsentinel nodes. Using the Memorial Sloan-Kettering nomogram, the median likelihood of additional positive nodes in the sentinel node-only group in the prospective Memorial Sloan-Kettering Cancer Center cohort was 34%, similar to what was found in ACOSOG Z11. This nomogram is not used at Memorial Sloan-Kettering Cancer Center to determine the need for axillary dissection nor the need for axillary irradiation. At a median follow-up of 13 months (range, 1–29 months), no axillary recurrences have occurred in this patient cohort, but longer follow-up is needed. At this time, it is uncertain whether or not additional fields are needed to treat the full axilla in patients estimated to have a high risk of positive non-sentinel nodes. If a decision is made to add additional fields, the full axilla should be treated.

Morbidity of Whole Breast Irradiation

Treatments require only 15 to 30 minutes each day, and most patients can continue their daily routines with minimal interruptions. Two short-term complications that occur in the majority of patients are fatigue and mild breast dermatitis. The degree of fatigue varies a great deal among individuals and generally improves to baseline within a month after treatment. In some patients, fatigue can last for months. The skin reactions associated with radiation delivered with modern techniques are typically mild. Erythema, warmth, mild discomfort, and pruritis typically develop toward the end of treatment and improve shortly after treatment completion. Some patients experience desquamation, especially if skin folds are present. Patients commonly experience "twingy" breast pain for an extended period of time. Post-treatment skin edema and mild hyperpigmentation may persist many months.

Modern treatments are very safe, with a very low likelihood of a permanent normal tissue injury. The most common complication after irradiation is mild fibrosis of breast tissue. However, most series report that 80% to 95% of patients have good to excellent aesthetic outcomes after breast irradiation to total doses of 45.0 to 50.4 Gy in daily fractions of 1.8 to 2.0 Gy (89). The development of a second cancer induced by radiation treatments of the breast is a very unusual event. In an analysis based on the Connecticut cancer registry database of 41,109 breast cancer patients, Boice et al. (90) reported that breast irradiation may increase the incidence of contralateral breast cancer in women 45 years of age or less who survived for at least 10 years after diagnosis (RR 1.33). The EBCTCG meta-analysis of the data from all radiotherapy trials in breast cancer (including trials investigating postmastectomy radiation) reported a 1.18 ratio of rates for developing a second breast cancer for irradiated vs. nonirradiated patients (p = .002) (1). Given these data, it is important to optimize techniques to minimize scatter radiation dose to the contralateral breast. The newer modulated techniques that provide three-dimensional dose compensation with multileaf collimated subfields have the additional benefit of decreasing the dose to the contralateral breast by 65% to 82% (91). The EBCTCG meta-analysis also indicated an increased risk of lung cancer development in patients who received radiation (HR, 1.61), although this included patients receiving older techniques of postmastectomy RT where the amount of lung irradiated is much greater than with currently used breast irradiation (1). Data from the NSABP indicated that this risk was dependent in part on the volume of lung included in the radiation fields. Specifically, an increased risk was found in patients treated in the NSABP B-04 trials where treatment included multiple fields to target the regional lymphatics in addition to the breast and chest wall, but not the B-06 trial where breast-only treatment fields were used (92). Smoking is recognized as an important cofactor for the development of lung cancer after breast cancer radiation treatments. Kaufman et al. (93) conducted a population-based case-control study using the Connecticut Tumor Registry and reported that non-smoking breast cancer patients who received radiation did not have a higher risk of lung cancer development, but irradiated breast cancer patients who were smokers did have a significantly increased risk. These data were similar to a case-control study published by the group from the University of Texas MD Anderson Cancer Center who also found that smoking was a significant independent risk factor for lung carcinoma after breast cancer, and that smoking and radiation combined enhanced the effect of either alone (94). A rare, but frequently fatal, radiation-related malignancy is lymphangiosarcoma of the treated skin. This is an unusual second cancer in that it can be seen prior to 5 years post treatment.

One of the most significant potential sequelae of whole breast irradiation is cardiovascular disease with associated cardiac-related death. The meta-analysis from the EBCTCG indicated that patients treated with radiation had a 1.27 RR of death from heart disease compared to the patients who did not receive radiation (1). This result was predominantly seen in relatively older postmastectomy radiation studies that utilized treatment techniques and dose schedules no longer in use. With the advent of improved technologies, radiation treatments are much less likely to cause adverse cardiac events. For example, a study evaluating the SEER database suggested that radiation treatments increased cardiac-related deaths for patients treated in the 1970s, but there was no increase in cardiac deaths in the patients treated in the 1980s (95). Similarly, a study that evaluated the SEER-Medicare database found no increase in cardiac events in patients over 65 years of age who were treated with radiation for a left-sided breast cancer (96). However, a study from the University of Pennsylvania indicated that patients treated with radiation as a component of BCT for a left-sided breast cancer had an increased risk of coronary artery disease compared to those treated for a right-sided breast cancer (97). Additionally, investigators from Duke University have shown that inclusion of some of the left ventricle in tangential fields used to treat left-sided breast cancers can result in cardiac perfusion abnormalities (98). The period from treatment to radiation-induced cardiac disease is protracted and typically greater than 10 to 15 years, so avoiding direct cardiac exposure is particularly important in younger patients.

Based on these data, it is very important that the risk of radiation-associated heart disease be minimized or completely avoided by ensuring that the heart is not within the treatment fields. For patients with upper outer quadrant tumors, a small heart block can be used, which shields a small volume of the far medial and far lateral lower breast tissue. Studies have reported that use of heart blocks do not increase the risk of in-breast recurrence (99). For tumors in the lower quadrants, new techniques are available to physically displace the heart from the tumor bed through breath-hold techniques.

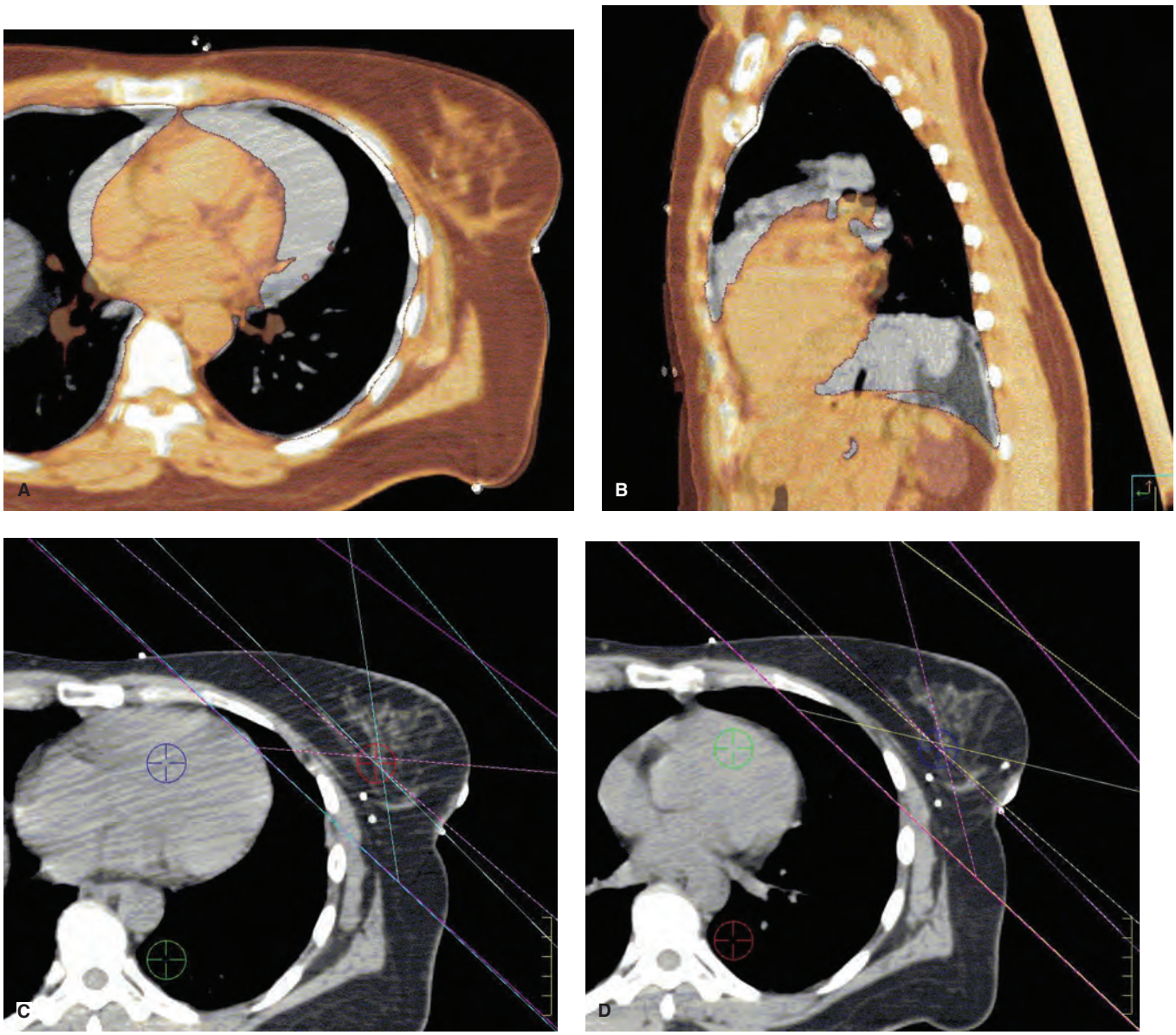

FIGURE 35-6 **An example of a treatment that is gated to deep inspiration in order to displace the heart from the radiation field.** As seen on the fused axial **(A)** coronal **(B)** image of a free-breathing scan and a breath-hold scan, deep inspiration lowers the diaphragm and displaces the heart inferomedially. The next two axial images show the relationship of the heart to the radiation fields under free-breathing conditions **(C)** and breath-hold conditions **(D)**. In this example, the treatment beam is only turned on during breath-hold periods to ensure that the heart is outside of the field.

In this procedure, patients can monitor their respiratory cycle and hold their breath in a predefined volume that achieves cardiac displacement. During deep inspiration, the diaphragm pulls the heart down and medial relative to the left breast. An example of this technique is shown in Figure 35-6. In-room monitoring is necessary to make sure that the patient is in the correct position for treatment, and a variety of techniques are available to do this. For patients with superficial tumors, another approach to avoiding cardiac irradiation is to use a prone (or decubitus), rather than supine, technique. Nodal irradiation, particularly full axillary RT combined with axillary dissection, increases the risk of lymphedema and rarely results in brachial plexopathy, a devastating complication that can lead to loss of function in the arm.

POSTOPERATIVE SURVEILLANCE

In patients who are treated with BCS and postoperative RT, annual mammography and physical exam one to two times yearly are appropriate follow-up procedures given the low risk of both ipsilateral recurrence and contralateral cancer in most patients. Some groups obtain a new baseline mammogram of the treated breast 4 to 6 months after the completion of RT, although the value of this remains unproven.

MANAGEMENT SUMMARY

- Based on long-term results demonstrating both efficacy and safety, BCT consisting of breast-conserving surgery for removal of the primary with negative margins of resection followed by whole breast irradiation is an appropriate option for the majority of patients with early-stage breast cancer.
- No patient subset based on clinical and pathology features has been identified that has a low risk of LR without RT. Breast-conserving surgery and hormonal therapy is an option in elderly women with small node-negative, hormone receptor positive breast cancer, particularly if the patient has co-morbid illnesses. However, short-course breast irradiation is also an option.
- Whole breast irradiation reduces the 10-year risk of any first recurrence with a rate ratio of about half (0.52, $2p < 0.00001$), and reduces the 15-year risk of breast cancer death with a rate ratio of about one-sixth (0.82, $2p = 0.00005$).
- Following whole breast irradiation, a boost of additional irradiation is given to the primary site, particularly in younger patients.
- Absolute contraindications to BCT include previous RT to the chest or breast, RT required during a pregnancy, diffuse malignant appearing microcalcifications on mammography, and inability to achieve a negative margin of resection. The use of BCT is generally contraindicated in patients with multicentric cancer or with active connective tissue disease involving the skin.
- Patients can be reliably selected for BCT with a history, physical examination, and diagnostic mammography. Evidence that MRI or screening whole breast ultrasound improves outcomes is lacking.
- A margin with no ink on tumor is sufficient for the majority of patients undergoing breast conservation. Factors, such as patient age, ER, progesterone receptor, and HER2 status, amount of tumor close to the margin, and use of neoadjuvant chemotherapy need to be considered when determining if larger margins are needed in individual cases.
- The use of adjuvant systemic therapy developed to reduce distant metastasis has been demonstrated to substantially reduce LR when combined with breast irradiation.
- When a patient will receive both BCT and adjuvant chemotherapy, RT generally follows chemotherapy. Adjuvant hormonal therapy or trastuzumab can be given with or after RT.
- Computed tomography simulation with contouring of critical volumes is important and should be done for all patients, especially those with left-sided breast cancer. The treatment technique should attempt to exclude the heart from the treatment fields. Appropriate measures should be used to provide homogeneous irradiation.
- Accelerated whole breast irradiation and APBI are appropriate options for patients considered suitable by ASTRO consensus guidelines. There is limited level I data supporting APBI, however.

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CHAPTER 36

Breast Reconstruction

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CHAPTER CONTENTS

Breast reconstruction is an important component of breast cancer management and improves quality of life and psychosocial well-being (1). Improvements in techniques have resulted in more natural reconstructions, decreased morbidity, and improved outcomes. Breast reconstruction has traditionally been considered reconstruction after mastectomy, however, more recent studies have reported improved outcomes even after segmental resection in some circumstances. Therefore, plastic surgeons are important members of a multidisciplinary breast team and by working closely with breast surgeons, medical oncologists, and radiation oncologists, they can help individualize and optimize breast cancer care.

In general, most women who undergo breast surgery for cancer treatment are candidates for reconstruction and there are no absolute contraindications. However, most reconstructive surgeons consider inflammatory breast cancer requiring massive skin resection and significant medical comorbidities that increase risk of medical complications as relative contraindications. In addition, reconstruction in women who will require postmastectomy radiation therapy is hotly debated and the ideal approach remains unknown. However, even in these circumstances reconstruction is warranted in some cases and must be considered on an individual bases. For example, a patient with inflammatory breast cancer who requires extensive skin resection may need reconstruction as a component of her care simply to close the resulting mastectomy skin defect.

The type of reconstruction that is performed is dependent on a number of factors including oncologic considerations, patient desires and expectations, body habitus, and surgical risk factors. Patients should be evaluated by a qualified plastic surgeon who can evaluate these considerations and advise the patients on their best reconstructive option and the ideal time to initiate the process based on their individual circumstances.

IMMEDIATE VERSUS DELAYED RECONSTRUCTION

Reconstruction can be performed either at the time of mastectomy or segmental breast resection or in a delayed manner after adjuvant treatment is completed. The timing of reconstruction is dependent on oncologic considerations and patient factors. In general, the vast majority of patients are candidates for immediate reconstruction and this approach has a number of advantages. For example, reconstruction at the time of mastectomy is associated with improved aesthetic outcomes by preserving the breast shape and envelope (Fig. 36-1). Immediate reconstruction is also easier to perform technically since there is usually less scarring and contracture. Immediate reconstruction does not delay or hinder diagnosis of a recurrence and, in most cases, does not alter its treatment (2). In addition, immediate reconstruction has important psychological benefits resulting in decreased anxiety and improved self-image, and enabling patients to cope with their diagnosis and treatment (3). From a practical standpoint, immediate reconstruction saves the patient an additional trip to the operating room.

There are, however, some potential disadvantages to immediate reconstruction. One consideration is an increased risk of complications associated with combining oncological treatment and reconstruction. Although this idea makes intuitive sense, very few studies have actually compared complication rates in the same patient cohorts. In addition, the majority of complications that occur in the setting of immediate reconstruction are minor in nature and rarely delay adjuvant therapy (4,5). Mastectomy skin flap necrosis is much more common after immediate reconstruction and likely reflects the more extensive dissection that is performed at the time of mastectomy. Some patients are

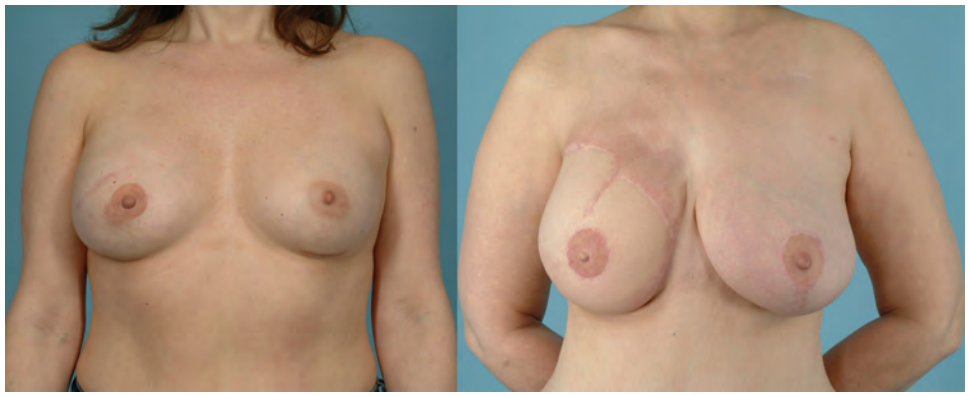


FIGURE 36-1 Postoperative photographs of patients with right breast cancer treated with immediate (*left*) or delayed (*right*) TRAM flap reconstruction. Note that although both outcomes have excellent shape or contour, patients treated with delayed reconstruction have longer and more noticeable scars.

also overwhelmed with the number of decisions they need to make for immediate reconstruction, leading to increased anxiety in some cases.

IMPLANT VERSUS AUTOGENOUS RECONSTRUCTION

Breast reconstruction can be categorized broadly into implant based or autologous tissue (i.e., the patient's own tissue) reconstruction (Table 36-1). Implant reconstructions make up the bulk of breast reconstructions that are performed annually in the United States. Implant reconstruction is simpler to perform, is associated with low rates of complications, and does not significantly increase hospital stay or recovery as compared with mastectomy alone. Although most patients are candidates for implant reconstruction, there are some relative contraindications including severe medical comorbidities, oncologic factors necessitating massive skin excision, severe immune deficiency, heavy smoking history, massive obesity, and history of breast irradiation. These circumstances increase the rates of complications associated with implant reconstruction, but do not preclude their use in select cases.

TABLE 36-1

Advantages and Disadvantages of Implant-Based or Autogenous Tissue–Based Breast Reconstruction

	Advantages	*Disadvantages*
Implants		
	Simple	Implant leak
	Low operative morbidity	Implant infection
	Short hospital stay	Feel and shape
	Quick recovery	Contralateral symmetry
		Capsular contracture
Autogenous Tissues		
	Softer, more natural	Longer operation
	Symmetry	Longer recovery
	Ages with patient	Donor site issues
	No capsule	

A disadvantage of implant reconstructions is that implants require maintenance and need to be replaced if they rupture or leak. Although implant technology has improved considerably over the past two decades, most modern implants have an average life span of approximately 10 years. A recent study demonstrated a 4-year leak rate of 4% to 15% in saline implants depending on the manufacturer used (6). In addition, because implants are a foreign substance and are placed underneath the pectoralis muscle, these reconstructions do not feel as natural as a normal breast. It is also difficult to obtain perfect or near perfect symmetry with implants in unilateral reconstructions even when contralateral symmetry procedures such as augmentation, reduction, or mastopexy are performed. Asymmetry of implant reconstructions with the normal breast tends to worsen over time, particularly if patients gain or lose weight, since the implant size does not change and the implant pocket does not sag. Thus, although aesthetic results have improved over the years, the primary goal of implant reconstructions is to have reasonable symmetry in clothes, a bra, or a bathing suit. By far the biggest disadvantage of implant reconstructions is the potential for developing capsular contracture. A capsule is a fibrous covering that develops around any prosthetic device that is placed subcutaneously. Capsular contracture develops when the capsule surrounding the implant becomes thickened and tight, causing patients to complain about tightness, pain, or implant malposition. The degree of contracture can be quantified using the Baker scale and uses a four-point scale based on physical exam and symptoms. Grade I is a normal-appearing, soft breast; grade II refers to breast implants that are firm but appear normal; grade III includes implants that are firm and appear abnormal; grade IV capsular contracture is the most severe and includes breasts that are hard, painful, and appear abnormal often with severe distortion. Most women who undergo implant reconstruction have grade I or II capsular contracture (89.6%) (7).

Breast reconstruction can also be performed using a patient's own tissues (autologous reconstruction). In these procedures, a combination of skin, fat, and muscle is transferred to the breast to reconstruct either the entire breast or a portion thereof. Tissues can be transferred from adjacent areas such as the back (latissimus flap) or abdomen or from sites located distant to the breast including the gluteal region or the inner thigh. Reconstruction can be performed either purely with autologous tissues or in combination with an implant. Autologous tissues are transferred to the breast site either by keeping their local blood supply intact (pedicled flaps) or by disconnecting and reconnecting the arterial and venous circulation using microsurgical techniques (microsurgical or free flaps). Similar to implants, autologous tissue reconstruction has high success rates and patient satisfaction.

Autologous tissue reconstruction is indicated in women who wish to avoid using implants, have failed implant reconstruction previously, or who are poor implant reconstruction candidates. For example, a patient who has undergone mastectomy and radiation is unlikely to have a successful reconstruction using an implant alone since the remaining mastectomy skin has been injured. In these circumstances, a portion of the damaged mastectomy skin is usually replaced by healthy tissues from a distant flap donor site and reconstruction is completed. Another example is a patient who has very large, ptotic breasts that are unlikely to be adequately matched with an implant reconstruction.

The main advantage of autologous tissues is the fact that reconstruction is performed with *living* tissues. These tissues age with the patient, changing over time to maintain symmetry with the contralateral breast. In contrast to implants, autologous tissues are tailored to the patient and more likely to have symmetry immediately after reconstruction. Tissue reconstructions feel and look more natural because, unlike implants, the tissues are placed in the subcutaneous plane simply replacing the breast rather than in a subpectoral position. Tissue reconstructions also do not develop fibrous capsules and can help replace damaged tissues to break up scar and relieve contracture. As a result of these advantages, tissue-based reconstructions are considered the gold standard for aesthetic reconstruction.

Of course, all good things come at a cost. The "cost" in the case of autologous tissues is donor site morbidity that increases recovery time and can have long-term consequences. At the minimum, patients reconstructed with their own tissues will have donor site scarring that in some cases may be unaesthetic. Chronic donor site pain and bothersome loss of sensation have also been reported for patients reconstructed with various types of autogenous tissues. Functional issues such as abdominal wall weakness, bulging, or hernia complicate abdominal tissue–based reconstructions in some patients. Similarly, patients reconstructed with latissimus flaps may have decreased upper extremity strength and range of motion that in some cases may necessitate physical therapy.

IMPLANT-BASED RECONSTRUCTION

In general, most patients are candidates for implant reconstruction including elderly patients and those with medical comorbidities that may preclude more complex forms of reconstruction. Absolute contraindications to implant reconstruction include severe tissue deficiency from resection or secondary to tissue damage from radiation. Relative contraindications for implant reconstruction are severe life-threatening medical comorbidities, massive obesity, and possibly long-standing heavy cigarette smoking. Some surgeons also consider the need for postmastectomy radiation therapy as a relative contraindication; however, this concept has been debated and there is no uniform consensus.

The ideal patient for implant reconstruction is thin, has moderate-sized breasts (B to C cup), minimal ptosis, and well-defined breast shape (Fig. 36-2). Although most women who undergo implant reconstruction do not have these characteristics, reasonable reconstructions with good symmetry in clothes, bra, or bathing suits is possible, particularly if contralateral breast symmetry procedures are performed. These issues are less critical in bilateral reconstructions since a similar implant is used for the contralateral breast, resulting in even better symmetry, and likely contributes to the higher rates of satisfaction in this cohort (8).

It is difficult to achieve symmetry with implant-based reconstructions in women with either very small or very large breasts. Reconstruction of very small breasts is complicated by the fact that low-volume implants needed in these cases typically have a small base diameter (the width of the implant). This issue makes it difficult to simultaneously match the volume and diameter of the breast, resulting in a wide space between the breasts. An alternative approach for improved symmetry in these cases may be contralateral augmentation to increase the volume of the normal breast.

Reconstruction of massive breasts or very obese patients with implants is also difficult due to the fact that the largest implant currently available in the United States is 800 to 850 cc. Although this is a large size, and suitable for most large-breasted women, in some women with massive breasts or those who are morbidly obese, these large implants are simply inadequate volume to achieve sufficient projection for an aesthetic outcome or to match the contralateral breast. Even if a large reduction is performed in the contralateral breast, these procedures may be inadequate to sufficiently decrease the volume, projection, or base diameter of the remaining breast, resulting in a reconstructed breast that is too small, flat, or narrow, respectively, to fit the patient's chest wall. In these cases, patients may require a small external prosthesis for improved symmetry or may be advised to undergo reconstruction with alternative measures.

Implant reconstruction can be performed either immediately after mastectomy or in a delayed fashion. The ideal incision for implant reconstruction is debated; however, incisions placed along the lines of relaxed skin tension lines (i.e., Langer's lines) are selected by most surgeons since these incisions enable maximal skin expansion. Skin-sparing

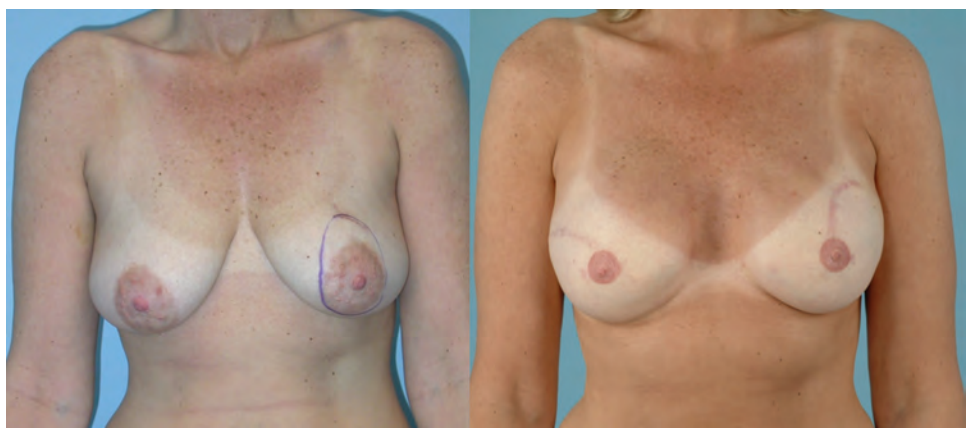


FIGURE 36-2 Pre- (*left*) and postoperative (*right*) photographs of a patient 1.5 years following reconstruction with bilateral silicone implants.

mastectomies in appropriate candidates preserve the breast envelope and enable more rapid expansion. Skin preservation is important even in non-skin-sparing procedures since there is a limit to the amount of expansion that can be performed. Overexpanded skin may become thin, shiny, and lose elasticity, resulting in impaired aesthetics, discomfort, and implant exposure. Although the oncologic risks of nipple-sparing mastectomy is still undefined and remains a source of debate, there is little doubt that these techniques have excellent cosmetic outcomes in appropriately selected patients.

The majority of implant reconstructions are performed as a two-step procedure with placement of a tissue expander initially and then conversion to a permanent implant at a later time. Tissue expander sizing is based on the dimensions of the breast pocket (width and height) and to a lesser degree the volume of the breast. With popularization and wide adoption of skin-sparing and nipple-sparing mastectomies, several groups have reported single-stage direct to implant reconstructions that avoid expander insertion (since the skin does not need to be expanded). In general, these studies have reported good to excellent results with reasonable safety profiles; however, the vast majority of these reports maintain that careful patient selection is important. These studies require validation in large prospective studies as most reports have been on limited numbers of patients and performed in a retrospective manner.

Implants and expanders for breast reconstruction are placed underneath the pectoralis major muscle. Total submuscular coverage of the implant can be obtained by elevating a portion of the rectus abdominis fascia inferiorly and serratus anterior muscle or fascia laterally to completely cover the expander. This technique is thought to decrease implant infections by providing vascularized coverage (7).

Some surgeons have criticized the total submuscular coverage technique with concerns about lower pole expansion, implant projection, and maintenance of the inframammary fold. These concerns have led to a variety of techniques including dis-insertion of the inferior insertion of pectoralis major muscle or the use of acellular dermal matrices. Over the past 10 years or so, the use of acellular dermal matrices such as AlloDerm or FlexHD to provide lower pole coverage of the expander/implant have gained significant popularity. In these procedures, the pectoralis major muscle is elevated and dis-inserted inferiorly. The lower/lateral portion of the implant is then covered with acellular dermis sutured inferiorly to the inframammary fold/lateral chest wall, and superiorly to the elevated pectoralis major muscle. Although some authors have reported excellent cosmetic results with low rates of complications (9), other reports have suggested that the use of acellular dermal matrices is associated with small, though statistically significant increases in the risk of implant infection and reconstructive failure (10). Large, prospective studies will be necessary to resolve this debate.

Once the expander is placed in the subpectoral pocket, the expander is filled intraoperatively with the final volume determined by tension on the skin and muscle. Expander filling in the office starts usually 2 weeks after surgery with 30 to 120 cc of sterile normal saline per expansion until the final volume is reached. If chemotherapy is not needed, then exchange to permanent implant is performed once the mastectomy skin flaps have completely healed. These procedures are usually performed 4 to 12 weeks following completion of chemotherapy in patients who required adjuvant treatments. The second stage of reconstruction is usually performed in an outpatient setting.

The main advantage of saline implants is the fact that if they leak, then the saline solution is simply absorbed and the implant is exchanged. However, saline implants tend to have more visible rippling and are not as comfortable as silicone implants. This latter contention is supported by recent studies utilizing validated quality of life questionnaires showing that patients with silicone implants have higher quality of life and increased satisfaction as compared with saline implants (11).

The main disadvantage of silicone implants is that leaking silicone is not absorbed and requires surgical removal. The leaking silicone is usually contained in the breast implant pocket; however, silicone extravasation can cause inflammation and capsular contracture and may be taken up by regional lymph nodes. Anecdotal reports in the late 1980s linked leaking silicone implants with a variety of ailments including autoimmune disorders and increased risk of malignancies, leading to the withdrawal of these implants by the Food and Drug Administration (FDA) in 1992 (except for procedures performed as a part of an FDA-approved research protocol). However, large-scale studies performed both in the United States and in Europe failed to find a statistically significant relationship in these outcomes and the implants are now approved by the FDA both for reconstructive and cosmetic procedures. Recent reports have suggested that textured implants in general (both saline *and* silicone) may be associated with a rare form of lymphoma, with an estimated incidence of 1 in 1 million; however, these reports need further study and validation (12).

Advancements in implant technology have introduced newer silicone implants filled with a silicone gel that is semisolid and therefore thought to be less likely to leak. These implants, referred to as form-stable, cohesive, or "gummy bear" implants, have some advantages including better shape in some patients and possibly a lower risk of leakage; however, long-term studies are needed to confirm these concepts.

Implant reconstructions are safe and well tolerated with low rates of major and minor complications (5). There were no cases of life-threatening complications (pulmonary embolus, myocardial infarction, major systemic complication) in a recent review of over 1,170 consecutive reconstructions performed at Memorial Sloan-Kettering Cancer Center (5). The majority of complications that did occur were minor and included skin necrosis (8.7%), infections (3.4%), infection requiring implant removal (1.5%), and seroma/hematoma (3.2%).

Capsular contracture is the most significant long-term risk with implant reconstructions and remains a problem even with improvements in implant technology and surgical techniques (7). The reported rates of capsular contracture vary significantly likely due to the fact that the diagnosis of this complication is somewhat arbitrary and not uniform. Most studies use the Baker scale as noted above; however, this scale has been criticized since it is not quantitative and primarily dependent on subjective assessment of "normal" or "abnormal" breast shape. This subjective assessment is likely responsible for the significant variability in the reported rates of capsular contracture and overall success rates of implant reconstructions in the plastic surgery literature.

Another important issue in comparing aesthetic outcomes in implant reconstruction is the methods used for analysis. By far the vast majority of previous studies have relied on photographic analysis by surgeons or laypeople to analyze various measures including symmetry, scars, volume, shape, and so on. Although these results are important and provide useful information, they do not address patient perceptions and may either over- or underestimate the success rates of various reconstructive needs. This deficiency

has been addressed recently with the use of validated patient reported outcome studies such as the Breast-Q, which aim to analyze how patients perceive their reconstruction in terms of physical, psychosocial, and sexual well-being as well as satisfaction with breast, outcomes, and care (13). The addition of these measures is exciting and provides surgeons with better insight about how patients perceive their reconstruction. This information can therefore help guide reconstructive techniques, preoperative teaching and preparation, and critical analysis of outcomes that can be standardized across centers.

In the past, a major concern limiting access of patients to immediate reconstruction was a hypothetical increase in the risk of breast cancer or delay of diagnosis of a recurrence in this setting. However, several large-scale studies have shown that immediate reconstruction with implants has little effect on recurrence, survival, or diagnosis of recurrence (5). The majority of recurrences in these cases were skin or subcutaneous in nature and identified by routine physical exam or serological markers. For this reason, follow-up of patients with implant reconstruction is usually limited to careful physical exams rather than mammography or other radiological measures. Even when patients were discovered to have a recurrence, implant reconstruction in the majority of cases did not alter additional treatment (5).

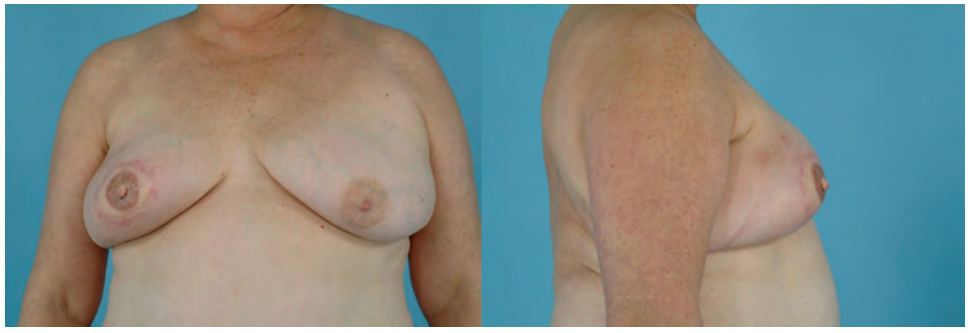
A number of risk factors predict complications after implant based breast reconstruction. In a study of 1,170 consecutive reconstructions using multivariate analysis, McCarthy and colleagues demonstrated that obesity, hypertension, age greater than 65, and smoking were independent predictors of complications (2). The adjusted odds ratio of these factors ranged between 1.8 (obesity and smoking) to more than 2 (hypertension and age over 65). Univariate analysis of reconstructive failure demonstrated that obesity, smoking, and hypertension significantly increased the risk of reconstructive failure (i.e., implant removal).

Several studies have reported satisfaction with implant reconstructions and most have reported high rates of satisfaction in the early years following reconstruction. However, a consistent theme is decreasing satisfaction over time that may be attributable to a number of factors including lack of change in the implant over time, the need for implant maintenance (either for symmetry or due to rupture), and capsular contracture. Many of the reported studies have used nonvalidated questionnaires, thereby making their findings somewhat less useful. However, recent reports have begun to use validated patient reported outcomes in large populations of patients enabling us to better understand the factors that contribute to patient satisfaction AND dissatisfaction after mastectomy and implant reconstruction.

LATISSIMUS FLAP

The latissimus flap is a commonly used method for breast reconstruction and involves subcutaneous tunneling of the ipsilateral latissimus dorsi muscle with or without skin or subcutaneous tissues to the breast area (Fig. 36-3). In most patients the latissimus flap does not have enough volume for a full breast reconstruction, and for this reason, it is usually combined with an immediate implant or expander placement.

The latissimus flap can be used in primary breast reconstruction after mastectomy or as a salvage procedure for patients who have failed other forms of breast reconstruction. Although most surgeons use the latissimus flap for unilateral reconstructions, bilateral reconstructions have also been reported. The use of the latissimus flap enables the plastic surgeon to transfer a considerable amount of soft tissues to the breast and can result in excellent reconstructions particularly in women who have large, ptotic breasts, or those who have undergone a previous subglandular



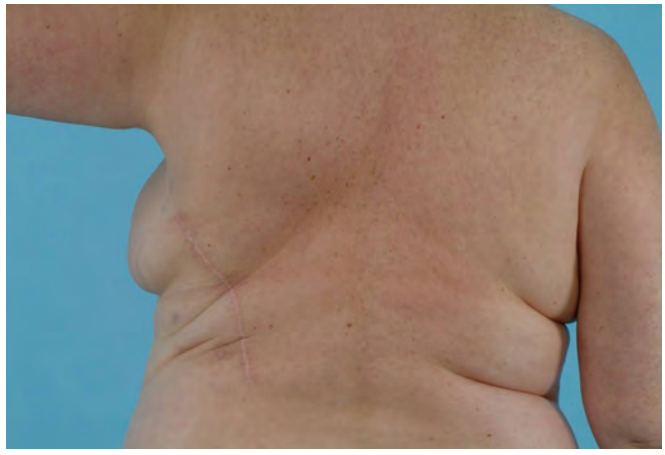


FIGURE 36-3 Pre- (*top left*) and postoperative (*top right*) photographs of a patient 1 year following right breast reconstruction with a latissimus dorsi flap and silicone implant. Donor site scar is also shown (*bottom*).

breast augmentation. The latissimus flap is an excellent option in morbidly obese patients with massive breasts (14) and in smokers, although the risk of minor wound healing complications in this population remains elevated as compared with normal weight women and nonsmokers, respectively.

The main contraindication to the latissimus flap is a previous thoracotomy operation that transects the latissimus muscle/pedicle, or a history of pedicle ligation. The blood supply or pedicle for the latissimus dorsi flap is the thoracodorsal vessels, which may on occasion be injured during the course of axillary lymph node biopsy or dissection. Testing the ability of the patient to flex the latissimus dorsi muscles is a simple way to test the integrity of the pedicle vessels since the thoracodorsal nerve, artery, and vein are intimately associated. Therefore, if the thoracodorsal nerve function is preserved it is likely that the vessels are likewise preserved. Even if the thoracodorsal vessels have been ligated, the latissimus flap can be transferred based on retrograde flow from the serratus anterior muscle–long-thoracic vessels, although these procedures increase the risk of venous hypertension.

A variety of skin paddle designs have been reported for the latissimus transferring a variable amount of skin and soft tissues to the breast. In some cases, no skin is necessary in which case the muscle can be harvested through several short incisions to decrease the donor site scarring. The horizontal (bra-line incision) is commonly performed and best for skin-sparing mastectomies in which the latissimus skin paddle is used to reconstruct the defect that remains after resection of the nipple–areola complex. The oblique flap design has a more noticeable donor site scar but is more useful if a larger skin paddle, such as may be needed in a delayed reconstruction, is necessary. The Fleur-de-lis modification combines both vertical and horizontal components and enables transfer of a large amount of tissues in many cases obviating the need for an implant (15). However, this flap design results in a T-shaped scar with a confluence of three incisions at the point of maximal tension and can be, as a result, associated with increased rates of donor site wound healing complications and contour deformity. Harvesting subcutaneous fat located below Scarpa's fascia and transferring parascapular and lumbar fat together with the latissimus dorsi muscle can increase the volume of the latissimus flap and may obviate the need for an implant in some cases.

In most cases an implant is also necessary to obtain the necessary volume and projection of the contralateral breast. In some cases (i.e., skin-sparing mastectomy with good skin flaps) it is possible to place an immediate implant for reconstruction. However, most commonly, a tissue expander is placed in order to adjust for latissimus muscle atrophy and to more slowly expand the breast pocket. This expander is replaced as an outpatient procedure 3 to 5 months later with a permanent implant.

The latissimus flap has low complications rates with a very low reported incidence of total flap loss even in high-risk patients (e.g., obese) (14). However, partial necrosis of the distal portions of the flap does occur on occasion, particularly in smokers and obese patients. This region can usually be excised during the course of the procedure with limited consequences. The most commonly reported early complication of the latissimus flap is donor site seroma formation, resulting in prolonged need for subcutaneous drains. The incidence of this complication can be greatly decreased with quilting sutures placed in the subcutaneous tissues to close off the dead space that is created from wide skin flap elevation (16). Hematomas can also be problematic if care is not taken to securely ligate intercostal perforators to the flap.

Late complications of the latissimus flap include donor site pain or tightness, widened scar, decreased range of motion, and implant-related complications (17). Surprisingly, most patients do not complain of long-term weakness from latissimus harvest, although careful pre- and postoperative quantitative analyses of back muscle function have been performed only in relatively small studies (18). Widened scars may also occur as a consequence of these factors and is particularly problematic in oblique incisions since these incisions crosa relaxed skin tension lines. Unfortunately, these incision patterns are necessary in some patients because they provide the greatest amount of skin on the breast for reconstruction. Limitation of ipsilateral arm range of motion and frozen shoulder may be problematic in some patients (19). This is of particular concern in elderly patients, those previously treated with axillary lymph node dissection and radiation, and patients with preexisting shoulder pathology. Aggressive physical therapy and rehabilitation may be necessary in these cases.

Implant-related issues (infection, rupture, capsular contracture) are also a source of complications in latissimus flap reconstruction. The reported rates of infection after latissimus flap reconstruction are variable; however, most studies report low single digit rates of infection and implant/expander loss (20). The rates of capsular contracture after latissimus flap transfer have been reported by only a few studies and, although somewhat variable, the incidence of severe capsular contracture (Baker grade III or IV) is low (3.6%) (21). The rate of significant capsular contracture is increased in women with a history of prior breast irradiation even when reconstruction is performed with a latissimus dorsi flap. For example, in a retrospective study of 35 patients with prior breast irradiation treated with salvage mastectomy and latissimus dorsi flap reconstruction, Disa et al. found that 17% of patients developed grade III capsular contracture after a mean follow-up of 4.1 years (22).

ABDOMINAL FLAPS

In 1982, Hartrampf and colleagues pioneered the use of abdominal-based flaps for breast reconstruction and, in doing so, revolutionized modern breast reconstruction techniques (23). These authors demonstrated for the first time that large amounts of skin and subcutaneous fat can be transferred based on the blood supply of the rectus muscle, thereby enabling surgeons to reconstruct breasts without implants. More importantly, development of the transverse rectus abdominis myocutaneous flap (TRAM) flap demonstrated that it is possible to combine reconstruction with aesthetic principals and elevated the goals of reconstruction from "restoration of a breast mound" to a natural looking and feeling reconstruction that ages with the patient and in some cases is indistinguishable from a normal breast (Fig. 36-4). These concepts also applied to the donor site of the TRAM flap that, contrary to other options available at the time (i.e., latissimus dorsi flap), could actually improve the contour of the abdomen rather than create unsightly scars. Over the years, the techniques of TRAM flap reconstruction have evolved to limit donor site morbidity by decreasing the amount of rectus muscle and fascia that is harvested and improving the blood supply of the tissues. As a result of these advancements, the TRAM flap is considered the gold standard for aesthetic breast reconstruction by which all other forms of reconstruction are judged.

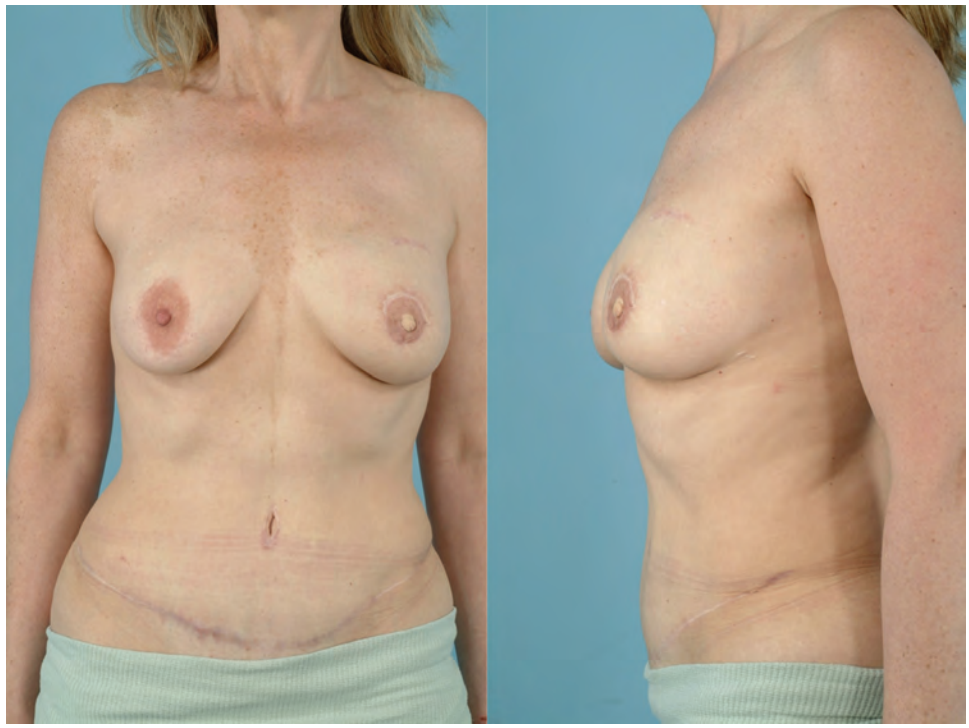


FIGURE 36-4 One-year postoperative photographs of a patient reconstructed with a left unilateral DIEP flap.

The TRAM flap is indicated for unilateral or bilateral breast reconstruction in patients who have an appropriate body habitus and are motivated to have autologous reconstruction. The ideal patient for a TRAM flap has enough tissues in the lower abdominal areas to aesthetically replace the volume of the breast with adequate skin laxity to enable closure of the abdominal defect. TRAM flaps can also be used in some patients with adequate skin laxity but insufficient volume; however, in these cases an implant is usually needed to restore the projection of the breast.

Absolute contraindications for TRAM flap reconstruction are previous abdominal operations that have disrupted the blood supply of the TRAM flap. For example, the TRAM flap cannot be performed in patients who have previously undergone abdominoplasty. Relative contraindications for TRAM flap include smoking, the need for postmastectomy radiation therapy, severe medical comorbidities that may increase the risk of prolonged anesthesia or the risk of wound healing complications, and a desire for future pregnancy. A history of neoadjuvant chemotherapy (chemotherapy within 6 weeks of surgery) is associated with an increased rate of wound healing complications; however, in most cases these complications are minor and rarely cause significant morbidity (4).

In the past, many surgeons advised against TRAM flap reconstructions in patients who require postmastectomy chemotherapy; however, several large-scale studies have recently shown that adjuvant therapy is rarely significantly delayed in these patients. For example, in a 10-year retrospective study of 170 patients with stage IIB or worse breast cancer treated at UCLA Medical Center with microsurgical breast reconstruction, chemotherapy was delayed in only 8 patients (4.7%) with a maximal delay of 3 weeks (24). However, these conclusions have been debated depending on the definition of delay that is used. For example, in a relatively small study, Kontos and colleagues compared 27 patients who had immediate breast reconstruction with TRAM flaps with 139 patients who did not and found that the mean time to the start of adjuvant chemotherapy was delayed by 15 days (55 vs. 40) in patients who had immediate breast reconstruction with TRAM flaps (25). In addition, the authors found that fewer patients who had TRAM flap reconstruction initiated their adjuvant treatment within 6, 8, or 10 weeks. Similarly, Lewis and Kontos reviewed the current literature and found that the delivery of adjuvant therapy is delayed in 3% to 72% of patients who undergo autologous tissue reconstruction with an increase of 13% to 36% in the period of time needed to start chemotherapy as compared to patients treated with mastectomy alone (26). Whether or not these delays are clinically significant or if there is a difference when compared to other forms of breast reconstruction (i.e., implants) remains unknown. Nevertheless, patients who will require chemotherapy postoperatively should be advised of this risk in order to make an informed decision.

The TRAM flap has a dual blood supply and can be transferred either as a pedicled flap based on the superior epigastric vessels or as a microsurgical (free) flap based on the inferior epigastric artery and vein. In the United States, pedicled flaps are more commonly performed as compared to free TRAM flaps due to differences in availability of microsurgeons and the institutional support necessary for the more complex microsurgical procedures. However, the safety and efficacy of pedicled TRAM flaps has long been established by numerous studies demonstrating that, when performed by expert surgeons, these procedures have low rates of morbidity and very low rates of flap loss.

In the pedicled TRAM flap technique, the lower abdominal tissues are harvested together with perforating vessels arising from the upper portion of the ipsilateral or contralateral rectus muscle. The rectus muscle is transected inferiorly and the muscle/flap are tunneled into the breast area by elevating the abdominal skin flaps. This procedure reliably transfers a little more than half of the TRAM flap (the hemi-TRAM ipsilateral to the rectus muscle as well as a small portion of the skin that crosses the midline). In rare cases when the entire TRAM flap skin or volume is needed for reconstruction, both rectus muscles are harvested (bipedicled

TRAM) maximizing the blood supply of the overlying skin. For bilateral breast reconstruction, the TRAM flap is divided in the midline and the tissues are transferred by harvesting both rectus muscles and transferring each hemi-TRAM individually into the breast. The fascia is either repaired primarily, or, more commonly repaired with mesh. The skin donor site is then closed using standard abdominoplasty techniques to recontour the abdomen.

A "supercharged" pedicled TRAM flap is a technique in which the abdominal flap is transferred to the breast based on the superior epigastric vessels and, in addition, the inferior epigastric vein is re-anastomosed to improve venous drainage. These procedures primarily developed as a bridge to the adoption of microsurgical flaps and aimed to address the theoretical disadvantages of both types of procedures: impaired blood supply of pedicled flaps and the risk of total flap loss with microsurgical flaps. However, as experience with microsurgical TRAM flaps increased the risk of total flap loss approximated that of pedicled flaps (<1%) leading to more widespread adoption of free flap transfers.

Microsurgical or free TRAM flaps were developed in an effort to improve the blood supply of the skin paddle and to decrease the amount of rectus muscle that is harvested, thereby decreasing abdominal wall morbidity. These efforts were based on anatomic studies demonstrating that the dominant blood supply of the TRAM flap is based on the inferior epigastric vessels with the superior epigastrics serving a secondary role. Early studies demonstrated clearly that the blood supply of the TRAM flap is improved with microsurgical transfer. In these cases, similar to the pedicled TRAM, all of the tissues ipsilateral to the rectus muscle are well perfused. The difference, however, is the amount of tissues that are well perfused across the midline (i.e., contralateral to the rectus muscle/pedicle). In most cases, one-third to one-half of this tissue can be reliably transferred to improve aesthetic reconstruction. Although a wide range of complications rates have been reported, numerous studies have shown that free TRAM flaps have significantly decreased rates of partial flap loss, fat necrosis, and abdominal wall hernia as compared with pedicled TRAM flaps.

In microsurgical TRAM flap procedures, a varying amount of muscle is harvested together with the inferior epigastric vessels that are ligated and transferred to the breast; microsurgical anastomosis is then performed to reestablish blood supply. Efforts aimed at decreasing the abdominal morbidity have led to changes in the amount of muscle that is harvested ranging from the entire width of the muscle (free TRAM) to just the central portion of the muscle, leaving a lateral and/or medial region of the muscle intact (muscle sparing TRAM). More recently, microsurgical techniques have evolved to the point in which the perforating vessels arising from the inferior epigastric artery and vein are dissected out of the rectus muscle thereby preserving the entire muscle. This technique is referred to as a deep inferior epigastric perforator flap (DIEP) or simply a perforator flap. The superficial epigastric vessels can also be used in some patients with suitable anatomy to transfer the lower abdominal skin flap (SIEA flap). These flaps are thought to incur the least amount of damage to the abdominal wall since the rectus fascia and muscle are not incised. However, due to anatomic variability in the size and positioning of the superficial epigastric vessels, this option is available in only 5% to 30% of patients (27).

Common recipient vessels for microsurgical repair include the thoracodorsal artery and vein or the internal mammary artery and vein. Over the past decade or so, most surgeons have shown a preference for the internal mammary vessels based on the fact that these vessels are located more centrally, thereby facilitating flap inset and contouring. This trend has also been influenced by the decreased rates of axillary lymph node dissection that is performed as a consequence of sentinel lymph node biopsy (28). This change in breast cancer management had two effects on microsurgical breast reconstruction. First, the thoracodorsal vessels are no longer exposed during the mastectomy if axillary lymph node dissection is performed. Therefore, exposure would require disruption of the axillary lymphatics and possibly increase morbidity. In addition, reoperation in patients with a false-negative sentinel lymph node biopsy potentially increases the risk of injury to the vascular pedicle of the TRAM flap if anastomosis is performed in the axilla.

The routine use of anticoagulants after microsurgical breast reconstruction is debated and a variety of approaches including no anticoagulation, aspirin, low molecular weight heparin, intravenous heparin, or a combination of the above have been reported (29). However, despite the debate, the routine use of anticoagulants to prevent deep venous thrombosis is recommended and supported by level 1 prospective studies (30). In the early years of microsurgery, intravenous dextran was used as a volume expander and anticoagulant to reduce the risk of microvascular thrombosis. However, this practice has largely been abandoned based on high rates of systemic complications (congestive heart failure, pneumonia, myocardial infarction). For example, in a prospective, randomized control study of 100 consecutive patients treated with microsurgical free flaps, Disa and colleagues reported a 7.2-fold increase in the risk systemic complications in patients treated with Dextran and aspirin as compared with aspirin alone (31).

The blood supply of microsurgical TRAM flaps is monitored carefully for 3 to 5 days postoperatively. This length of monitoring is based on large retrospective studies demonstrating that the vast majority of microvascular complications occur within the first 72 hours after surgery. For example, Chen et al. retrospectively reviewed their experience with 1,142 free flaps and found that 95.6% of microvascular thromboses occurred within 72 hours of surgery (32). Postoperative monitoring is performed using clinical exam to monitor skin color, temperature, and capillary refill. In addition, a Doppler ultrasound is routinely used to audibly check the blood supply of the TRAM flap. The Doppler primarily provides information about arterial flow; however, careful examination can also provide clues about venous outflow. A number of new technologies, including tissue oximetry and infrared spectroscopy, have been reported to facilitate the diagnosis of microsurgical thrombosis. Early reports with these devices have been promising and warrant additional research (33).

Frequent monitoring of free flaps, particularly in the first 24 to 48 hours after surgery, is critical since multiple studies have shown that earlier diagnosis of microvascular thrombosis is a predictor of salvage versus failure. For example, Bui et al. reported their experience with 1,193 free flaps and found that flaps reexplored within 4 hours of detection of thrombosis were nearly two times more likely to be salvaged than those explored more than 9 hours after detection (34). Although the reported salvage rates for breast microsurgical free flaps vary, most large centers report overall salvage rates of 50% to 80% (35).

The typical recovery period after a microsurgical or pedicled TRAM flap procedure is 6 to 8 weeks. Drains in the abdominal and breast area are typically removed by 2 weeks after surgery. Patients are advised to avoid pressure on the flap for 4 to 6 weeks until the blood supply is reestablished by collateral vessels. During this period they are encouraged to wear a light bra and to wear an abdominal

binder or abdominal support to help decrease abdominal pain and prevent abdominal bulging or hernia. Most patients can return to normal activities of daily living within 6 to 8 weeks and return to work. Adjuvant chemotherapy, if necessary, can also be started at this time.

Breast reconstructions with abdominal flaps are well tolerated with low rates of major complications. In a study of 952 patients who underwent microsurgical breast reconstruction, Mehrara and colleagues reported an overall complication rate of 27.9%, with the majority of these complications (17.3%) comprised of minor complications (4). Less than 1% of patients had a severe or life-threatening complication. Overall, 21% of patients experienced minor complications including fat necrosis (11.2%), infection and wound healing problems (9.2%), abdominal wall laxity or hernia (3%), and transient brachial plexus injury (1.1%). Major complications occurred in 7.7% of patients and consisted of flap loss (0.5%), partial flap loss (2.3%), hematoma (2%), moderate-severe congestive heart failure (0.9%), sepsis (0.3%), and deep venous thrombosis (0.1%). There were no deaths and only one patient required prolonged ICU care. Similar low (i.e., <1%) rates of total flap loss for free muscle sparing and deep inferior epigastric artery perforator flap reconstructions (DIEP) have more recently been reported in large-scale studies from other major medical centers (36,37).

A recent prospective study that performed bilateral duplex ultrasound examination in 118 patients who underwent microsurgical TRAM flap breast reconstruction demonstrated that as many as 3.4% of patients develop so-called silent DVTs (30). Although there were no cases of venous thromboembolism in this report, this complication has been previously reported (4) and deep venous thrombosis prophylaxis with compression, low-molecular weight heparin, and early mobilization is recommended.

Large retrospective studies have also reported low rates of major complications in patients treated with pedicled TRAM flaps. For example, Padubidri et al. reported a 29.6% overall complication rate in 196 pedicled TRAM flaps (38). Similar to the experience with free TRAM flaps, the vast majority of these complications were minor and related to delayed wound healing. In addition, the total flap loss rate of 1% reported in this series was also similar retrospective studies on microsurgical TRAM flap reconstruction. Most studies comparing free and pedicled TRAM flaps have reported lower rates of abdominal wall complications (i.e., hernia or laxity) in patients treated with microsurgical flaps (39). However, the reported rates of these complications vary widely between publications ranging from as low as 0.5% to as high as 15%. This wide range of reports may reflect differences in techniques used abdominal closure rather than perceived benefits of microsurgical harvest. However, recent head-to-head comparisons strongly suggest that muscle-sparing or DIEP flap reconstructions have lower rates of abdominal wall complications. For example, Garvey et al. retrospectively compared 96 DIEP and 94 pedicled TRAMs and reported that abdominal wall hernias occurred more frequently in pedicled TRAMs (16%) as compared with DIEPs (1%) (40).

A number of studies have attempted to determine if patients who undergo microsurgical TRAM flap reconstruction have better abdominal wall function as compared with pedicled TRAMs. In a systematic review of the literature, Atisha and Alderman found that although the objective measures of abdominal wall function were overall better in patients who underwent microsurgical reconstruction as compared with pedicled TRAM flaps, these differences did not reach statistical significance (39). In contrast, studies comparing microsurgical TRAM flaps with DIEP flaps using these measures reported significantly higher flexion ability in patients treated with DIEP flaps. Not surprisingly, patients who had bilateral pedicled or free TRAM flap reconstruction reported a significantly decreased ability to perform sit-ups and decreased subjective ability to perform activities of daily living. Patients who had unilateral reconstructions had similar subjective measures of abdominal function regardless of the type of procedure that was performed. However, the authors note that most studies analyzed in this systematic review had significant limitations in study design, therefore additional prospective studies are required.

In the study by Mehrara et al., obesity (BMI >30 kg/m^2) was a significant independent predictor of complications increasing the risk of overall, major, and minor complications (4). Obese patients were three times more likely to experience partial flap loss or have donor site morbidity. Smoking was associated with increased rates of donor site complications but was not an independent predictor, perhaps due to the very low number of smokers in this series. These findings were supported by a retrospective study of 936 patients treated with microvascular TRAM flaps at the MD Anderson Cancer Center demonstrating a 1.5-fold to 2-fold increase in the risk of donor site and wound healing complications in patients with a BMI >30 as compared with those that had a BMI <30 (41). The risk of complications in obese patients is likely to be even higher in patients who undergo pedicled TRAM flaps. This concept is supported by a retrospective study by Moran and Serletti of 78 obese patients reconstructed with microsurgical TRAM flaps as compared with 36 patients who underwent reconstruction with pedicled TRAM flaps demonstrating a nearly twofold increase in the risk of wound healing complications in obese patients (42).

Interestingly, neoadjuvant chemotherapy also appears to be a significant independent predictor of complications (4). Patients treated with chemotherapy within 6 weeks of surgery were two to three times more likely to experience minor complications comprised primarily of wound healing complications and fat necrosis. Deutsch et al. reported similar results in a retrospective study of 31 patients treated either with pedicled (n = 9) or free (n = 22) TRAM flaps (43). These authors noted a complication rate of nearly 55% with most patients experiencing minor complications that resolved with conservative management.

Not surprisingly, several studies have shown that active smokers have a higher risk of both flap- and wound-related complications following pedicled or free TRAM flap reconstruction. For example, in a retrospective study of 200 patients who underwent pedicled TRAM flap reconstruction over a 10-year period, Ducic and colleagues found that both active and former smokers were at significantly increased risk (twofold increase) of complications including infection and delayed healing in the abdominal and breast sites as compared to never-smokers (44).

Prior abdominal surgery is also associated with increased rates (one- to twofold) of partial flap loss, donor site complications, abdominal wall laxity/hernia, and fat necrosis (4). The most problematic incisions are upper abdominal/subcostal incisions, which result in decreased blood flow to the upper abdominal skin flaps.

Surveillance for breast cancer recurrence in patients treated with TRAM flaps is usually performed with physical examination with confirmation using radiologic studies as necessary. In a retrospective study of 419 TRAM flap breast reconstruction performed in 395 patients with a mean follow-up of 4.9 years, Howard et al. reported a local recurrence rate of 3.8% with a mean time to diagnosis of 1.6 years (45). This rate was in line with long-term local recurrence

rates after mastectomy without reconstruction reported in the literature. In most cases, local recurrences were treated with wide local excision and adjuvant therapy. The TRAM flap required removal in only 3 of 16 patients.

OTHER DONOR SITES

A variety of other donor sites have been reported for microsurgical autologous breast reconstruction. These include the superior gluteal, inferior gluteal, lateral thigh, and gracilis flaps. These flaps can be performed either as myocutaneous flaps (e.g., skin and fat harvested together with a portion of the muscle in which the flap pedicle vessels course) or as perforator flaps in which no muscle is harvested. These options are indicated in women who are not TRAM flap candidates (e.g., inadequate abdominal tissues or abdominal scars) but desire autologous reconstruction, have failed implant reconstruction, or are not candidates for implant reconstruction. Free flaps in general, including these secondary donor sites, are relatively contraindicated in patients with known coagulopathies, patients with severe or potentially life threatening comorbidities, and in heavy smokers.

The gluteal flaps can be based either on the superior or inferior gluteal artery and vein and, in the appropriately selected patient, can be used to transfer large volumes of tissues. Gluteal flaps, similar to the abdominal flaps, can be transferred as a myocutaneous flap (i.e., skin, fat, and portion of the gluteus muscle) or as a perforator flap in which the blood vessels are dissected and the muscle is preserved. Perforator flaps based on the superior gluteal vessels are referred to as superior gluteal artery perforator flaps (SGAPs) while flaps based on the inferior gluteal vessels are termed inferior gluteal artery perforator flaps (IGAPS).

The primary advantage of the gluteal flaps is their utility even in relatively thin women since adequate tissues are available in most patients even when abdominal tissues are insufficient. The main disadvantage of these procedures is the fact that the microvascular anatomy and dissection is more difficult than the TRAM flap. This is particularly true of the superior gluteal flap and is likely the source of the higher reported rates of microvascular complications and flap loss as compared with the TRAM flap. For example, Baumiester et al. retrospectively reviewed their experience with 75 superior gluteal artery perforator flap (SGAP) reconstruction and reported a free flap failure rate of 7% (46). Although this success rate is excellent, it is considerably lower than the rates of success for TRAM or DIEP flaps (>99%) reported in large series from tertiary medical centers. In addition, the gluteal flap donor site can result in contour deformities that may necessitate additional procedures on the contralateral gluteal region for symmetry. Further, sensory changes after may also occur after flap harvest resulting in dysesthesia or discomfort.

Lateral thigh flaps are occasionally used for breast reconstruction and harvest skin and soft tissues in the so-called saddle-bag areas. The blood supply of these flaps is based on the lateral femoral circumflex vessels, which are reliable and relatively easy to dissect. In the appropriately selected patient, a moderate volume of tissues can be transferred. Unfortunately, the donor scars from these flaps are difficult to hide and can be a source of patient dissatisfaction.

Gracilis musculocutaneous flaps have gained some favor for breast reconstruction over the last decade. Although a variety of skin patterns have been described, the transverse upper gracilis (TUG) skin paddle design is most commonly performed. The TUG flap is simple to harvest and can reliably transfer a moderate amount of tissues as a free flap for breast reconstruction. Buntic and colleagues retrospectively evaluated their results with 32 TUG flaps and reported a 100% flap survival rate with no fat necrosis or functional loss (47). The primary disadvantage of this flap is donor site wound healing complications. The incision in this flap design is typically placed just below the inguinal fold and has a tendency to break down as a result of tension with leg abduction. For example, Bunitic et al. reported a 25% wound breakdown rate resulting in delayed healing (47). However, in general, patients are satisfied with these reconstructions as evidenced by a retrospective study by Pulzl and colleagues who evaluated the cosmetic results of 22 patients who underwent TUG flap reconstructions (48). These authors found that 70% of patients had good to excellent scars and all patients would choose the same operation again if given a choice.

MANAGEMENT OF THE CONTRALATERAL BREAST

A major goal of breast reconstruction is to have reasonable symmetry with the remaining breast. In some patients with well-defined breast shape or minimal ptosis it is possible to achieve this goal without altering the contralateral normal breasts. However, in most patients a contralateral procedure such as a reduction, lift, or augmentation can improve symmetry or improve the breast shape. It is important to note that it is rarely possible to achieve exact symmetry after contralateral procedures to match a breast reconstructed with implants. The goal in most instances is to obtain *reasonable* symmetry in clothes, bra, or bathing suit (Fig. 36-5). This goal is attained in most patients and has been shown to be associated with high rates of satisfaction. Contralateral symmetry is more likely to be achieved in patients who have undergone reconstruction with autologous tissues due to a variety of factors including subcutaneous position of the reconstructed tissues, more natural texture and shape, potential for autologous tissues to gain or lose weight with the patient as she ages, and lack of capsular contracture.

Reduction mammoplasty is commonly performed for symptomatic macromastia and is associated with high rates of patient satisfaction and improved quality of life (49). Similarly, reduction mammoplasty is helpful as a symmetry procedure in patients who have undergone breast cancer treatment or mastectomy with reconstruction. These procedures are particularly helpful in implant reconstruction due to limitations in breast implant sizes and shapes and also due to the fact that implants are placed in the submuscular position thereby positioning them higher on the chest wall. Breast reductions are also useful in patients treated with autologous reconstructions, particularly in cases in which the patient has symptomatic macromastia at baseline (i.e., neck or upper back pain, shoulder grooving, inframammary fold irritation).

Many different techniques have been described for breast reduction; however, in the United States the inferior pedicle technique is most commonly performed. In this procedure, the nipple–areola complex is isolated on an inferiorly based breast glandular flap to enable repositioning of the nipple in a more aesthetic manner (i.e., at or just above the level of the inframammary fold and centered on the breast mound). A variety of other breast pedicles (i.e., superior, bipedicled, or central mound) have been described for repositioning of the nipple and have been reported to have excellent results.

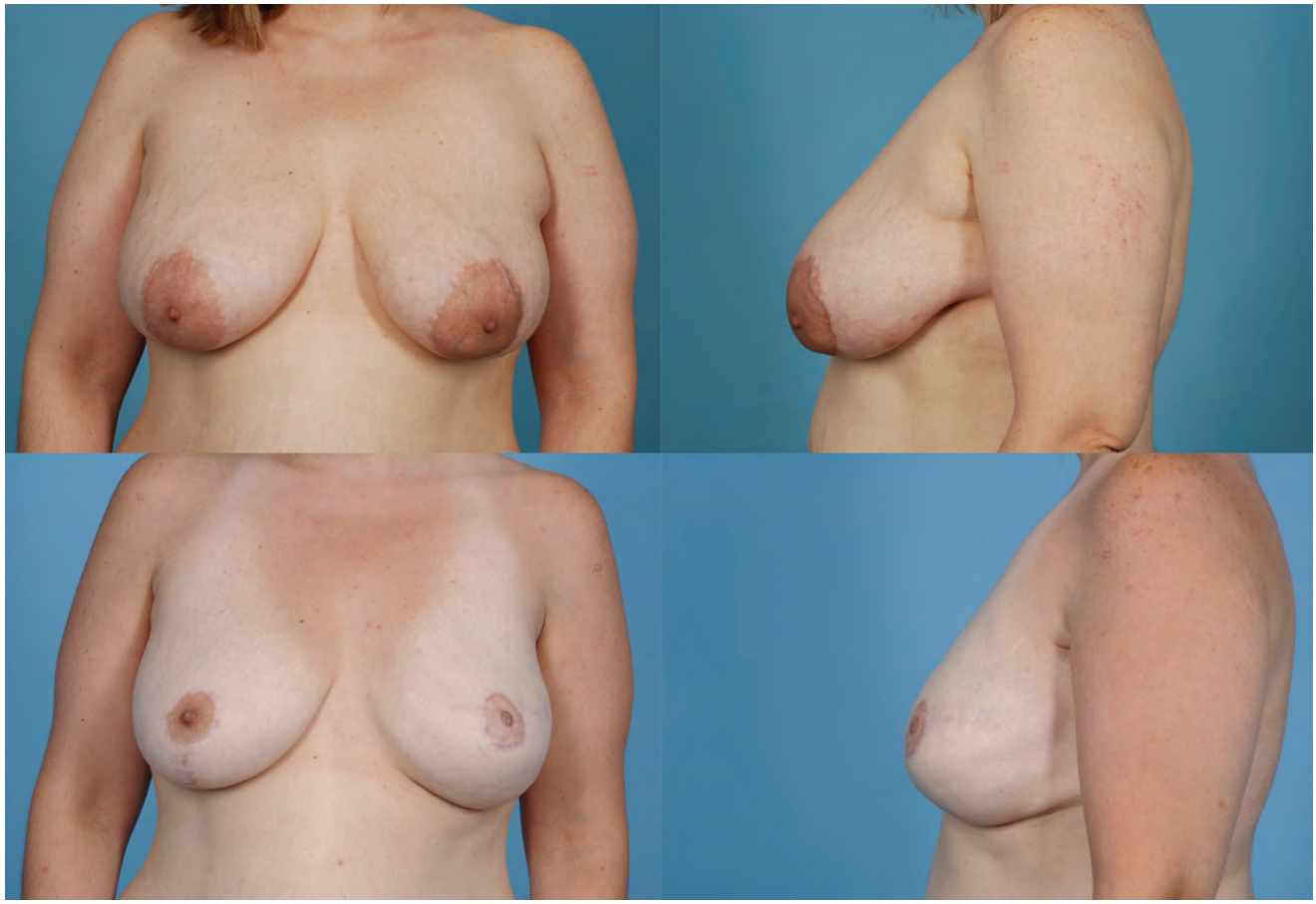


FIGURE 36-5 Preop (*top*) and 2-year postop (*bottom*) photographs of a patient treated with left mastectomy and silicone implant reconstruction and right breast reduction.

The Wise pattern breast reduction pattern is the most common skin pattern design used to reduce and lift the breast and was originally based on patterns used for making bras. In this technique, a variable amount of skin is removed from the horizontal and vertical portions of the breast in order to lift the breast and reposition the nipple centrally on the breast mound. The resulting anchor-shaped incision is the end result. Although some authors have criticized the aesthetic outcomes (long scars, boxy-wide breasts) and durability (late ptosis or bottoming out) of this pattern for breast reduction or lift, it remains the workhorse for most plastic surgeons in the United States. This is based on the fact that if properly performed, the Wise pattern can have excellent cosmetic outcomes and the incisions are mostly hidden in the inframammary fold. However, a number of other patterns have been reported to address some of these concerns. For example, the vertical pattern utilizes only the vertical limb of the incision in an effort to avoid the long horizontal inframammary incision and is useful in some patients (e.g., minimal ptosis or low-volume reductions).

Mastopexy, or breast lift, is performed to remove excess skin and reposition the breast more centrally on the chest. Similar to breast reductions, Wise patterns are used commonly due to their ease and proven reliability. However, other skin patterns such as circumareolar or vertical can also be used depending on the amount of excess skin, breast size and shape, and skin tone. Skin-only mastopexies refer to breast lifts that rely primarily on tightening the breast skin to reshape the breast. However, these procedures often fail to have long-lasting results with stretching of the skin and recurrent ptosis. As a result, a variety of breast parenchymal procedures have been described that aim to lift the breast by reshaping the breast and simply redraping the skin. These techniques are applicable also to some patients for partial breast reconstruction (see below).

Augmentation mammoplasty is also commonly performed as a symmetry procedure after mastectomy reconstruction. These procedures are most useful in small-breasted women to match a contralateral implant reconstruction and can be performed either with or without a simultaneous mastopexy. The mastopexy in these cases is performed to center the nipple–areola complex over the implant or to match the position of the contralateral breast (or both). Augmentation of the nonreconstructed breast can also be performed to match a larger autologous tissue reconstruction. In some cases, augmentation is performed to augment an autogenous tissue reconstruction. This scenario is encountered in cases where the amount of autogenous tissues available (e.g., in the TRAM flap) is inadequate to match the volume or projection of the native breast or in patients who undergo bilateral reconstruction and desire to have increased volume or projection.

Implants used for augmentation are most commonly placed under the pectoralis muscle; however, the implant is not completely covered by the pectoralis. Instead, similar to cosmetic augmentation procedures, implants used for augmentation of the native breast in cancer survivors are covered by only the muscle superiorly. The inferior portion of the pectoralis flap is dis-inserted such that the lower portion of the implant is in a submammary position. This enables

centering of the implant on the breast and avoids upward malposition. Subpectoral implant placement is thought to decrease the rate of capsular contracture, diminish visible rippling of the implant, and facilitate mammographic surveillance of the breast.

The most common surgical complication of breast reduction or mastopexy is minor wound healing complications. These occur most commonly at the "T-point" where the vertical and horizontal incisions come together. Fortunately, most of these complications are minor and heal spontaneously with conservative management. Hypertrophic scars or keloids can also be troublesome particularly in African American or Asian patients. These complications can, on occasion, be treated with steroid injections, laser, or reexcision. Reexcision combined with low-dose radiation therapy delivered directly to the scar immediately after scar excision is very successful with low rates of recurrence but require coordination with radiation oncologist (50).

It is estimated that 3% to 5% of women who undergo mastopexy or reduction experience loss of nipple sensation (51). On rare occasions (<1%), women complain of long-term pain after mastopexy, reduction, or augmentation. The cause of these pain syndromes is unknown but likely reflects nerve damage or scarring. Late infections (more than 3 months after surgery) are also a rare complication but can present with erythema, pain, and fevers. These complications usually respond to antibiotic treatment but on occasion require imaging, long-term antibiotic treatment, or drainage.

Another rare complication in these cases is diagnosis of incidental breast cancers or high-grade lesions. A study of breast reduction in nonselected patients (i.e., not restricted to breast cancer survivors) reported a rate of 1% for incidental breast cancers in the resected specimen. Surprisingly, reports in breast cancer survivors treated with contralateral procedures have reported even lower rates most likely reflecting the fact that this patient population is more closely followed with breast imaging (52). The main problem in cases of incidental breast cancer diagnosis is positive margins. Although it is occasionally possible to return to the OR for additional resection and margin clearance, this is often not possible due to rearrangement of breast tissues and inability to localize precisely the area of resection at the time of the second operation. This situation creates a treatment dilemma and in some cases may require conversion to mastectomy.

PARTIAL MASTECTOMY RECONSTRUCTION

Partial mastectomy reconstruction can be performed either at the time of the initial resection or in a delayed fashion after definitive treatment has been completed. Reconstruction at the time of cancer resection is an option in patients with large or ptotic breasts who desire a breast reduction or lift. These procedures often use standard surgical approaches for reduction or mastopexy and can reshape the breast to minimize contour deformities, nipple malposition, or size asymmetry that may occur after partial breast resection without reconstruction (Fig. 36-6). Partial mastectomy in conjunction with breast reduction may also enable the oncologic surgeon to remove large portions of the breast (larger than would be ordinarily removed during a partial mastectomy), thereby increasing the size of the margin and potentially decreasing the risk of positive margins or local recurrence. A key issue in performing these procedures at the same time as oncologic resection is margin clearance. A positive margin may be more difficult to deal with in this setting because the breast tissue has been rearranged to a certain extent and additional resection may require opening the entire breast incision. Innovative approaches to this problem such as additional margins at the time of resection, marking the borders of the resection with clips, and so called immediate-delayed procedures in which the reconstructive procedure is performed shortly after confirmation of definitive negative permanent margins may decrease the potential for these problems (53).

Breast reduction or lifts are well tolerated and associated with a low rate of complications. The primary complications include minor wound healing issues, seroma, hematoma, loss of nipple sensation, and breast asymmetry. Of these complications, asymmetry is particularly problematic due to the fact that these patients are treated with unilateral radiation therapy that may cause unexpected breast tissue shrinkage or skin fibrosis. For this reason, patients are advised that follow-up procedures may be necessary in the future to correct these problems.

Patients with small or nonptotic breasts may also be candidates for immediate partial breast reconstruction in an effort to avoid mastectomy or significant contour deformities that may result from partial mastectomy. In these cases, local tissue flaps from the back, or more rarely, from the abdomen, are transferred to the breast at the time of tumor resection to replace breast tissue or skin and restore the normal contours of the breast. This approach is somewhat controversial since some reconstructive surgeons argue that a potential option for reconstruction is lost in case the patient has a recurrence and requires a mastectomy. Those in favor of these procedures note that breast recurrence in these patients is relatively infrequent particularly if postoperative radiation is performed and that other options or donor sites are frequently available even if there is a recurrence. Unfortunately, well-controlled patient-reported outcome studies comparing satisfaction and quality of life of patients who undergo partial breast reconstruction with those who had mastectomy and reconstruction or those who had partial mastectomy alone have

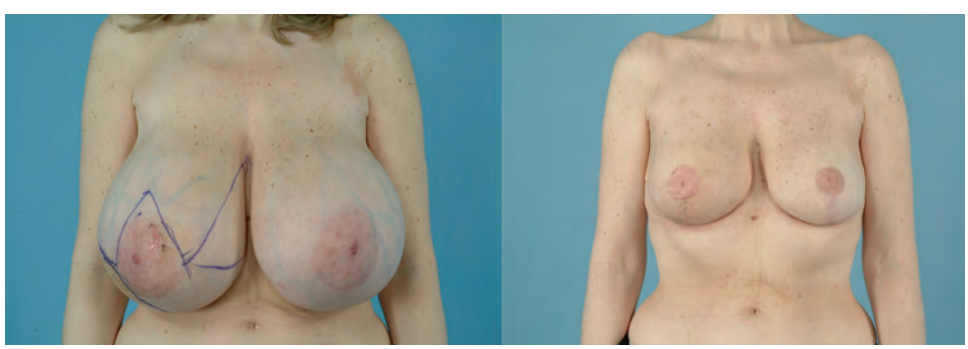


FIGURE 36-6 Preop (*left*) and 1-year postoperative (*right*) photographs of a patient treated with right partial breast excision and simultaneous breast reduction.

not been performed and are needed to determine if these procedures are worthwhile.

Plastic surgeons are also frequently consulted for reconstruction of partial mastectomy defects in patients who had previously undergone breast resection and radiation. These patients usually present with breast asymmetry due to resection or radiation-induced fibrosis, contour deformities, or nipple malposition. Asymmetry in these cases is often due to a combination of breast volume deficit and skin fibrosis causing decreased relative ptosis of the radiated breast. Although reconstruction in this setting is more difficult due to increased scarring and history of radiation, a number of techniques are available ranging from relatively simple to more complicated. Naturally, the most important prerequisite is ensuring that the breast is cancer free with imaging procedures as necessary and consultation with the patients' breast surgeon and oncologist.

Simple techniques for delayed reconstruction of partial mastectomy defects include tissue rearrangement, scar releases, breast augmentation, and fat injection. Breast tissue rearrangement or scar releases are occasionally helpful in patients with minor deformities; however, more often than not these procedures are unsuccessful or have limited utility due to breast changes resulting from radiation. Similarly, breast augmentation with implants is rarely indicated in patients who have a history of partial mastectomy and radiation due to the high incidence of capsular contracture. Fat grafting for breast contour deformities has been recently described by a number of groups and shows some promise (54,55). In these procedures, fat is harvested from another region of the body using standard liposuction techniques, washed, and then simply injected into the region of the contour deformity to replace the missing breast tissue and restore the normal shape of the breast. This process may be repeated over several sessions as necessary and is best reserved for patients who have minor volume deficiency rather than combined volume and skin defects. Fat injection is thought to improve breast contour defects not only by restoring volume but also by transferring mesenchymal stem cells that aid in repair of radiation damaged tissues (56). The latter concept is based on the fact that adipose tissues are a known source of pluripotential mesenchymal stem cells (57) and anecdotal reports demonstrating significant tissue improvement after fat injection into chronically radiation-damaged tissues (56).

Fat injection or lipotransfer is simple to perform and well tolerated with a low incidence of reported complications that include minor donor site contour deformities, fat necrosis or oil cysts in the recipient site, reabsorption of the injected fat, and macrocalcifications on mammography (58). Although dramatic improvements in breast shape and contour have been reported in a few relatively small case series, large prospectively performed studies are needed to assess the efficacy and safety of fat injection in partial breast reconstruction. In addition, recent laboratory reports have suggested that transfer of mesenchymal stem cells may alter the behavior of tumor cells in animal models (59); however, retrospective clinical studies have failed to show these adverse effects in patients (58).

More complicated procedures for symmetry in patients with a history of breast conservation include breast reduction or lift and vascularized tissue transfers. Breast reduction/lift is helpful in patients who have macromastia or breast ptosis and are performed using standard techniques (see above on symmetry procedures). Asymmetric skin or breast parenchymal resection on the ipsilateral and contralateral breasts is performed to improve breast symmetry and shape. It is important to note, however, that due to the inherent changes in the breast tissue and skin envelop resulting from radiation it is rarely possible to obtain absolute symmetry or symmetry that is comparable to purely aesthetic breast reductions or mastopexy. Instead, patients are advised that the goal of the procedure is to have improved symmetry. In addition, although these procedures are usually well tolerated with a low risk of wound healing complications, patients with a history of radiation should be advised that they are at higher risk for these events. Of particular concern is the risk of nipple necrosis since the patient's previous surgery or radiation may have disrupted the blood supply to the nipple–areola complex. In these cases, the nipple–areola complex may be replaced as a free graft.

Vascularized tissue transfers can be performed in a delayed setting for patients with significant contour deformities or volume deficiency. In these cases, the breast defect is recreated by completely resecting the scar and surrounding fibrotic tissues, and the volume is restored by transferring tissues from another region (i.e., the back or abdomen) based on a known vascular supply. The latissimus flap or its variant, the thoracodorsal artery perforator flap (TDAP), are commonly used for these procedures due to the proximity of the back to the breast. In these cases, the back skin and subcutaneous tissues are transferred either together with a portion of the latissimus muscle and its blood supply (latissimus flap) or without muscle based solely on a branch of the thoracodorsal artery/vein (TDAP) (60). These procedures are particularly helpful in patients who have large-volume defects of the breast in combination with breast skin deficiencies since the muscle, fat, and subcutaneous tissues of the flap can be used to restore breast volume while the back skin can be used to replace the missing breast envelope.

CHEST WALL COVERAGE

Chest wall coverage, rather than breast reconstruction, is necessary in some patients with extensive or recurrent tumors. This scenario occurs most commonly in patients with large, fungating tumors, recurrent tumors in patients with a history of radiation, and in patients with inflammatory breast cancers. In addition, wide skin resections are also commonly performed in patients with radiation-induced angioscarcomas. In these cases it is often not possible to primarily close the breast skin and additional reconstructive procedures are necessary.

The simplest option for chest wall coverage is a split thickness skin graft. This option is best reserved for patients with relatively small wounds and good recipient beds (i.e., not contaminated or radiated). Skin grafts can also be performed secondarily in some cases after the initial wound is treated with dressing changes or vacuum assisted closure (VAC). The downsides to skin grafting for chest wall coverage include prolonged healing time (often more than 6 weeks), unstable coverage resulting in skin sloughing or complications particularly when postop radiation is needed, and tightness due to skin graft contracture.

Adjacent tissue transfers wherein local tissues are rearranged to provide coverage are an alternative to skin grafting and can be used in patients with larger defects and in those with defects that are unsuitable for grafting (e.g., history of radiation). These procedures include relatively simple operations where the lower mastectomy skin flap is elevated below the inframammary fold and advanced up to close the defect. Alternatively, local rotation flaps such as an external oblique flap based on perforating blood vessels

arising from the intercostal arteries and veins in the external oblique muscle can be performed to rotate large areas of vascularized skin into the chest wall defect. This procedure is simple to perform, does not require intraop repositioning, and can be used safely to cover large defects of the lower breast even in patients who have significant comorbid conditions (61).

Pedicled flaps are also useful for chest wall coverage and can provide massive amounts of skin with or without muscle to cover complex defects. The pedicled latissimus flap is a reliable means of transferring a large amount of muscle and some skin to provide coverage of complex defects such as composite skin/skeletal resections of the chest wall. Pedicled TRAM flaps can also be performed in patients with suitable abdominal donor sites and can provide large amounts of skin for chest wall coverage. However, closure of the abdominal donor site may result in increasing the size of the breast wound (by pulling the abdominal skin inferiorly). In addition, the blood supply to the pedicled TRAM flap may be inadequate in some patients thereby increasing the risk of partial flap loss and wound healing complications. A safer pedicled option in these cases may be a vertically oriented rectus myocutaneous flap (vertical rectus abdominis myocutaneous or VRAM flap) (62). In this scenario the skin paddle is oriented vertically over the rectus muscle thereby improving the blood supply. In addition, closure of the VRAM donor site does not change the size of the breast/chest wall defect. The omentum flap can be used to provide coverage of chest wall defects; however, concerns about donor site morbidity (adhesions, abdominal hernia) and the need for skin grafting limit its utility.

Free flaps provide the most freedom in transferring tissues for chest wall coverage because the tissues are anastomosed to vessels located anatomically close to the defect and have high rates of success (62). Tissues can be harvested from a variety of donor sites and are selected based on the defect or reconstructive needs and donor site options. Microsurgical thrombosis is the most dreaded complication in these cases but is fortunately rare (<2%) in most cases. Donor site may also be problematic but are fortunately in most cases infrequent. Patients who undergo these extensive procedures are also at risk for medical complications (e.g., DVT/PE, pneumonia, myocardial infarction), particularly if they have premorbid conditions, therefore consultation and coordination with appropriate support services are necessary to maximally optimize the patients preoperatively and monitor and treat postoperatively.

RADIATION AND RECONSTRUCTION

Postmastectomy radiation therapy (PMRT) is a critical component of breast cancer management in patients with locally advanced breast cancers. Multiple randomized trials have shown that PMRT significantly reduces the risk of local recurrence in the chest wall and regional draining lymphatics (63,64). The 2005 Oxford Overview by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) demonstrated that this decrease in local recurrence translates into a statistically significant improvement in overall survival for women with positive axillary lymph nodes (65). As a result of these studies, an increasing number of patients who undergo mastectomy are treated with radiation therapy. This paradigm shift in breast cancer management has created difficulties in reconstruction because it is sometimes difficult to determine which patients will require PMRT, therefore complicating the preoperative consultation and planning.

Not surprisingly, breast reconstruction in women who will require PMRT is among the most hotly debated topics in plastic surgery. Virtually all aspects of reconstruction in this setting are debated. In addition, the timing of reconstruction (i.e., immediate vs. delayed after completion of radiation), the type of reconstruction that is performed (i.e., implants vs. autogenous tissues), the timing of expander-to-implant exchange (i.e., exchange before or after radiation), even the optimal time to perform reconstruction in a patient who has previously been treated with radiation are all debated. However, despite intense debate there is little consensus and the optimal method remains unknown. All of these approaches have advantages and disadvantages that must be individualized and discussed preoperatively if possible.

The majority of plastic surgeons in the United States recommend delayed reconstruction in patients who will need PMRT (66). The precise reasons for this bias are unknown but are likely multifactorial reflecting risk aversion, medicolegal concerns, and a concern about potential delays to postoperative adjuvant therapy in case of complications related to reconstruction. Risk aversion in these cases is supported by studies demonstrating increased rates of complications, decreased satisfaction, and impaired aesthetics in patients who undergo immediate reconstruction and PMRT.

For example, Carlson et al. (67) and Lee et al. (68) reported that patients who had radiation therapy after autologous tissue reconstruction were two to four times more likely to have complications compared to nonirradiated women. These complications included wound healing issues, partial flap losses, twofold increased rate of clinically significant fat necrosis, and flap shrinkage/fibrosis. Perhaps as a result of these complications, these authors found that patients who underwent autologous reconstruction followed by PMRT were significantly more likely to have impaired aesthetics and decreased satisfaction as compared to nonirradiated patients. These findings were supported by a recent study by Crisera and colleagues reporting their experience with 103 women who underwent immediate autologous breast reconstruction and PMRT (24). In this study, the authors found that nearly 30% of patients experienced fibrosis of their flap, 13% had severe distortion, 7% required an additional flap for reconstruction, and 4% experienced partial flap loss after radiation.

Radiation-induced complications are not unique to patients with autologous reconstructions. Studies of patients who have received PMRT to implant-based reconstructions have also demonstrated that radiation to be an independent risk factor for complications (odds ratio of 3.8 to 4.8), resulting in a two- to threefold increase in the risk of significant capsular contracture (Baker grade III or IV), increased rates of reconstructive failure (three- to fivefold increase), decreased satisfaction, and decreased cosmetic outcomes (69,70).

Some plastic surgeons recommend immediate implant reconstruction in women who will require PMRT but are otherwise good candidates for implant reconstruction. These surgeons argue that the benefits of immediate reconstruction are significant and outweigh the risks in most cases when compared to delayed reconstruction (70). These benefits include preservation of the breast envelope with use of skin-sparing mastectomies, placement of the mastectomy scar at a desired location, decreased number of operations, and psychological benefits of immediate reconstruction. In addition, recent retrospective studies have shown that although the risk of complications in patients treated with PMRT is higher than nonirradiated cohorts, this risk is still relatively low and that most patients successfully complete reconstruction and are satisfied with the results. In a retrospective study of 315 patients treated at Memorial

Sloan-Kettering Cancer Center, Cordeiro et al. found that 90% of patients treated with PMRT successfully completed reconstruction (vs. 99% who did not have PMRT), that the majority of patients (approximately 60%) had acceptable reconstructions with Baker grade I or II capsular contracture, and over 70% were satisfied with their outcome and would recommend the procedure to a friend or family member (7). It is important to note that even if patients were to develop complications following irradiation of an implant necessitating removal, the use of implants at the initial procedure preserves other options (e.g., autologous tissues) for reconstruction at a later date.

Preservation of the breast envelope in reconstructed patients who will require PMRT is also an important consideration when choosing immediate versus delayed reconstruction. Reconstruction after skin-sparing mastectomy is significantly easier and more aesthetic, since the reconstruction is aimed at replacing the breast volume rather than missing breast skin. Consequently, the final breast scars are typically small and more easily concealed with nipple–areola reconstruction. In contrast, in delayed reconstruction after PMRT, a significant portion of the remaining breast skin is damaged and needs to be replaced. The skin below the breast incision is often severely fibrosed and necessitates either partial or complete replacement with healthy skin from a donor site (e.g., TRAM flap or latissimus flap) in order to adequately reconstruct the breast contours. This need results in a large skin paddle on the breast that not only limits the amount of tissues available for reconstruction but also lengthens the breast scars, making them harder to conceal. Based on these differences, it is therefore more valid to compare the aesthetic outcomes of irradiated women who have undergone immediate versus delayed reconstruction, rather than to compare the aesthetic outcomes of reconstructed patients with PMRT to those who have not received PMRT. Prospective studies are needed for more accurate assessment of complication rates and aesthetic outcomes in these patient populations.

The timing of exchange of the expander to the permanent implant relative to radiation has also been a source of debate. Traditionally, most plastic surgeons prefer to wait until the completion of radiation to perform the exchange procedure. This preference is likely due to concerns regarding potential delays to radiation therapy, infections in a fresh surgical field in response to radiation, or desire to perform capsulectomy or capsule releases after radiation. More recently, however, several groups have shown that exchanging the expander to the implant prior to the start of radiation therapy is associated with decreased rates of complications and improved aesthetics. For example, Cordeiro and McCarthy used a retrospective approach with 315 patients comparing implant reconstruction success rates in patients who had undergone immediate expander reconstruction after mastectomy and exchange to final implant prior to radiation with nonirradiated patients and found a high rate of overall success (90%) (7). This rate was significantly less than nonirradiated patients (99% success rate) but was markedly higher than previous reports on implant exchanges following irradiation. In a follow-up study from Memorial Sloan-Kettering, Ho et al. evaluated long-term disease outcomes in a cohort of 151 patients with stage II to III breast cancer who underwent expander/implant reconstruction using the following treatment algorithm: (a) a modified radical mastectomy with immediate placement of expanders, (b) initiation of chemotherapy with expansion performed throughout treatment, (c) exchange of the expander for implant after the completion of chemotherapy, and (d) initiation of PMRT (71). Overall, the 7-year combined permanent implant removal or replacement rate was 29%. The most common causes for permanent implant failure were severe capsular contracture and infection. These findings have more recently been confirmed by a report by Nava et al., who retrospectively demonstrated that their overall rate of success was 94% when implant exchange was performed prior to radiation versus 60% when it was done following radiation (72).

In some cases it is not possible to exchange the expander to a final implant prior to radiation. For example, in patients treated with neoadjuvant chemotherapy, there is often inadequate time to complete expansion, perform exchange, and achieve adequate tissue healing prior to initiating radiation. In these cases, it may be helpful to delay the exchange procedure until the tissues have recovered from radiation injury. This concept is supported by a recent study by Peled and colleagues comparing complication rates in patients treated with PMRT in whom the exchange procedure was performed either early (within 3 months) or late (after 6 months) after radiation. In this study, the failure rate in patients who underwent exchange more than 6 months after completing radiation was nearly threefold lower (7.7% vs. 22.4%) than in patients who underwent surgery less than 6 months following radiation (73). These findings make intuitive sense, since skin changes due to radiation injury (erythema, desquamation, hypersensitivity) often take a significant time to resolve after treatment.

Kronowitz at the MD Anderson Cancer Center has proposed a concept the author terms delayed-immediate reconstruction (71). This concept is also based on the idea that immediate reconstruction has significant merits as compared to delayed approaches and aims to identify patients who will need PMRT before committing to autologous tissue reconstruction. With this approach, patients who are judged to be at high risk for needing PMRT undergo placement of a tissue expander at the time of mastectomy in order to maintain the breast envelope. Over the next several weeks the histology of the breast specimen and lymph nodes are reviewed by a multidisciplinary panel to determine if PMRT is necessary, in which case the expander is left in place until completion of radiation and then definitive reconstruction is performed using autologous tissues. In contrast, if radiation is not needed, then the patient returns to the operating room, the expander is removed, and autologous tissue reconstruction is performed. Long-term studies with validated patient reported outcomes will be helpful in these cases to analyze the efficacy of this approach.

NAR RECONSTRUCTION

Nipple reconstruction is an important adjunct to breast reconstruction helping to restore the normal appearance of the breast and also often helping to cover the mastectomy scar and improve symmetry and increasing patient satisfaction (74). Nipple reconstruction can be safely performed in most patients who have undergone breast reconstruction. Relative contraindications to nipple reconstruction include a history of radiation, very thin skin flaps, or previous failed nipple reconstruction. These patients have higher rates of complications with nipple reconstruction but may be candidates if they understand the risks.

A large number of techniques have been reported for nipple–areola reconstruction. By far, the vast majority of these techniques use local breast skin flaps to reconstruct the nipple (e.g., C-V flap, Skate flap, double opposing tab flaps, etc.). Nipple sharing is a less commonly used approach in which a portion of the normal contralateral nipple is harvested and used as a full-thickness graft to reconstruct the nipple in the reconstructed breast. A theoretical concern in these

procedures, however, is that the transplanted nipple graft may have breast ducts and as such may serve as a nidus of breast cancer recurrence.

By far the most common complication of nipple reconstruction is loss of projection (75). This complication occurs despite the fact that in most instances the size of the reconstructed nipple is overestimated. Minor wound breakdown also occurs on occasion; however, in the vast majority of cases these complications respond nicely to conservative management with dressing changes and antibiotics.

Areola reconstruction is performed using tattoo or with a full-thickness skin graft. Tattoo is simple to perform, requires minimal downtime, and is rarely associated with infection or other complications. However, tattoos can sometimes appear two-dimensional and usually fade over time. In addition, it is often difficult to precisely match the color of a contralateral areola particularly when the color chosen is very light. In contrast, although skin grafts are more invasive and result in a donor site scar, these areola reconstructions often appear more natural because they have both color and texture. The color match of the graft can be improved by harvesting skin from a naturally darker area of the body such as the inner groin crease. This donor site also hides the scar in a relatively inconspicuous area. Complete skin graft loss is rare; however, partial losses do occur and can result in distortion of the areola. In addition, donor site complications may also occur but fortunately are rare and usually heal with conservative management.

MANAGEMENT SUMMARY

- Most patients are candidates for reconstruction.
- Immediate reconstruction after mastectomy has significant advantages.
- Reconstruction is associated with low rates of major complications.
- Obesity, smoking, and hypertension increase the risk complications.
- Implant reconstructions are associated with rapid postoperative recovery but require maintenance and may be complicated by capsular contracture.
- Autogenous tissue reconstructions enable more aesthetic reconstructions but are more invasive and have longer recovery periods.
- Partial breast reconstruction can be performed using local tissue rearrangement or transfer of distant flaps.
- Chest wall irradiation has significant detrimental effects on reconstruction.
- Exchange of expander to implant prior to radiation may decrease infection or implant loss rates.
- Nipple–areola reconstruction is an important adjunct and increases patient satisfaction.

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CHAPTER 37

Sentinel Lymph Node Biopsy

Alice P. Chung and Armando E. Giuliano

CHAPTER CONTENTS

INTRODUCTION

Axillary lymph node dissection (ALND) has been an integral component of the staging, prognosis, and treatment of invasive breast cancer and is discussed in Chapter 38. Surgical management of the axilla, however, has undergone a paradigm change since the concept of lymphatic mapping of the breast was introduced at the John Wayne Cancer Institute (JWCI) in 1991, and sentinel lymph node biopsy (SNB) has replaced ALND for axillary staging in clinically node-negative early breast cancer. Although tumor characteristics and molecular markers are increasingly contributing to the understanding of the biology of breast cancer, the status of the axilla remains the most important prognostic indicator for overall survival. The current algorithm for axillary management of invasive breast cancer incorporates outcomes information from SNB, ALND, and axillary irradiation as well as data from the effects of systemic therapies on axillary metastases. This chapter addresses the current understanding of the role of SNB in surgical management of the axilla for breast cancer.

SENTINEL NODE CONCEPT IN CANCER

In the early 1970s, Kett et al. (1) reported that the first regional lymph node, the "Sorgius node," could be identified in breast cancer using direct mammalymphography. This was a cumbersome technique that required a formal ALND to isolate the suspected lymph nodes, radiographic evaluation of the resected nodes to identify the suspicious ones, and determination of concordance through histopathologic confirmation.

Ramon Cabanas (2) coined the term *sentinel node* as a specific lymph node group in penile carcinoma, located in a constant anatomic location in the pelvis. The sentinel node (SN) concept evolved from this observation of specific anatomic nodal drainage and postulates that a primary tumor is drained by an afferent lymphatic channel that courses to the first, "sentinel," lymph node in that specific regional lymphatic basin (3). If the tumor has metastasized, it will do so to this node. The tumor status of the SN reflects the tumor status of the nodal basin. Morton et al. (4) tested the hypothesis that the SN in a given regional basin can be identified

by an indicator dye in a feline model and then validated it in the clinical setting in a group of patients with melanoma.

Identification of a Sentinel Node in Breast Cancer

The feasibility of identifying an SN intraoperatively in breast cancer was first investigated at the JWCI by Giuliano et al. (5). In October 1991, the authors' group began to investigate the feasibility of lymphatic mapping and sentinel lymphadenectomy with isosulfan blue vital dye in breast cancer as a more accurate and less morbid approach to stage breast cancer (Fig. 37-1). This prospective study demonstrated that SNB of the axilla is technically feasible, safe, and without added complications. With a defined technique and experience, a 100% accuracy to predict the status of the axilla was subsequently achieved (5,6). In addition to vital dye-directed lymphatic mapping, three other technical approaches for SN identification in breast cancer with accuracy rates comparable to the blue dye have evolved: radio-guided surgery, radio-guided surgery with preoperative lymphoscintigraphy, and the combination of vital dye and isotope techniques. The most commonly used agents are isosulfan blue dye and filtered technetium sulfur colloid. An increased SN identification rate with the use of the combination of blue dye and radioisotope is well documented. However, there has been only one prospective randomized trial comparing blue dye alone to the combined use of isotope and blue dye, and in this study Morrow et al. showed no difference in SN identification between the two groups (7). The authors found the number of cases performed by an individual surgeon to be the most significant predictor of successful SN identification, demonstrating that surgeon experience impacts SN identification and false-negative rates. Experienced surgeons are extremely successful in accurately identifying the SN regardless of technique. SN identification in breast cancer is technically feasible, safe, and an accurate predictor of the status of the axilla using several different technical approaches.

Proof of Principle

The SN hypothesis for breast cancer has been tested in the clinical setting by several groups of investigators who performed complete histopathologic evaluation of the SN and non-SNs using the same pathologic processing with step sectioning, hematoxylin and eosin (H&E) and immunohistochemistry (IHC) for all H&E negative axillary lymph nodes (8). Turner and colleagues identified 33/103 (32%) patients with a tumor-bearing SN by H&E. IHC evaluation of 157 negative SNs upstaged 10 patients (14.3%). In 60 patients whose SNs were negative by H&E and IHC, 1,087 non-SNs were examined at two levels by IHC and only one additional tumor-positive node was identified. In 57.3% of patients the SN was negative. In the 44 patients with a tumor-positive SN, 56.8% had involvement of the SN alone. Additional studies, including an NCI-sponsored multicenter trial that examined all non-SNs with the same rigorous histopathologic analysis, reported similar findings for cases with negative SN that had further evaluation of non-SN with IHC (9). The SN concept has been validated by these studies enabling widespread clinical application of this technique.

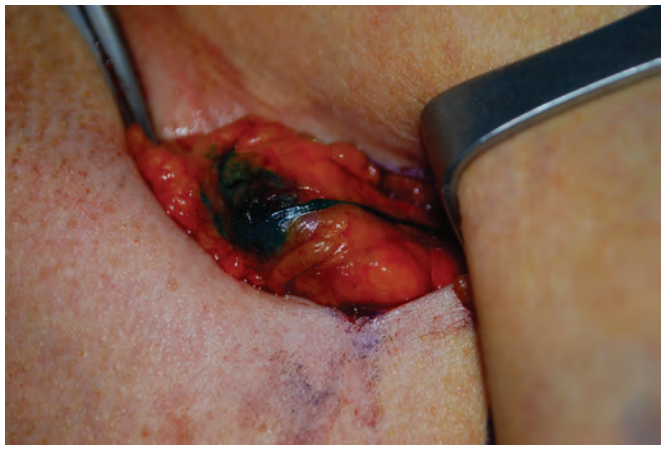

FIGURE 37-1 Axillary sentinel node and lymphatic tract stained with blue dye. (From Chung A, Giuliano AE. Lymphatic mapping and sentinel lymphadenectomy. In Cameron JL, Cameron AM. *Current surgical therapy*, 10th ed. Mosby, 2011.)

LYMPHATIC ANATOMY OF THE BREAST AND IMPLICATIONS FOR SENTINEL NODE IDENTIFICATION

Anatomy

The axilla is bordered by the latissimus dorsi posteriorly, the axillary vein superiorly, the chest wall medially, the pectoralis muscles anteriorly and extends laterally to where the vein crosses between the lateral edge of the pectoralis major and latissimus dorsi muscles. Level I nodes are located inferior and lateral to the pectoralis minor muscle, level II nodes posterior to the pectoralis minor and below the axillary vein, and level III nodes are medial to the pectoralis minor and below the clavicle. Lymphatic drainage generally follows an orderly sequential pattern from level I to level II nodes and rarely to level III. SNB is a staging procedure that removes one or more lymph nodes from the axillary basin. The SN is found in level I in 83% of cases, level II in 15.6%, in level III in 0.5%, internal mammary in 0.5%, supraclavicular in 0.1%, and elsewhere in 0.3% (10).

Patterns of Regional Nodal Drainage

The axilla is the primary site of drainage in about 95% of breast cancer cases, with isolated internal mammary drainage seen in less than 5% (10). Primary drainage to other nodal pathways, such as supraclavicular, cervical, intercostal, and contralateral lymph nodes, is extremely uncommon. Lymphoscintigrams can accurately identify nodal uptake of radioisotope preoperatively (Fig. 37-2).

Although the axilla is the primary drainage site, with other regions receiving limited lymphatic flow, the prognostic value of the internal mammary nodal status is high, particularly when both axillary and internal mammary nodes are either negative with better survival than with either basin having metastases or with the worst prognosis when both basins are involved (11). In those rare cases, with small tumors and sole drainage to nodal stations other than the axilla, identification of tumor positive regional nodes may be important for adjuvant therapy recommendations or to determine external beam irradiation fields. There have been several groups who have investigated the impact of internal mammary nodal drainage identified by preoperative lymphoscintigraphy on outcome. Kong et al. (12) reviewed their database of 1,172 patients with stage I to III invasive breast cancer who had

FIGURE 37-2 Preoperative lymphoscintigraphy demonstrates a left anterior oblique view of a sentinel node.

preoperative lymphoscintigrams following peritumoral injection of radiocolloid and identified 334 patients with drainage of radiocolloid to the internal mammary nodes. These patients were significantly younger, less likely to have upper outer quadrant tumors, and more likely to have smaller and medial tumors than patients without drainage to the internal mammary nodes. Rates of internal mammary irradiation did not differ between the two groups. With median follow-up time of 7.4 years, internal mammary drainage was significantly associated with a worse distant disease-free survival (DFS)but not locoregional recurrence or overall survival. The data from the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-32 trial demonstrated that the majority of positive SNs came from levels I and II of the ALND, and only 1.2% of the positive SN specimens came from non-axillary locations (13). In general, nodal status is becoming less relevant in determining adjuvant therapy.

Early anatomists studied the lymphatics of the breast by injecting mercury into the lactiferous ducts of female cadavers (14). In 1874, Sappey concluded that all of the lymphatics arising from the breast drained to the axilla via the subareolar plexus. As techniques for visualizing the lymphatics have evolved, our understanding of the lymphatic drainage in the breast has changed (14). Analysis of the superficial and deep lymphatic anatomy of the breast and upper torso from human cadaver studies supports the SN concept. Suami and colleagues (15) studied 24 breasts in 14 human cadavers and found that superficial lymphatic collectors drain into the same first-echelon node close to the lateral edge of the pectoralis minor muscle (Fig. 37-3). In most cases, the drainage was to only one SN. In several cases, however, there was at least one other first-echelon node from a collecting lymphatic that passed directly through the breast. The investigators also found that lymphatics of the nipple–areola complex are different from other areas of the breast and drain only into the first-echelon pectoral node shown in Figure 38-3 in green, but not to the depicted orange node that receives lymphatic drainage that passes through the breast. This study did not identify any direct anastomosis between the superficial collecting system and the collectors associated with internal mammary vessels, an observation consistent with the findings of studies that have used lymphoscintigraphy to study patterns of lymphatic drainage by site of injection (16).

The findings in Suami's anatomic study may explain the clinical experience with lymphatic mapping and the persistence of a false-negative (FN) rate of 8% to 11% (13,16). Dye injected deep into the parenchyma along the purple-colored track (depicted in Fig. 37-3) reaches both the depicted green and orange lymph nodes in the pectoral group, whereas dye injected into the subareolar or intradermal location reached only the depicted green node. SNB using the intraparenchymal injection technique would track to both nodes and suggests that the intraparenchymal route of injection may be more likely to track to both first-echelon nodes and result in a more accurate staging of the axilla. The proof of principle study discussed above was performed with the intraparenchymal injection method and had one FN node (8).

Pan et al. (17) used combined preservation techniques with computed tomographic lymphangiography to obtain a three-dimensional analysis of the lymphatics in the bilateral breasts and anterior upper torso of a human cadaver. They found a predominance of superficial lymphatics with radial drainage to the axilla, and asymmetry between the right and left breasts with high variation in number and size of lymphatic vessels between sides.

Blumgart and colleagues (18) evaluated lymphoscintigraphic data from 2,304 breast cancer patients (2,284 female, 20 male). All patients received four peritumoral injections of technitium 99m sulfur colloid followed by lymphoscintigraphy with documentation of drainage patterns. Unlike Pan, they found that lymphatic drainage and tumor distribution were symmetric between both breasts. There were no differences in drainage patterns between males and females. They also found that among 2,304 patients, axillary (2,263, 98.2%), interpectoral (n = 15, 0.7%), internal mammary (n = 813, 35.5%), infraclavicular (n = 25, 1.1%) and supraclavicular (n = 70, 3.0%) nodal fields directly drain the breasts with variable frequencies, and that patients usually drained to one nodal field (64%) but it was possible for drainage to occur to multiple nodal fields (36%).

Cumulative Experience of Sentinel Node Identification for Staging

Investigators from academic centers and the surgical community worldwide have introduced SNB into clinical practice as a staging procedure. Several multicenter lymphatic mapping trials have confirmed the feasibility of SNB as a staging procedure and reported data on identification and FN rate (Table 37-1) (13,19,20). The identification rate ranges from 86% to 97% with accuracy from 96% to 98% and a FN rate from 4% to 16.7%. Most of the multicenter trials required some formal instruction or validation prior to participation of each institution, however early on most surgeons were self-taught. SN identification rate and accuracy are highly dependent on surgeon experience, more so than technique.

The NSABP B-32 trial randomized patients with clinically node-negative invasive breast cancer to either SNB followed by a level I or II ALND (group 1), or observation of the axilla if the SN was tumor free (group 2) (13). Five thousand six hundred eleven women were randomly assigned to the treatment groups, 3,986 had pathologically negative SN with follow-up information. The study reported an SN identification rate of 97.2%, accuracy rate of 97.1%, and a FN rate of 9.8%. With a mean follow-up of 95.6 months, there was no significant difference between the two groups with respect to overall survival, disease-free survival, and regional control (21).

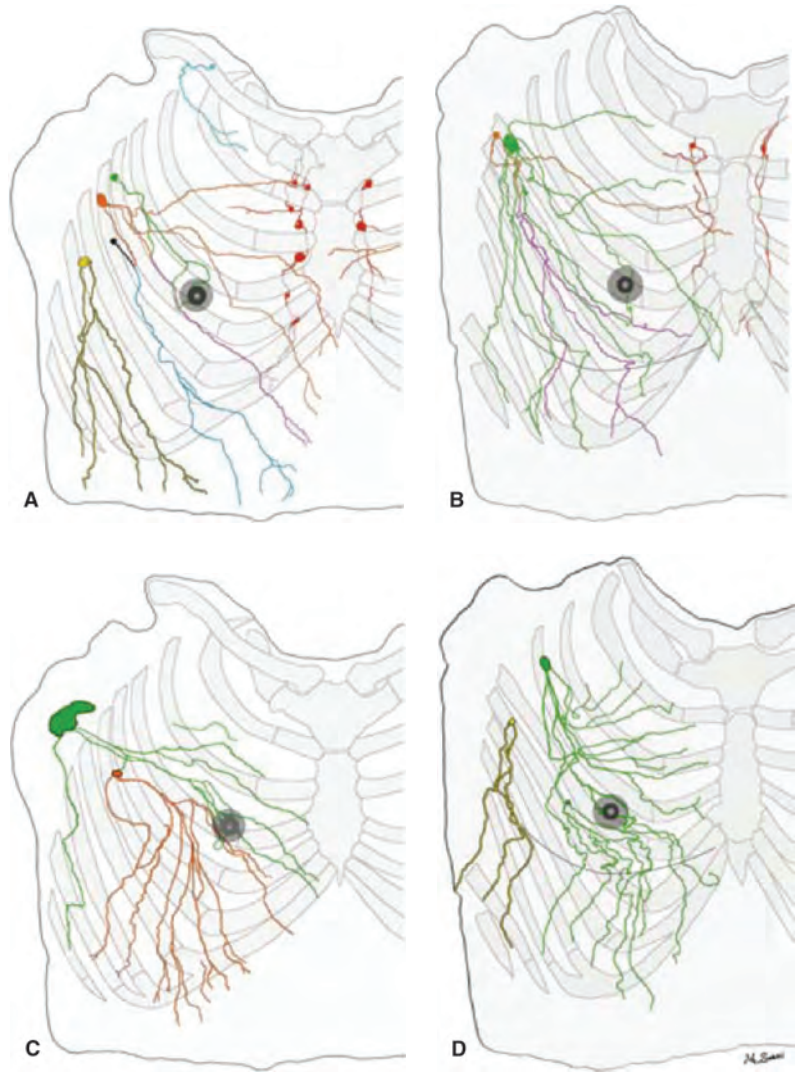

FIGURE 37-3 Tracing distally of lymphatics of both hemi upper torsos (male: **(A)** and **(C)**, female: **(B)** and **(D)**) from each first-tier lymph node color coded: pectoral node (*green, orange, black*, and *yellow*), subclavicular node (*light blue*), and internal mammary node (red). Note: that the lymph collecting vessels from the nipple and areolar region on each specimen drain into the green-colored lymph node; the similar pattern of chest and breast drainage between the male and female studies; the breast lies in the pathway of collecting lymphatics that start peripherally; and although the majority of the breast drains to one sentinel node in **D**, every breast area is drained by more than one first-tier node in each study. (From Suami H, Pan W-R, Mann GB, et al. The lymphatic anatomy of the breast and its implications for sentinal lymph node biopsy: a human cadaver study. *Ann Surg Oncol* 2008;(3):863–871.)

TABLE 37-1

Identification Rate and False-Negative Rate of Selected Multicenter Sentinel Lymph Node Trials That Evaluated the Status of the Axilla with Sentinel Lymph Node Dissection Followed by Completion Axillary Lymph Node Dissection

Study/Author	*No. of Cases*	*SN Identification Rate (%)*	*FN Rate (%)*
Canavese (2009) (109)	202	97.1	6.5
Veronesi (1999) (110)	376	98.7	6.7
Krag (1998) (111)	443	91.0	11.0
Tafra (2001) (71)	529	87.0	13.0
SNAC (19)	1,080	94.5	5.5
NSABP-B32 (21)	5,611	97.1	9.8
ALMANAC (20)	803	96.1	6.7
ACOSOG Z010 (27)	5,283	98.7	0.3 (estimated)
Sentinella/GIVOM (36)	697	95.0	16.7

SNB, sentinel lymph node biopsy; FN, false-negative; SNAC, Sentinel Node Biopsy versus Axillary Clearance; NSABP, National Surgical Adjuvant Breast and Bowel Project; ALMANAC, Axillary Lymphatic Mapping Against Nodal Axillary Clearance; ACOSOG, American College of Surgeons Oncology Group; GIVOM, Gruppo Interdisciplinare Veneto di Oncologia Mammaria.

The Axillary Lymphatic Mapping Against Nodal Axillary Clearance (ALMANAC) trial was a two-phase trial that required surgeons to demonstrate a 90% identification rate and a FN rate of less than 5% prior to proceeding to phase II, which was the two-armed prospective trial that randomized 1,031 patients into SNB followed by ALND (n = 516) or to SNB alone (n = 515) if the SN was tumor free (20). If the SN was positive for tumor cells, the regional treatment was ALND or axillary irradiation. SNB was performed with a 96% success rate with the combined use of blue dye and radioisotope and a 5% FN rate. The investigators reported a significantly lower rate of lymphedema, sensory deficits, and impairment in shoulder function in the SNB arm with patient-recorded quality of life scores statistically significantly better in the SNB arm. A report on long-term outcomes is pending.

The Royal Australian College of Surgeons (RACS) SN versus Axillary Clearance (SNAC) multicenter randomized study was a phase III trial with a two stage design similar to the ALMANAC trial. A sensitivity of 95%, FN rate of 5%, and a negative predictive value of 98% were reported for SN biopsy in stage I. Stage II randomized 1,088 clinically node-negative women with invasive breast cancer less than 3 cm to SNB alone versus axillary clearance to compare rates of axillary morbidity. The average increase in arm volume was 2.8% in the SNB alone group and 4.2% in the axillary clearance group ($p = .002$). Patients in the SNB alone group gave lower ratings for arm swelling ($p < .001$), symptoms ($p < .001$), and dysfunctions ($p = .02$), but not disabilities ($p = .5$) (19).

HISTOPATHOLOGIC PROCESSING

When the authors' group at the JWCI compared ALND alone to SNB followed by completion ALND, axillary metastases were identified in 29% of the ALND-alone group compared to 42% in the SNB group ($p < .03$) (22). H&E analysis of multiple levels of the SN increased the sensitivity to detect micrometastases for SNB versus ALND (9.2% vs. 3.0%, respectively; $p < .004$), and when both H&E and IHC were used, there was increased sensitivity (16.0% vs. 3.0%, respectively; $p < .0005$) (Fig. 37-4). Focused histopathologic analysis of the SN is a more sensitive method to detect micrometastases by both H&E and IHC and leads to improved accuracy of axillary staging for a tumor-positive axillary lymph node. The hope was that ultra-staging of the SN would lead to the identification of H&E node-negative patients who were at higher risk for recurrence.

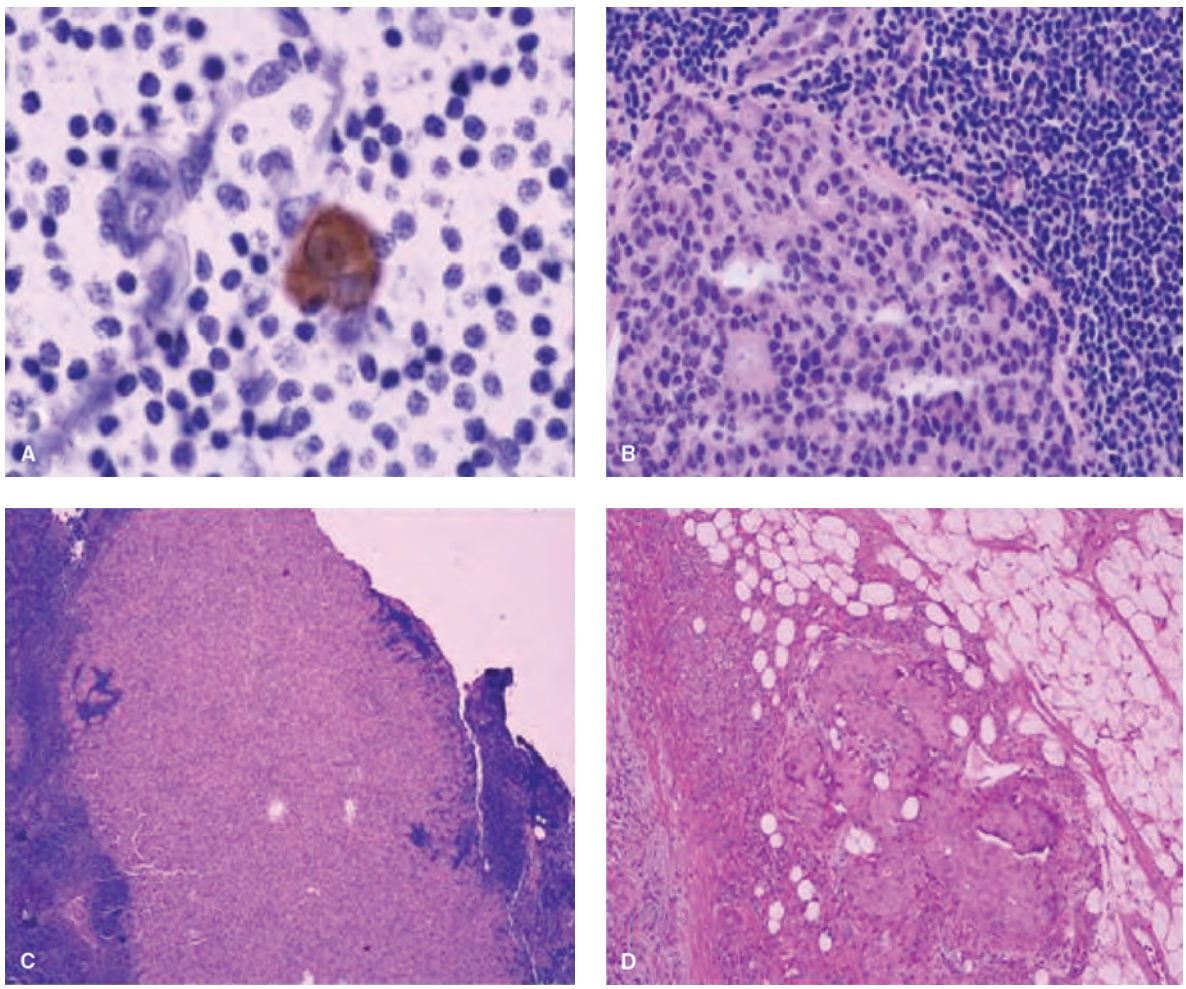

FIGURE 37-4 **Sentinel node metastases. (A)** Demonstrates a single immunohistochemistry-positive cell. **(B)** Demonstrates a high power view of a hematoxylin-eosin metastasis. **(C)** Demonstrates a low power view of a macrometastasis. **(D)** Demonstrates extracapsular extension of a sentinel node micrometastasis.

In view of the identification of small tumors in the SN, the American College of Pathologists established guidelines to process the SN with frozen sections, imprint cytology, or permanent formalin processed specimens (23). The SN is bivalved along the longitudinal axis, serially sectioned at 1.5 to 2.0 mm thickness blocks and each block is sectioned at three levels. If metastases are identified in the SN (see Fig. 37-4), the size of the metastasis is reported as macrometastases (>2.0 mm), micrometastases (>0.2 and ≤2.0 mm), or isolated tumor cells (≤0.2 mm), and the method of detection of the metastasis by H&E, IHC, or reverse transcription-polymerase chain reaction (RT-PCR). In the new American Joint Committee on Cancer (AJCC) guidelines (seventh edition), small clusters of cells not greater than 0.2 mm, or nonconfluent or nearly confluent clusters of cells not exceeding 200 cells in a single histologic cross section of a lymph node are classified as isolated tumor cells.

Molecular analysis of the SN is an area of emerging technology and interest. Some investigators feel that this is a more objective assessment of the tumor burden in the SN, is more reproducible, can be standardized, and evaluates more tissue in a shorter period of time (24). Quantitative RT-PCR (qRT-PCR) evaluation demonstrates a 98% accuracy and can be performed in 40 minutes or less. A prospective trial to evaluate lymph node metastases with a multiplex RT-PCR-based assay detected 98% of metastases greater than 2 mm and 88% of those greater than 0.2 mm, and results were superior to frozen section histology or imprint cytology (24). In a prospective multicenter trial that conducted molecular analysis of SN by qRT-PCR as well as serial sectioning and staining with H&E and with or without IHC in 547 patients, investigators compared the two groups with respect to clinical outcome with mean follow-up of 7 years (25). While molecular staging of SN detected more nodal metastases not seen by standard histologic evaluation, these metastases were not shown to be a significant predictor of disease recurrence. Similar results were observed by Fisher and colleagues (26) who analyzed seven breast cancer associated genes, known to be overexpressed in metastatic breast cancer, in axillary lymph nodes of 501 patients with T1–T3 invasive breast cancer who were followed for 5 years with no impact on clinical outcome. Molecular analysis of SN is unlikely to be of clinical relevance in view of recently reported results of the ACOSOG Z10 and NSABP-B32 trials on micrometastases, discussed later in this chapter. In the absence of participation in a clinical trial, the reasonable management approach should be based on the H&E evaluation of axillary nodes; however, in clinical practice IHC is used in many centers for SNs that are found negative by H&E.

FACTORS INFLUENCING THE SUCCESS AND ACCURACY OF SENTINEL LYMPH NODE DISSECTION

In order to reduce the FN rate of SNB, causes of failure have been sought. Potential explanations for failure include improper surgical technique, lack of surgeon and pathologist experience, lymphatic physiology, aberrant lymphatic patterns, and patient and tumor characteristics.

Effect of Sentinel Lymph Node Dissection Technique on Accuracy

A variety of technical factors, which include type of dye or radioisotope, filtered versus unfiltered isotope, timing of surgery after injection, and site of injection (peritumoral, subdermal, intradermal, subareolar) influence the performance of SNB. A high degree of accuracy and a low FN rate with resection of only one or two lymph nodes is seen in most cases. Differences in the ability to find the SN are reflections of variations in patient characteristics (e.g., obesity, age) and surgeon experience more than technique. Internal mammary nodes are visualized less often with intradermal injection than with peritumoral injection. Subareolar injection of isotope offers some advantages over peritumoral injection; for example, when the tumor is nonpalpable, it increases the distance from the injection site of radioisotope to the axilla for upper outer quadrant lesions, reducing the shine through, and is a good choice for multicentric disease.

In the multi-institutional American College of Surgeons Oncology Group (ACOSOG) Z0010 trial, 198 surgeons enrolled 5,237 patients and used blue dye with radiocolloid in 79.4% of cases, blue dye alone in 14.8%, and radiocolloid alone in 5.7% with a success rate of 98.7%, corresponding to a failure rate of 1.7% (27). The percent of failed SNB with blue dye was 1.4%, radiocolloid 2.3%, and the combination 1.2% (p = .2813). The number of cases (≤50 compared to >50) enrolled was associated with a statistically significant failure rate. Increased body mass index and age were also associated with decreased SN identification in this study. Morrow et al. evaluated isosulfan blue dye alone and compared it to dye with isotope (7). Surgeons achieved equal results with either method. A study from New Zealand confirms this work and reports that identification of the SN is similar with blue dye alone compared to a triple modality approach (lymphoscintigraphy, intraoperative gamma probe, and intraoperative blue dye) (28). The blue dye had an accuracy of 98% and a sensitivity of 96% compared to the triple method accuracy of 95% and sensitivity of 91%. There has been a manufacturing shortage of isosulfan blue in the United States and methylene blue has been used as an alternative vital dye. The success rate of methylene blue with radioisotope is reported to be equivalent to isosulfan blue with isotope (29).

The site of injection of the tracer may influence the outcome of SNB. A prospective randomized trial compared intradermal, intraparenchymal, and subareolar routes of injection and demonstrated a significantly higher rate of localization and more rapid transit by lymphoscintigraphy, and shorter time to surgery with the intradermal injection (16). Another randomized multicenter trial compared periareolar and peritumoral injection of radiotracer and blue dye (30). The intraoperative success was similar for blue dye or gamma detection (99.1%). The detection rate was higher for the periareolar site for each tracer, but this was not statistically significant. The SN was blue in 94.7%, hot in 97.1%, and both in 92.6%. The concordance was 91.5% with the peritumoral injection and 95.6% with the periareolar injection. The blue dye and radiocolloid concordance for the positive SN patients was 94.5% and, when assessed by site of injection, 96.2% in the periareolar group and 92.9% in the peritumoral group.

The SNB procedure has been adopted by surgeons in both academic and community settings throughout the United States as well as internationally. The efficacy of the method, dye, isotope, or both, is more likely a reflection of training and experience than variations in the success of the method itself. The importance of quality control and appropriate training cannot be overemphasized.

Effect of Surgeon Experience: Training and Performance of Sentinel Lymph Node Dissection

Formal lymphatic mapping instruction with hands-on experience leads to a 90% to 95% identification rate and a 3.8% to

4.3% FN rate when more than 30 cases are performed (31). The NSABP B-32 trial required a minimum of five prequalifying cases and reported a technical success rate of 97% (13). Surgical volume impacts identification rates. Surgeons who performed fewer than three cases per month had a success rate of 86.23% ± 8.30%, for three to six cases 88.73% ± 6.36%, and for six or more SN biopsies 97.81% ± 0.44% (31).

The studies just described show individual variation in learning the skills and identify some of the pitfalls in learning the technique. Instruction in SNB is now part of surgical residency training in the United States. For those not trained in the technique during residency, formal instruction, use of dual agents, performance of approximately 20 SNB procedures with a backup ALND, and an adequate volume of cases to maintain skills are all factors that contribute to successful identification of SN and reduced FN rate. In 2005, a consensus statement from the American Society of Breast Surgeons suggests that prior to abandoning ALND for a negative SN, 20 cases of SNB be performed with an identification rate of 85% and a FN rate of 5% or less (32). These should be adapted on an individual basis, with more cases performed by those with lower identification rates and higher FN rates and vice versa. One problem with their application is that most patients are SN negative, making the FN rate more difficult to determine with a high degree of certainty.

Effect of the Number of Sentinel Nodes Removed

Increasing the mean number of SNs removed may improve accuracy (13,33). The number of SNs removed statistically affected the FN rate in the NSABP B-32 trial, where a median of 2 SNs was removed in each treatment arm. The FN rate was 17.7% when one node was removed, 10% for two, 6.9% for three, 5.5% for four, and 1% for five or more nodes removed. In the University of Louisville Breast Cancer Sentinel Lymph Node Study, the mean number of SNs removed per patient was 2.2 and 58% of the patients had multiple SNs removed (33). The overall SN identification rate was 90% with an 8.3% FN rate. If a single node was removed, the FN rate was 14.3% compared to 4.3% when multiple SNs were removed ($p < .0004$). The first two or three SNs removed predict the status of the axilla in about 98% of cases, but additional positive SNs will be identified when four or more nodes are removed, improving the FN rate (13). The removal of all blue, or radioactive, nodes with a count equal to or greater than 10% of the most radioactive node has been shown to decrease the FN rate in these studies. This increase in staging accuracy may be obtained at the cost of an increased rate of complications, especially lymphedema, but the goal is accurate staging for treatment decisions. Fewer nodes may be removed with increasing surgeon experience.

Effect of Patient and Tumor Characteristics

The data from the multi-institutional, randomized prospective NSABP B-32 trial reports a FN rate of 9.8% and an overall accuracy of 97.1% (13). Differences in tumor location (inner and central location vs. lateral and outer), no hot spot identified preoperatively, small tumor size, older age, and type of diagnostic biopsy (excision/incisional biopsy higher than fine-needle aspiration [FNA] or core needle biopsy [CNB]) increased the FN rate. In the ALMANAC study, increased body mass index (BMI), upper outer quadrant location, and nonvisualization on lymphoscintigraphy were significantly associated with failed identification ($p < .001$, $p = .008$, $p < .001$, respectively) (34). None of the following, age, tumor size, tumor histology, tumor grade, or multifocality, affected identification. In the ACOSOG Z0010 trial, a higher failure to identify a SN occurred with increased BMI and age of 70 or older (27).

Impact of Sentinel Lymph Node Dissection on Regional Control and Survival for Sentinel Node–Negative Patients

Results from randomized controlled trials examining local recurrence after SNB alone are summarized in Table 37-2. A meta-analysis of 48 studies that included 14,959 SN-negative patients followed for a median of 34 months demonstrated an axillary failure in 67 patients (0.3%) (35). In the European Institute of Oncology Trial the predicted failure was eight cases, but only one case of overt axillary metastases was seen at 7.2 years of follow-up after surgery. The possibility that the occult metastases in the FN nodes may never become overt has been suggested by several single institution studies, the Swedish multicenter trial, and from the European Institute of Oncology trial at a relatively short follow-up.

One multicenter trial to report results on patients randomized to SNB alone or SNB followed by ALND was the Sentinella/GIVOM trial (36). This study reported a FN rate of 16.7%. Despite this high FN rate, there was only one axillary failure in the SNB-alone group at 55.6 months. The overall survival was 95.5% in the ALND group and 94.8% in the SNB-alone group at 5 years of follow-up.

In the European Institute of Oncology randomized study, women with tumors less than 2 cm were randomized to SNB

TABLE 37-2

Comparison of Outcomes in Five Randomized Controlled Trials of Sentinel Lymph Node Biopsy versus Axillary Lymph Node Dissection

Study/Trial	*No. Patients*	*F/U (months)*	*LRR: SNB vs. ALND*	*DFS: SNB vs. ALND*	*OS: SNB vs. ALND*
Canavese (109)	225	66	0% vs. 1%	93.5% vs. 93.8%, 5y	97.2% vs. 97.2%, 5y
Veronesi (38)	516	102	2.3% vs. 2.3%	88.8% vs. 89.9%, 10 y	93.5 vs. 89.7, 10y
Sentinella/GIVOM (36)	697	56	4.6% vs. 1%	87.6% vs. 89.9%, 5y	94.8% vs. 95.5, 5y
NSABP-B32 (21)	5611	95.6	3.1% vs. 3.1%	81.5% vs. 82.4%, 8y	90.3% vs. 91.8%, 8y
ACOSOG Z011* (51,52)	891	75.6	1.6% vs. 3.1%	83.9% vs. 82.2%, 5y	92.5% vs. 91.8%, 5y

No., number; F/U, follow-up; LRR, locoregional recurrence; DFS, disease-free survival; OS, overall survival; SNB, sentinel node biopsy; ALND, axillary lymph node dissection; y, year; GIVOM, Gruppo Interdisciplinare Veneto di Oncologia Mammaria; NSABP, National Surgical Adjuvant Breast and Bowel Project; ACOSOG, American College of Surgeons Oncology Group; *, SN-positive by H&E.

alone if the SN was tumor free or to SNB followed by ALND (37). In the ALND group, 32% had a positive SN and 8 of 174 SN-negative patients had a FN node. The SN was positive in 36% of the SNB-only group with one axillary failure at a median follow-up of 79 months. Because there were eight FNs in the ALND group, there should have been eight FNs in the SNB alone group, but there was only one axillary failure. The overall survival was the same for the ALND group compared to SNB alone (96.4% vs. 98.4%, respectively; $p = .6$). The SNB-alone group had decreased morbidity and cost.

The NSABP-B32 prospective randomized trial of SNB followed by ALND (group 1) versus SNB alone with ALND only in SN-positive patients (group 2) reported outcomes after longer follow-up. Among 5,611 women, there was no difference in regional control between the two groups after median follow-up of 95.6 months (eight regional recurrences in group 1 vs. 14 in group 2, $p = .22$) (21). Eight-year Kaplan-Meier estimates for overall survival were 91.8% (95% CI, 90.4–93.3) in group 1 and 90.3% (88.8–91.8) in group 2, and for disease-free survival were 82.4% (80.5–84.4) in group 1 and 81.5% (79.6–83.4) in group 2. Veronesi et al. conducted a randomized trial at a single institution involving 516 patients with breast tumors of 2 cm or less in size who were randomly assigned to either SNB followed by ALND or SNB with ALND only if the SN contained metastatic disease (38). With a median follow-up of 102 months, there was no difference between the two groups with respect to disease-free survival (89.9% in the SNB arm, vs. 88.8% in the ALND arm) or overall survival (93.5%, compared to the ALND arm, 89.7%, $p = .15$). Of note, there were only two (0.01%) axillary recurrences in this study, both of which occurred in the SNB only group. SNB appears to provide regional nodal control equal to that of ALND when the SN is negative. Standard tangent breast fields may contribute to axillary control in those who undergo breast conservation and receive whole breast irradiation, but several investigators show that they do not encompass all the level I and II lymph nodes (39).

Summary

SNB has met with success in single institution studies and several multicenter trials with credentialed teams. There is a large body of evidence showing that SNB is an accurate staging procedure in expert hands, and it is now the standard of care for staging clinically node-negative invasive breast cancer.

Reliable staging with SNB depends on the success of SN identification, a low FN rate, and histopathologic accuracy. Almost two decades of experience with sentinel lymphadenectomy as the sole axillary treatment at a number of large single institution trials and several randomized trials with long follow-up prove that this is a safe, reliable, and effective procedure for staging.

MANAGEMENT OF THE AXILLA IN THE PATIENT WITH A POSITIVE SENTINEL NODE

ALND has traditionally been the recommended treatment for a positive SN. However, trends to omit ALND in SN-positive patients have been documented over the last 15 years, especially among patients with low tumor burden in the SN. Bilimoria and colleagues (40) identified 97,314 clinically node-negative patients found to have a positive SN from the National Cancer Database from 1998 to 2005. Approximately 20% of SN-positive patients did not have completion ALND and from 1998 to 2005, the proportion of patients with micrometastatic SNs who had SNB alone increased from 25% to 45%. With a median follow-up of 63 months, the authors did not find a difference in regional recurrence or survival between those who had SNB with completion ALND and those who had SNB alone. Similar findings were observed in a review of the Surveillance, Epidemiology, and End Results (SEER) database, where Yi et al. (41) identified 26,986 patients with a positive SN from 1998 to 2004. Approximately 16% of patients had SNB alone without completion ALND. From 1998 to 2004 the proportion of patients with micrometastatic SN who had SNB alone increased from 21% to 38%.

One of the factors influencing a decrease in completion ALND for positive SN may have been the introduction of nomograms that were shown to predict involvement of non-SNs. Van Zee et al. (42) developed a nomogram to help estimate the risk of additional nodal disease when the SN is positive. The nomogram uses pathologic size, tumor type, nuclear grade, lymphovascular invasion, multifocality, estrogen-receptor status, histopathologic method used to detect a positive SN, and the ratio of the number of positive SN removed to the total number of SN removed to predict the likelihood of additional positive non-SNs. Retrospective data were used to create the model, which was tested prospectively at Memorial Sloan-Kettering Cancer Center and found to be predictive of metastases. The receiver operating characteristic (ROC) was 0.76 in the retrospective data set and 0.77 in the prospective group. Several groups have tested the nomogram and found fair to good reliability, but at the same time they have questioned the clinical usefulness (43). Others did not find good correlation, in particular with micrometastatic disease (44,45). Other nomograms have been developed at the Mayo Clinic (45), MD Anderson Cancer Center (46), and Stanford University (47).

There are several studies that have reported the short-term outcomes in SN-positive patients who declined ALND and had no treatment of the axilla (48,49). In these studies, the tumor size was small and the majority of patients had micrometastatic disease. There were no locoregional failures at short follow-up (29 to 32 months). A review from Memorial Sloan-Kettering Cancer Center on SN-positive patients who declined ALND investigated the clinical findings, pathologic features, nomogram scores, and axillary failure rate in 287 SN-positive patients (50). This group of patients was older, had more favorable tumors, had a higher rate of breast conservation, and had a lower estimate of residual nodal disease calculated by a nomogram than the group undergoing axillary dissection. The axillary relapse rate in the untreated group was 2% compared to 0.4% in the group who had a completion ALND ($p = .004$).

The appropriate management of the axilla after a positive SN has been addressed in a number of prospective clinical trials. The ACOSOG Z0011 was a prospective Phase III non-inferiority trial that randomized subjects with clinical T1 or T2N0M0 breast cancer with a tumor-positive SN to completion ALND or observation of the axilla (51,52). Treatment of the breast was breast conservation and whole breast radiotherapy. No third field was given to the axillary lymph nodes. The primary end point of this study was overall survival; morbidity and disease-free survival were secondary end points. A secondary aim was to evaluate surgical morbidity with SNB plus ALND versus SNB alone. The purpose of this study was to determine the therapeutic role of axillary dissection. Unfortunately, this study closed early due to poor accrual and a low event rate.

Results of this study were recently reported and have created a significant amount of controversy in the oncologic community. From May 1999 through December 2004, 891

patients were enrolled from 115 sites: 445 were randomized to ALND, 446 were randomized to no further axillary treatment. There was no significant difference between the two groups with respect to age, tumor size, estrogen-receptor (ER) status, presence of lymphovascular invasion (LVI), grade, or histology. Ninety-seven percent of patients received adjuvant systemic therapy reflecting practice patterns in the United States. The two groups varied naturally by number of LNs removed with the ALND arm averaging 17 nodes and the SNB only arm averaging only two nodes per patient. There was also a difference between the two groups with respect to number of nodes removed and size of metastases with the SNB alone arm having more patients with micrometastatic disease (p = .05). At median follow-up of 6.3 years, there was no difference between the two treatment arms with respect to locoregional recurrence (3.1% with ALND and 1.6% with SNB alone), OS (91.8% with ALND vs. 92.5% with SNB alone), and DFS (82.2% with ALND and 83.9% with SNB alone). Figure 37-5 demonstrates the comparison of outcomes between the SNB only arm and the ALND arm. Non-inferiority between the two arms was achieved with high statistical significance (p < .008). These findings have resulted in considerable controversy with many questioning whether radiation oncologists irradiated the axillary nodes in the SNB alone group, even though axillary irradiation was prohibited in the protocol. Concerns have also been raised regarding the number of patients accrued, length of follow-up, and the applicability of the results to the general population because the majority of patients in the Z011 trial had early metastatic disease. Goal accrual was 1,900, but the actual accrual was 891. However, not only was non-inferiority achieved with high statistical significance (p < .008), total locoregional recurrence, DFS, and OS were in favor of the SNB alone group, suggesting that observed results are not likely to change with an increase in sample size. The excellent locoregional control in the Z011 trial was due to many factors, including whole breast irradiation, routine use of adjuvant systemic therapy, early disease, and low burden of nodal metastases.

Another concern that critics have about this trial is the length of follow-up. Many argue that death from early ER-positive breast cancer tends to occur late and 6.3 years is not enough follow-up. However, axillary recurrences do tend to occur early. There is an abundance of data demonstrating that the median time to axillary recurrence ranges from 14 to 20 months (51,53,54). So 6.3 years should be more than enough time to detect these recurrences. In addition, there have been a number of landmark historical trials evaluating whether axillary treatment, either in the form of surgery or radiation therapy, affects survival (54–59). These are randomized trials on a large number of patients, with long follow-up, with none of them demonstrating a significant difference in breast cancer-specific survival or OS resulting from axillary nodal treatment. ACOSOG Z011 confirms the results of these earlier trials, that axillary treatment does not, in fact, affect survival.

Many argue that the large majority of the study population included older, ER-positive, less aggressive tumors and that the higher risk populations were under-represented in the trial. Therefore, completion ALND should be performed in younger, high-risk, ER-negative populations. In Z011, age ranged from 24 to 92 with 38% of patients under the age of 50. Among the younger patients, there was no difference between the two groups with respect to LRR, and most of the recurrences were in-breast recurrences—not nodal recurrences. In fact, there is no data from clinical trials documenting that younger women are at increased risk for isolated nodal recurrences. So the investigators argue that age should not limit the application of this study to practice. ER/PR-negative patients represented about 16% of the study population. In a subset analysis, there was no difference in survival between the two arms whether they had ER-positive or ER-negative tumors. Another important point is that ER-negative tumors are not more likely to metastasize to the nodes. Wiechmann and colleagues (60) performed immunohistochemical staining to determine subtype on over 6,000 breast tumors that had information on nodal status. They found that the basal subtype, or triple-negative subtype, was less likely than the other subtypes (Luminal A, B, or HER2) to have nodal involvement. Therefore, it is unlikely that patients in this subset would truly benefit from completion ALND any more than low-risk patients.

The other high-risk category is the HER2-overexpressing (Her2+) tumor. ACOSOG Z011 opened in 1999 when routine HER2 testing was not performed, so HER2 data was not consistently reported. While HER2+ tumors are more aggressive, they are not more likely to metastasize to the lymph nodes. Anti-HER2 targeted therapy is likely to reduce the tumor burden in any undissected nodes. Data from the landmark trastuzumab trials shows that trastuzumab significantly

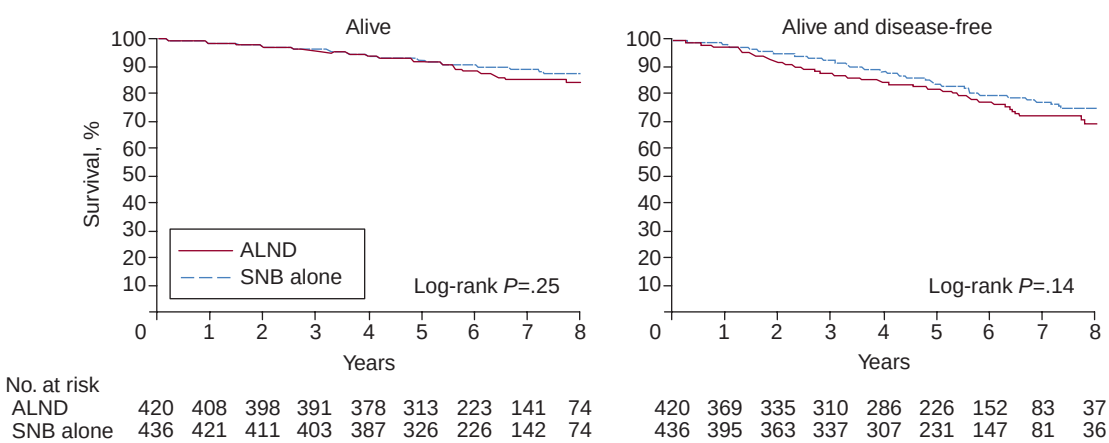

FIGURE 37-5 Comparison of outcomes of patients treated with SNB alone to those treated with SNB plus ALND in the ACOSOG Z011 trial. (A) Disease-free survival. **(B)** Overall survival. (From Giuliano AE, Hunt KK, Ballman KV, et al. Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. *JAMA* 2011;305(6):569–575, with permission.)

reduces the incidence of LRR (NSABP-B31 and N9831) (61,62). Therefore, patients with HER2+ breast cancer should not be excluded from the application of the Z011 trial data.

To address the above mentioned concerns, Dengel and colleagues prospectively assessed the applicability of the Z011 trial in a cohort of 341 consecutive SN-positive patients treated with breast conservative surgery according to a treatment algorithm based on the Z011 eligibility criteria (63). Of 253 patients with ≥1 H&E-positive SN, 212 (84%) had indications for SNB only, and ALND was indicated in 41 (16%) based on Z011 eligibility criteria. Comparison of patient and tumor characteristics did not identify any difference between the two groups with respect to age, hormone-receptor status, or HER2 status. Completion ALND was performed in 34 of the 41 patients where ALND was indicated, and additional tumor-involved nodes were found in 74%. In this study, ALND was avoided in 84% of SN-positive patients, and age, hormone receptor status and HER2 status were not predictive of tumor burden requiring ALND.

In summary, patients with a positive SN that may avoid ALND include those with clinical T1–2, N0 breast cancer with one or two positive SN who plan to undergo lumpectomy with whole breast radiation and systemic therapy. Patients in whom completion ALND should still be recommended include patients who received neoadjuvant therapy, those with a positive SN who are treated with mastectomy, patients with three or more positive SNs, those with significant extra-nodal extension, patients who do not receive adjuvant systemic therapy or whole breast irradiation, and patients with clinically palpable nodes. The results of the Z011 trial represents level I data that should result in practice changes and render nomograms obsolete (64). In addition, although the Z011 trial excluded patients whose SN had micrometastases detected only by IHC, the results can rationally be applied to patients with SN micrometastases. Since the results of ACOSOG Z011 have been reported, the utility of frozen section analysis to evaluate SNs has been questioned. Weber and colleagues (65) evaluated time trends and variation between surgeons in the use of frozen sections for SNB and ALND in over 7,500 patients with clinically node-negative invasive breast cancer. From 1997 through 2006, the use of frozen section analysis of SNs decreased from 100% to 62% ($p < .0001$) and varied widely by surgeon (66% to 95%), demonstrating a diminishing rate of frozen section analysis of SNs over time. While there was no significant trend in ALND with a positive SN detected by frozen section or routine H&E during this time period, the investigators did observe a significant decrease in ALND for those with metastases detected by serial sectioning or IHC. The authors applied the ACOSOG Z011 selection criteria to their cohort of patients and calculated that 66% of SN frozen sections (4,159 of 6,327) and 48% of ALND (939 of 1,953) would have been avoided, sparing 13% of all patients the morbidity of ALND. The American Society of Breast Surgeons released a position statement on the management of axillary lymph nodes following the presentation of ACOSOG Z011 results, stating that intraoperative frozen section analysis of SN can be avoided if clinical suspicion of nodal involvement is low and the patient otherwise meets the entry criteria for the Z011 trial (66). This position includes the use of clinical suspicion; however, this cannot be supported by data.

MANAGEMENT OF MICROMETASTATIC DISEASE IN THE SENTINEL NODE

The ACOSOG Z0010 trial is a prospective observational study of subjects with stage I or II clinically node-negative invasive breast cancer treated with breast conservation, SNB, and bilateral iliac crest bone marrow aspirations. If the SN was free of tumor by H&E examination, no further ALND was undertaken. The aim of this study was to determine the prevalence and significance of IHC-positive micrometastases in lymph nodes, bone marrow metastases identified by immunocytochemistry (ICC), or both, and to determine the risk of regional recurrence. The secondary aim was to determine the morbidity associated with SNB. Blinded analysis of the SN by IHC and bone marrow by ICC was performed in a central processing site on the SNs that were histologically negative by H&E. Adjuvant treatment recommendations were made on the basis of H&E examination of the axillary nodes. Among 5,184 patients with SN, 1,239 (23.9%) had metastases identified by routine H&E. IHC detected an additional 350 (10.5%) with SN metastases. SN metastases detected by IHC did not appear to have a significant impact on 5-year overall survival. Bone marrow micrometastases were identified by IHC in 105/3,491 (3.0%) of cases examined and bone marrow IHC positivity was significantly associated with worse OS. A subset analysis of the NSABP-B32 trial (67) evaluated the prognostic significance of occult metastases in 3,887 tissue blocks from histologically negative sentinel nodes that were re-examined with serial sectioning and IHC, detecting 15.9% with occult metastases. Five-year Kaplan-Meier estimates of overall survival among those with occult metastases, and those without occult metastases, was 94.6% and 95.8%, respectively. The authors concluded that the difference in OS was so small and that there is no added clinical benefit to performing additional sectioning and IHC of H&E negative SN. The IBCSG 23-01 trial was a randomized trial that specifically compared ALND to no ALND in 931 patients with clinical T1N0 invasive breast cancer and at least one micrometastasis in the SN (68). After a median follow up of 5 years, there was no difference between treatment arms with respect to 5-year disease-free survival (87.8% vs. 84.4%, respectively), cumulative incidence of breast cancer related events (10.8% vs. 10.6%) and overall survival (97.6% vs. 97.5%). ALND can be safely avoided in patients with early breast cancer and limited SN involvement. The seventh edition of the AJCC TNM staging system in breast cancer has incorporated changes to reflect the findings on the prognostic significance of micrometastases. Stage I has been subdivided into Stage IA and Stage IB, where Stage IB includes small tumors (T1) with exclusively micrometastases in the lymph nodes (N1mic). Following reports of the ACOSOG Z011 and NSABP-B32 trials, the American Society of Breast Surgeons released a position statement on SN micrometastases in August 2011, stating that SN micrometastases detected only by IHC are clinically insignificant and that routine use of IHC staining of SNs is unnecessary and should be limited to selective use at the discretion of the pathologist. IHC is of value to detect metastases from infiltrating lobular carcinoma which may be difficult to detect with H&E.

SENTINEL LYMPH NODE BIOPSY

Axillary Sentinel Lymph Node Biopsy Technique

If using radioisotope, intradermal, subdermal, or peritumoral injection of a single dose of 0.3 to 1.0 mCi of technetium-99m sulfur colloid is performed 3 to 24 hours prior to incision. Lymphoscintigraphy may be performed after injection to document migration of the radioisotope. Intraoperative subareolar or dermal injection of radioisotope approximately 40 minutes prior to incision has been reported to localize the SN in 98.6% of the cases (419/425) of subareolar

radiotracer alone, 94.8% (326/344) in dual injection, and 100% (6/6) in dermal injection (69). When radioisotope is used, the incision is made directly over the location of a focal site of increased activity and dissection proceeds until the SN is identified by quantitative counts and resected. A radioactive node has been defined as a node with a cumulative 10-second count of greater than 25, the hottest node by absolute counts, a 10 to 1 ratio of SN to background, or a fourfold reduction in counts after the SN is removed (70). Verification is done by *ex vivo* SN counts compared to residual *in vivo* background counts. Additional radioactive SNs are removed until the background is less than one-tenth the value of the hottest node. Lymph nodes with the highest radioactive uptake usually contain the greatest tumor burden, but on occasion tumor replaced nodes may have lymphatic obstruction, and if only the hottest node is removed, a positive SN with lower counts may be missed in 23% of cases (71). If blue dye is employed, 3 to 5 mL is injected approximately 5 to 10 minutes prior to incision. The addition of a post-injection massage has been shown to improve the uptake of blue dye by SNs, further increasing the sensitivity of this procedure (72). After a 2 to 3 cm transverse incision is made in the axillary fossa, a careful search for all blue nodes or lymphatics should be carried out. Palpation of the axillary space for any suspicious nodes will avoid missing a tumor-laden node that has occluded lymphatics and may not be blue or radioactive. All suspicious palpable nodes must be removed at the time of SNB, regardless of technique—isotope or dye.

Complications of Sentinel Lymph Node Biopsy

Dye Complications

Isolated case reports of adverse reactions with blue dye, including allergic urticaria and anaphylaxis, have been reported, but the rate is extremely low. Data from the NSABP B-32 trial shows 0.4% grade 1 and 2 allergic reactions and 0.2% grade 3 and 4 with no deaths (13). The data from ACOSOG Z0010 show 0.1% anaphylaxis with isosulfan blue alone or in combination with radiocolloid (73). Hives covering the trunk and upper extremities, not associated with hypotension, resolve within 24 to 48 hours after administration of methylprednisolone and diphenhydramine. Management of hypotensive anaphylaxis includes discontinuation of anesthetic agents, administration of fluids, epinephrine, diphenhydramine hydrochloride, and corticosteroids. Barthelmes and colleagues (74) reviewed 40 cases of patent vital blue dye associated anaphylaxis in SNB for breast cancer and melanoma documented in the literature. Thirty-one patients did not have a past medical history of allergy. The median interval between blue dye administration and allergic reaction was 15 min (range 1–180 min). Of 20 patients with hypotension, 18 received inotropes. Four patients had a fall in blood pressure as their sole symptom, 23 patients had urticaria or other allergic skin manifestations, 8 had blue wheals, 5 patients had bronchospasm, and 2 patients had a cardiac arrest but were successfully resuscitated. The median dose of blue dye was 2 mL (range 0.5–5 mL). Tryptase levels were elevated in 14 of 26 tested patients. Skin prick testing was positive in 24 of 30 tested patients. Intradermal testing was positive in all 13 tested patients. The authors concluded that the value of formal allergy skin testing for patent blue dye-related allergy lies in excluding other agents as the causative factor to avoid their exposure in the future.

Isosulfan blue can affect pulse oximetry with a pseudodesaturation (75). Surgeons and anesthesiologists must investigate and verify that the partial pressure of oxygen, arterial (PaO_2) is normal. Isosulfan blue can cause transient staining of the epidermis, which can take several weeks to several months to completely fade. There is a transient change in color of the urine and stool to a greenish hue. Although these are temporary events, unless patients are forewarned about what to expect this can cause a great deal of unnecessary distress.

Methylene blue is associated with skin erythema, superficial ulceration, or necrosis with intradermal injections. Partial skin loss usually is treated with topical silver sulfadiazine (Silvadene) therapy and generally does not require surgical debridement. Methylene blue dye appears to be associated with fewer allergic reactions. However, allergy tests in some patients have proven that there is cross-reactivity between isosulfan blue dye and methylene blue dye (76).

Surgical Complications

Axillary complications and adverse side effects are reported with ALND, SNB, and axillary radiation, but to a lesser extent with SNB alone compared to ALND (Table 37-3). The incision is smaller with SNB with less tissue disruption and results in much less morbidity than complete ALND, as reported in the randomized studies (20,37,38,77). There is less pain, less limitation of motion, and fewer neurological sequela. In the randomized European Institute of Oncology trial, axillary pain, numbness and paresthesias, and arm swelling persisted to a significantly greater extent in the ALND than the SNB group (37).

SNB is associated with elimination of an axillary drain, less patient discomfort, and decreased incidence of lymphedema or neurovascular injury. Postmastectomy pain syndrome is significantly reduced with SNB compared to ALND. The incidence of measured lymphedema has been reported to range from 0% to 22%, although the majority of studies report a 3% to 7% incidence (78) of lymphedema after SNB compared to 5%–50% for ALND (79). Risk factors for developing lymphedema include upper outer quadrant lesions, postoperative trauma or infection, axillary radiation, and previous axillary surgery.

The ACOSOG Z0010 trial, previously discussed, was a single arm SNB-only trial when the SN was negative. The secondary aim of the ACOSOG Z0010 trial was to determine morbidity of SNB (73). Anaphylaxis occurred in 0.1%, seroma in 7.1%, and wound infection in 1.4%. Younger age was associated with a higher incidence of paresthesias, while increased BMI was associated with lymphedema. In the ACOSOG Z0011 trial, surgical complications were statistically greater in the SNB plus ALND arm than the SNB-alone arm: wound infections ($p \leq .016$), seromas ($p \leq .0001$), paresthesias ($p \leq .0001$), and subjective lymphedema at 1 year ($p \leq .0001$) (77). Overall quality of life and arm functioning scores were better in the SNB group in the ALMANAC trial (20). The quality of life was improved in the SNB group ($p < .003$) with less use of drains, less lymphedema, fewer days in the hospital, and earlier return to normal activities.

Variations in arm lymphatics contribute to the risk of developing lymphedema. A concept under study to attempt to reduce lymphedema is axillary reverse mapping (ARM) (80). This technique uses 2.5 to 5.0 mL of isosulfan blue injected intradermally or subcutaneously in the tissue of the upper inner arm to map the lymphatics draining the arm. Combined with radioisotope injection for the SNB, ARM attempts to distinguish lymphatics originating from the arm from lymphatics originating in the breast, enabling the surgeon to spare the arm-draining nodes. This concept has been demonstrated in a number of feasibility studies (80–82). However, the data on whether ARM reduces

TABLE 37-3

A Comparison of Morbidity in Five Randomized Controlled Trials of Axillary Lymph Node Dissection Compared to Sentinel Lymph Node Biopsy

Study/Trial	*No. of Patients*	*ALND Morbidity (%)*	*SNB Morbidity (%)*	*P-value*
Veronesi (112)	257	Axillary pain 72%	Axillary pain 14%	
		Paresthesias 85%	Paresthesias 2%	
		Limited ROM 22%	Limited ROM 0%	
		No arm swelling 31%	No arm swelling 89%	
ALMANAC (20)	476	No arm swelling 87%	No arm swelling 95%	<.001
		No paresthesias 69%	No paresthesias 91%	<.001
ACOSOG Z011 (77)	399	Infection 8%	Infection 3%	.0016
		Seroma 14%	Seroma 6%	.0001
		Paresthesias 39%	Paresthesias 9%	<.0001
		Lymphedema 11%	Lymphedema 6%	.0786
SNAC (19)	1080	Increased arm volume 4.2%	Increased arm volume 2.8%	.002
		Limited ROM 4.4%	Limited ROM 2.5%	.02
		Seroma 36%	Seroma 17%	<.001
		Infection 14%	Infection 9%	.02
NSABP B-32 (113)	5611	Limited ROM 9%	Limited ROM 5.7%	<.001
		Arm swelling 14.3%	Arm swelling 7.5%	<.001
		Numbness 31.1%	Numbness 8.1%	<.001
		Tingling 13.5%	Tingling 7.5%	<.001

No., number; ALND, axillary lymph node dissection; SNB, sentinel node biopsy; ROM, range of motion; ALMANAC, Axillary Lymphatic Mapping Against Nodal Axillary Clearance; ACOSOG, American College of Surgeons Oncology Group; SNAC, Sentinel Node Biopsy versus Axillary Clearance; NSABP, National Surgical Adjuvant Breast and Bowel Project.

lymphedema is limited. Boneti et al. (81) enrolled 156 to a prospective study where SNB (114/156) or ALND (42/156) was performed in conjunction with ARM and patients were assessed for lymphedema, defined as an increase in arm volume of over 20% compared to the contralateral side. ARM nodes were preserved in 92.3% (144/156) of cases. With mean follow-up of 14.6 months, 2.9% (4/140) of the patients who had the ARM lymphatics preserved and 18.7% (3/16) who had it transected developed clinical lymphedema. However, a number of studies have found metastatic disease in ARM nodes (83–85), and the SN draining the breast was the same node as the ARM node draining the upper extremity in 13% to 28% of cases. It is clearly unacceptable from an oncologic perspective to preserve metastatic ARM nodes during ALND or to preserve an ARM node that is identified as the SN. Therefore, further investigation of ARM is needed and at present this technique should be considered experimental. The data comparing the morbidity of SNB to axillary dissection are summarized in Table 37-3.

INDICATIONS FOR SENTINEL LYMPH NODE BIOPSY

Guidelines for lymphatic mapping have been put forth by ASCO, National Comprehensive Cancer Network (NCCN) 2012, American Society of Breast Surgeons 2010, and single institution studies and are summarized in Table 37-4.

TABLE 37-4

Indications and Contraindications to Sentinel Lymph Node Biopsy

Routine SNB	*Controversial Applications of SNB*	*Contraindications to SNB*
Clinical stage I–IIIA (for T3 tumors, data is limited and ALND is advised if success of SN mapping is in question)	Prophylactic mastectomy	Inflammatory breast cancer
Clinically node-negative	Previous SNB or ALND	Clinical N2 axillary disease
Unifocal or multicentric disease	DCIS	
Either gender	Suspicious axillary lymph nodes	
All ages	Preoperative chemotherapy	
Previous fine-needle aspiration, core biopsy, or excisional biopsy		

SNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; DCIS, ductal carcinoma *in situ*.

Acceptable Circumstances

Patient-Related Factors

A variety of factors contribute to the success of SNB, including patient characteristics, tumor features, and technical expertise. SNB has been used successfully in both male and female patients (86) and in all age groups (5). There is no age at which SNB is contraindicated; however, the identification of the SN has been less successful in older patients (27,87). The failed identification rate is 0.3% for age 39 or less and 2.7% for age 70 or older (60). There is also a progressive increase in failure rate as BMI increases above 26 (27,34). Identification in these groups of patients can be improved with isotope and dye combination.

Tumor-Related Factors

SNB has been performed for invasive ductal carcinoma, invasive lobular carcinoma, and other histologic subtypes. SNB for ductal carcinoma *in situ* (DCIS) is recommended for mastectomy patients or in cases where there is suspicion of invasive disease (66). The routine use of SNB for patients with DCIS who are not undergoing mastectomy is not recommended and is discussed in detail in Chapter 23.

Multicentric Disease

Multifocality and multicentricity were initially considered relative contraindications to SNB, but this is no longer the case. There are a number of studies evaluating SNB in multicentric disease using a variety of methods that report an identification rate between 85.7% to 100%, FN rate of 0% to 33.3%, and an accuracy from 77.8% to 100%. A recent meta-analysis was reported evaluating 932 patients with multicentric or multifocal breast cancer who had SNB followed by ALND (88). The authors identified an overall accuracy rate of 96.7% with a FN rate of 7.7%. Among those with a FN SNB, 7/37 had either received neoadjuvant therapy or had tumor size greater than 5 cm. With exclusion of those with a relative contraindication to SNB, the FN rate was decreased to 6.3%. The anatomic studies discussed in the earlier section on Lymphatic Anatomy also support the use of SNB in multifocal or multicentric cancers.

Type of Operative Procedure

The SN can be identified successfully when performing breast-conserving surgery, mastectomy, skin-sparing and nipple-sparing mastectomy for unilateral disease, or synchronous bilateral lesions. When mastectomy with immediate reconstruction is planned, staged SN biopsy may be used before mastectomy, facilitating surgical planning to avoid the complications of discovering a tumor-positive SN after reconstruction, especially when autologous tissue, such as a free-flap, is used. In cases of nipple-preserving mastectomy where viability of the nipple areolar complex is a concern, it may be prudent to avoid injecting dye or isotope directly under the nipple areolar complex which could impair circulation.

The performance of a diagnostic surgical biopsy was considered a contraindication to SNB in some early studies based on the hypothetical premise that the draining lymphatics were transected and mapping would be unreliable (89). This concern was initially refuted by Haigh et al. (90) who demonstrated that biopsy method (FNA, CNB, or excision), excision volume, time from initial biopsy to SNB, tumor size, and tumor location did not affect identification or accuracy by univariate and multivariate analysis. These findings have been confirmed by others. A recent meta-analysis of 18 studies that determined FN rates and 68 studies that determined SN identification rates in head-to-head comparisons of patients with and without history of previous surgical manipulation of the primary breast lesions reported pooled SN detection rates of 91.3% and 92.8% in those with and without prior surgical breast biopsy, respectively (91). The use of SNB in prophylactic mastectomy is advocated by some because of a low but real incidence of occult invasive carcinoma (3.2%–5%) (92). The use of MRI has been evaluated to determine its utility in identifying patients who would benefit from SNB (93,94). In a study of 56 patients who underwent prophylactic mastectomy, 6 occult cancers, 5 DCIS, and 1 invasive ductal carcinoma were identified, all with negative SNBs. The use of MRI in addition to SNB increases costs and, in this study, failed to identify a significant number of patients with occult malignancies. In another study of prophylactic mastectomy, SNB was performed in 393 of 529 patients (74%), 178 of whom underwent MRI. Of these, occult cancer was found in 6 of 178 patients (3%), all of whom had negative SNB. Preoperative MRI was concordant with PM in four of six cases with occult carcinoma. In 136 patients undergoing prophylactic mastectomy with SNB, 57 had preoperative MRI. MRI detected five cancers and prophylactic mastectomy revealed an additional four occult carcinomas not detected by MRI. The authors concluded that MRI accurately ruled out the presence of an invasive cancer in the prophylactic breast, suggesting that MRI can be used to select patients for prophylactic mastectomy without SNB.

In general, high-risk patients who undergo prophylactic mastectomy may be considered for SN biopsy at the time of surgery because identification of an unsuspected cancer in the mastectomy specimen could potentially require an ALND that could have been avoided by the minimally invasive SNB.

CONTROVERSIAL APPLICATIONS OF SENTINEL LYMPH NODE DISSECTION

The greatest amount of information on SNB has been in patients with early stage disease that is clinically node-negative. These are the conditions under which the procedure has been validated. Attempts to incorporate this methodology for other clinical presentations, as listed next, have been reported in small single institution studies and should be considered as not having the same degree of validation.

Previous Axillary Surgery

SNB after prior breast conservation and axillary surgery has been successful at Memorial Sloan-Kettering Cancer Center (95). The SN was identified in 55% (64/117) of the cases that had had previous axillary surgery or a failed sentinel lymphadenectomy. Positive SNs were identified in 16% of the successful cases. The FN rate was 9% for reoperative SNB. The redo SNB was more likely to be successful after a previous SNB rather than an ALND. There was a higher rate of nonaxillary drainage with redo SNB than with primary SNB (30% vs. 6%; $p < .0001$). Reoperative SNB was feasible in this small series of patients, but more information is necessary before this can be recommended routinely. Several smaller studies reported successful reoperative SN mapping in 63% to 97% (96). In the study by Intra et al. (97) the SN identification rate was significantly higher because they excluded patients who had prior ALND for axillary staging. At median follow-up of 45.9 months, no axillary recurrences were observed.

Suspicious Axillary Lymph Nodes

Clinically suspicious axillary nodes have been considered a relative contraindication to SNB. Prior core or excisional breast biopsy for diagnosis can result in inflammatory

changes in lymph nodes that are free of tumor. The correlation of clinical examination and pathologic nodal assessment indicates that the risk of lymph node metastasis is 40.4% if the clinical assessment is negative, 61.5% if the lymph nodes are palpable but not suspicious, and 84.4% if clinically suspicious (98). Clinical examination is subject to false-positive results in 53% of patients with moderately suspicious nodes and 23% of those with highly suspicious nodes (99).

There is no reason to exclude such patients from SNB as long as the clinically suspicious node is resected and analyzed. Alternatively, a suspicious node can be evaluated preoperatively with axillary ultrasound and fine-needle aspiration (FNA) or core needle biopsy. Sensitivity of axillary ultrasound has been reported to range from 21% to 86% with sensitivity rates increasing with increasing size of lymph node metastases. Addition of FNA of lymph nodes that appear abnormal by ultrasound increases the sensitivity of detecting nodal disease to 82% to 89% (100). In patients with clinically suspicious axillary lymph nodes on examination, a negative axillary ultrasound would indicate that the patient is a good candidate for SNB. Any palpable or abnormal lymph nodes detected intraoperatively at the time of SNB should be resected as sentinel nodes, regardless of whether these nodes were mapped by blue dye or radioisotope. It is not clear that patients with a needle biopsy-proven nodal metastasis should be excluded from application of the Z011 data or that the involved node is in reality a SN identified by imaging.

CONTRAINDICATIONS TO SENTINEL LYMPH NODE BIOPSY

Pregnancy and Lactation

The safety of SNB with radioisotope in pregnancy has been studied by Pandit-Taskar et al. (101) at Memorial Sloan-Kettering Cancer Center. Retrospective data from nonpregnant women with breast cancer and SN biopsy was used in a phantom model calculation of the radiation-absorbed dose after a single intradermal dose of 99mTc-sulfur colloid 0.1 mCi on the morning of surgery or 0.5 mCi on the afternoon before surgery. The highest estimated dose received by the fetus was seen with the 2-day protocol, measured at 0.014 mGy, which is less than the National Council on Radiation Protection and Measurements limit to the pregnant woman. The clinical application in pregnancy or lactation has been limited and questioned. Spanheimer and colleagues (102) conducted a prospective study of 14 pregnant breast cancer patients who underwent SNB with lymphatic mapping by technetium sulfur colloid injection where total uterine radiation dose was calculated based on abdominal, perineal, and urinary radiation measurements. The investigators found that the average total uterine radiation dose following radioisotope injection and lymphoscintigraphy for SNB was significantly less than the average daily background radiation (1.14 +/- 0.76 microGy vs. 8.2 microGy, respectively).

Limited data exist for dye usage in pregnancy. Methylene blue dye has been shown to cause intestinal atresia secondary to vasoconstrictive effects of inhibiting nitric oxide, and is considered to be contraindicated in pregnancy (103). However, some argue that the dose of methylene blue delivered for SN mapping is far lower than the levels that could cause harm (104). A pharmacokinetic study of methylene blue dye in 10 non-pregnant women estimated a maximum dose of methylene blue dye to the fetus to be 5% of the administered dose after adjustment for increased volume of distribution, intravascular volume, and renal clearance. Investigators at Lee Moffitt conducted a prospective study where SNB was performed with isosulfan blue dye in eight breast cancer patients (six with technetium sulfur colloid, two with blue dye alone) who were an average of 15.8 weeks pregnant (105). All patients had successful SN mapping, and there were no intra-operative complications associated with use of the blue dye. All patients delivered healthy babies without any reported abnormalities at 1.82 years of follow-up with exception of one who chose to terminate her pregnancy prior to starting chemotherapy.

Although radiolabeled technetium is safe in pregnancy, clinicians are reluctant to use it. The 2012 NCCN guidelines state that radiocolloid appears to be safe for SNB in pregnancy; however, use of blue dye remains contraindicated. Isosulfan blue dye and methylene blue dye are currently considered Class C drugs in pregnancy.

Advanced Disease

Grossly palpable, N2 lymph nodes have been a contraindication for SNB. Axillary evaluation with ultrasound and needle biopsy of suspicious nodes can identify tumor-positive lymph nodes and avoid SNB. If the cytology or histology of the node is negative, staging with SNB is reasonable, as long as the palpable node is also removed. One contraindication to SNB after neoadjuvant chemotherapy is inflammatory breast cancer (106) where studies report SN identification rates of 80%–85% and high FN rates (6%–18%).

While SNB is contraindicated in locally advanced disease, one area of controversy exists in patients that initially present with documented axillary metastases but are converted to clinically node-negative status following a clinical response to neoadjuvant chemotherapy. Shen et al. (107) performed SNB followed by ALND in 69 patients treated with preoperative chemotherapy who had biopsy-proven axillary metastases prior to chemotherapy. SN identification rate was 92.8% but the FN rate was 25%, leading the authors to conclude that SNB is technically feasible but unreliable in this cohort of patients.

This question has been further addressed by the ACOSOG Z1071 trial where patients with clinical T1–4, N1–2 invasive breast cancer at initial diagnosis had SNB followed by ALND after neoadjuvant chemotherapy (108). A Bayesian study design with a noninformative prior was chosen to assess whether the primary endpoint, the FN rate of SNB, would be greater than 10%. The study accrued 756 patients from 136 institutions. Of those who had SNB followed by ALND (n = 643), the SN identification rate was 92.5% with FN rate of 12.6%. The authors concluded that the FN rate of SNB was greater than the pre-specified study endpoint of 10%, and that further analysis of factors associated with FN rates should be performed before performing SNB in these patients.

CONCLUSION

Evaluation of the status of the axilla in invasive breast cancer is important for staging, prognosis, and perhaps survival. Although the status of the axilla was formerly the most important factor for adjuvant treatment recommendations, other factors related to tumor size, tumor features, molecular profiles, and patient age are increasingly entering the algorithm. Axillary treatment by ALND or axillary irradiation achieves excellent regional nodal control. Such treatment is associated with a potentially significant degree of chronic morbidity. SNB has replaced ALND for axillary staging in clinically node-negative patients even in some whose SN is positive. Biologic factors of the primary tumor may prove to play a more significant role in determining prognosis and response to therapy with advances in molecular profiling and whole genome sequencing limiting the role of SNB.

MANAGEMENT SUMMARY

- SNB is a staging procedure that can be performed with vital dyes, radioactive tracers, or a combination of the two.
- SNB alone for a negative SN accurately stages the axilla and is associated with isolated recurrence in the axilla in fewer than 1% of cases.
- SNB alone is appropriate for clinically node-negative women with a tumor positive SN undergoing lumpectomy with radiation.
- The early and late postoperative morbidity of SNB is significantly lower than the morbidity of axillary dissection, but lymphedema occurs in about 5% of patients.
- SNB is contraindicated for inflammatory carcinoma and grossly palpable axillary disease.
- Age, tumor histology, tumor location, and biopsy type are not contraindications to the use of SLND.

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CHAPTER 38

Axillary Dissection

Hiram S. Cody III and George Plitas

CHAPTER CONTENTS

INTRODUCTION

For patients with operable breast cancer, axillary node status remains the single most important prognostic factor. The primary goal of axillary surgery is staging to govern the use and type of systemic therapy; secondary goals include local control and the possibility of a small survival benefit. Axillary lymph node dissection (ALND) has been regarded for most of the 20th century as the "gold standard" operation to achieve these goals, but has largely been replaced over the past decade by sentinel lymph node (SLN) biopsy, first reported by Krag et al. in 1993 (1) and Giuliano et al. in 1994 (2). SLN biopsy allows the avoidance of ALND in SLN-negative patients, sparing them the morbidity of a larger operation, and allows the routine performance of additional pathologic studies, potentially increasing the accuracy of staging. Sixty-nine observational series (3) of SLN biopsy validated by a "backup" ALND, three meta-analyses (4–6), and the early results of seven randomized trials (4) comparing ALND with SLN biopsy confirm that the morbidity of SLN biopsy is less than ALND, that staging accuracy is at least equivalent, and (in the single randomized trial reporting long-term results (7) that survival and other disease-related adverse events are comparable at 7 years' follow-up. While the role of ALND in the era of SLN biopsy has been reduced, it has not been eliminated, and this chapter surveys the historic evolution, current indications, operative technique, and morbidity of ALND. Looking ahead, prognostication through rapidly emerging genomic technologies may eventually rival (or even surpass) that of conventional histopathology, and the role of ALND will continue to change.

THE HISTORIC EVOLUTION OF ALND

Jean Louis Petit (1674–1750), director of the French Surgical Academy, was probably the first surgeon to articulate a unified concept for breast cancer surgery (8). He emphasized the importance of an *en bloc* resection of the breast and axillary nodes, but his insight came too early: even by the mid-19th century, breast cancer was widely regarded as incurable by surgery. Halsted's landmark 1894 (9) and 1907 (10) reports of his meticulous technique for "radical mastectomy" (RM, which included removal of the breast and pectoral muscles, with a complete ALND) were the first to demonstrate that coincident with a striking reduction in LR (from 51% to 82% reported by European center to 6%), 31% of patients (a significant proportion at that time) were disease-free at 5 years. This intuitive concept relating local control and survival made RM the standard operation for breast cancer over the next 70 years, despite subsequent reports of techniques that were less radical, including modified radical mastectomy (MRM) (11). In the "Halstedian" era, the goal for ALND (as for mastectomy) was to maximize cure by minimizing local failure.

Coincident with the acceptance of MRM in the 1970s, Fisher (12) proposed that breast cancer survival was largely a function of tumor biology and not surgical technique. The "Fisher hypothesis" was tested in National Surgical Adjuvant Breast and Bowel Project (NSABP) B-04 (1971–1974) (13); patients with clinically node-positive breast cancer were randomized to RM versus total mastectomy/radiotherapy (RT), and patients with clinically node-negative breast cancer were randomized to RM versus total mastectomy/RT

versus total mastectomy alone. At 25 years' follow-up there were no differences in any category of survival (overall, disease-free, distant disease-free) between the patients in the two node-positive arms, or in the three node-negative arms of the trial. B-04 confirmed the overwhelming prognostic significance of axillary node metastasis and for this reason, ALND was incorporated into all subsequent NSABP trials for invasive breast cancer.

With a series of remarkable meta-analyses from the Early Breast Cancer Trialists Collaborative Group (EBCTCG), it has become clear that breast cancer is best viewed as a disease with a wide spectrum of behavior (14), rather than a predominantly local (Halsted) or systemic (Fisher) process. Separate EBCTCG overviews show that local control and survival are related (15) but that there is no survival advantage for more radical versus less radical versions of mastectomy (or for mastectomy vs. breast conservation) (16), and that there is an incremental survival benefit from the addition of systemic adjuvant therapy to local treatment (17). At present, virtually all node-negative patients are staged by SLN biopsy alone and the principal goal of ALND is to maximize local control in patients already proven by SLN biopsy to be node-positive.

ALND VERSUS OTHER METHODS OF STAGING

ALND can be compared with other methods of axillary staging. These are (i) no axillary surgery (with or without axillary RT), (ii) axillary sampling, and (iii) SLN biopsy.

ALND versus No Axillary Surgery

The foremost trial comparing ALND with no axillary surgery is NSABP B-04 (13) (Table 38-1), as described above. Among patients randomized to total mastectomy alone, 18% developed axillary LR as the first sign of treatment failure and required a delayed ALND; 79% of axillary LR occurred within 2 years and 95% within 5 years. Two more recent trials demonstrate far lower rates of axillary LR in older patients treated without ALND. Martelli et al. (18) randomized 219 patients (aged 65 to 80) with T1N0 disease to breast-conservation surgery with or without ALND, and all patients received 5 years of tamoxifen. At 5 years' follow-up there were no differences in disease-free or overall survival, and axillary LR in the no-ALND arm was 1%. Rudenstam et al. (19) randomized 473 patients (aged 60 years or more) to breast surgery with or without ALND; all patients received 5 years of tamoxifen. At 6.6 years' follow-up there were no differences in disease-free or overall survival, and axillary LR in the ALND and no-ALND arms was 1% and 3%, respectively.

The addition of axillary RT improves local control in patients treated without axillary surgery (Table 38-1). In NSABP B-04 (13), locoregional recurrence at 10 years was lower with total mastectomy/RT than with total mastectomy alone (5% vs. 31%), as was axillary LR (3% vs. 19%). In the Cancer Research Campaign (King's/Cambridge) trial (20), 2,268 patients were randomized to total mastectomy/RT (to chest wall and axillary nodes) versus total mastectomy alone; again, crude LR was lower in the RT group (5% vs. 15%), as was axillary LR (2% vs. 13%). In a randomized trial from the Institut Curie, the authors compared the results of ALND and axillary RT in 658 patients; they observed a survival advantage for ALND at 5 years (21), but no survival differences between groups at 10 and 15 years (22). Axillary LR occurred slightly less often after ALND than after axillary RT (1% vs. 3%, $p = .04$). Finally, Veronesi et al. (23) randomized 435 patients, none of whom had ALND, to breast conservation with or without axillary RT. At 5 years' follow-up they found no differences in disease-free survival, and axillary LR in the axillary RT and no-ALND arms was 0.5% and 1.5%, respectively. Three observational studies also report high rates of axillary LR in the untreated axilla and also show that axillary LR is highly dependent on tumor size (Table 38-1) (24–26). Tumor characteristics alone, however, cannot reliably predict axillary node status with greater that 90% to 95% accuracy (27). Bevilacqua et al. (28) have recently developed a multivariate nomogram for the prediction of SLN metastases, using a sophisticated model based on 3,786 SLN biopsy procedures and prospectively validated in 1,545 subsequent procedures. They too find that the prediction of SLN status is imperfect, with only a 75% chance, between two randomly selected individuals (one of whom is node-positive), of correctly identifying the node-positive patient.

Others have asked whether noninvasive imaging can replace surgical staging. Neither CT nor MRI is adequate for lymph node staging. PET lacks the resolution to detect metastases smaller than 5 mm, so is subject to false-negative and false-positive results; in five reports, sensitivity ranges from 27% to 94%, and specificity from 43% to 97% (29–33). The results of axillary ultrasound (US) with fine-needle aspiration (FNA) vary widely, reflecting differences in methodology and case selection, but allow triage of FNA-positive patients directly to ALND (34). US-guided FNA of axillary nodes can spare patients the added time and cost of SLN biopsy, but is insufficiently sensitive to replace surgical staging.

ALND versus Axillary Sampling

As practiced in the United Kingdom, axillary sampling is a limited staging operation in which about four nodes are removed from the low axilla, guided by intraoperative palpation. Two randomized trials from Edinburgh have compared axillary sampling with ALND, for patients having mastectomy (with 11 years' follow-up) (35) or breast conservation (wide excision/breast RT, with 4 years' follow-up) (36) (Table 38-2). Node-positive patients in each trial received axillary RT. Between sampling and ALND, the authors observed a comparable proportion of positive axillae, comparable rates of axillary LR (5.4% vs. 3%), and comparable survival between the two arms of each study, but greater long-term shoulder morbidity for patients who had sampling/RT compared to ALND. Since none of the UK axillary sampling data have been validated by a backup ALND (as has been done for SLN biopsy), one cannot calculate the performance characteristics of this method. In a separate Swedish study by Ahlgen et al. (37), axillary sampling ("five node biopsy") was validated by a planned backup ALND in 415 patients, and sensitivity for cN0 patients was 95.5%.

ALND versus SLN Biopsy

Seven randomized trials compare ALND and SLN biopsy (4), allocating patients to ALND versus SLN biopsy (plus ALND for SLN-positive patients), and collectively confirm that the staging accuracy of ALND and SLN biopsy is comparable, and that the morbidity of SLN biopsy is less. For two of the trials (38,39) patients in the ALND arm also had SLN biopsy, confirming false-negative rates for SLN biopsy of 8.8% and 9.7%, respectively. In the one trial (7) reporting long-term follow-up there were no differences in survival or in any other disease-related adverse events at 7 years, and there was a single case of axillary node recurrence following a negative SLN biopsy.

TABLE 38-1

Studies of Axillary Treatment (ALND or RT) versus No Axillary Treatment in cN0 Breast Cancer

	NSABP B-04 (13) (1971–1973)	*Milan (18) (1996–2000)*	*SBCSG (19) (1993-2002)*	*King's/ Cambridge (20) (1970–1975)*	*Curie (22) (1982–1987)*	*EIO (23) (1995–1998)*	*Baum and Coyle (26) (1973–1977)*	*Baxter et al. (25) (1977–1986)*	*Greco et al. (24) (1986–1994)*
Design	RCT	RCT	RCT	RCT	RCT	RCT	Cohort	Cohort	Cohort
Breast treatment	Mastectomy	BCT	BCT or mastectomy	Mastectomy	Wide excision/ RT	BCT	Mastectomy	Wide excision/ RT	Wide excision/ RT[a]
Axillary treatment	ALND vs. Ax RT vs. none	ALND vs. none	ALND vs. none	Ax RT vs. none	ALND vs. Ax RT	no ALND vs. Ax RT	none	none	none
No. of patients	1,079	219	473	2,268	658	435	48	112	401
Follow-up	25 yr	5 yr	6.6 yr	1–5 yr	15 yr	5 yr	1–4 yr	10 yr	5 yr
Axillary local recurrence	ALND 1.4% Ax RT 3.1% none 19%	ALND 0% none 1%	ALND 1% none 3%	Ax RT 5% none 15%	ALND 1% Ax RT 3%	none 1.5% Ax RT 0.5%	21%	T1a, b 9% T1c 26% T2 33% *Overall 28%*	T1a 2.0% T1b 1.7% T1c 10% T2 18% *Overall 7%*
Overall survival	no difference	no difference	no difference	no difference	no difference	no difference	—	—	—
NED survival	no difference	no difference	no difference	no difference	no difference	no difference	—	—	—

SBCSG, Swedish Breast Cancer Study Group; EIO, European Institute of Oncology; ALND, axillary lymph node dissection; RCT, randomized controlled trial; RT, radiotherapy; NED, no evidence of disease; wide excision/RT indicates RT to breast only; ax RT indicates RT to axilla.
[a]96% had wide excision/RT and 4% had mastectomy.

TABLE 38-2

Studies of ALND versus Axillary Sampling

	Edinburgh I (35) (1980–1983) T1-3N0-1	*Edinburgh II (36) (1987–1995) T1-3N01*
Design	RCT Mastectomy: Randomized to ALND vs. sampling	RCT Lumpectomy/ breast RT: Randomized to ALND vs. sampling
No. of patients	417	466
Follow-up	11 yr	4 yr
Axillary local recurrence	ALND 3.0% Sampling[a] 5.4%	ALND 3.4% Sampling[b] 3.0%
Overall survival	no difference	no difference
NED survival	no difference	no difference

[a]All received axillary RT if node-positive.
[b]All received axillary RT if node-positive; 39 node-negative patients (1987–1990) also received axillary RT.

INDICATIONS FOR ALND

In the simplest sense, ALND would seem to be indicated for any patient with a "contraindication" to SLN biopsy. In fact, most of the putative contraindications to SLN biopsy (including, among others, prior surgical biopsy, nonpalpable lesion, multicentric tumor, and T2 to T3 disease) have been disproved, and SLN biopsy is suitable for virtually all patients with clinical stage T1-3N0 invasive cancers (40). While the role of ALND has diminished in the era of SLN biopsy, there are at least nine clear indications to perform it (Table 38-3).

A Clinically Positive Axilla

Most patients with clinically positive axillae require ALND. However, since clinical axillary examination is equally subject to false-negative and false-positive results (41), the clinically positive axilla is not an absolute indication for ALND and should be validated histologically. In our own experience (42), 25% of patients with highly suspicious axillary nodes on clinical assessment proved to be benign at the time of SLN biopsy. As noted above, there is a role for preoperative axillary US and US- or palpation-guided FNA, allowing patients with proven nodal metastases to avoid SLN biopsy and proceed directly to ALND (34).

TABLE 38-3

Indications for ALND in the Era of SLN Biopsy

Patients outside the ACOSOG Z0011 entry criteria[a]
Prior inadequate ALND
Validation trials of SLN biopsy
Failed SLN biopsy
Clinically suspicious nodes identified at surgery
T4 disease
Unavailability of SLN biopsy
Axillary local recurrence (ipsilateral or contralateral) in previously treated patients

[a]T3, clinically positive axilla and biopsy-proven nodal metastases, positive SLN with disease requiring mastectomy, more than two positive SLN or matted axillary nodes.

Prior Inadequate ALND

What constitutes an "inadequate" (or an "adequate") ALND? In the NSABP B-04 trial, Fisher et al. (41) found that the proportion of cN0 patients with positive axillae was the same whether 3 to 5, 6 to 10, 11 to 15, or 16 to 20 nodes had been removed (i.e., the removal of relatively few nodes was sufficient to establish whether the axilla was positive or negative), but that the proportion with 4 or more nodes positive was highest when 26 or more nodes had been removed (i.e., a more complete node dissection was necessary to correctly determine the *degree* of node involvement). They also observed no cases of subsequent axillary LR when 6 or more nodes had been removed.

The apparent adequacy of ALND is multifactorial. First, while the operative technique is well defined, the performance of ALND in practice varies widely. Second, there is wide variation in the thoroughness with which pathologists examine the ALND specimen. Finally, in a small minority of patients very few nodes will be found despite an anatomically correct ALND and a thorough pathologic assessment. For those patients who have had a recent ALND in which (i) the anatomic extent of surgery cannot be documented, (ii) the gross specimen is not available for reexamination, (iii) few nodes have been removed, and (iv) most are positive (raising concern about residual gross axillary disease), it is quite reasonable to perform a completion ALND, or to consider axillary RT.

A Positive SLN

ALND was considered the standard care for all patients with a positive SLN until recently. The ACOSOG Z11 trial randomized SLN-positive patients to ALND versus no further surgery; all had clinical stage T1-2N0 disease, no more than 2 positive SLN, and were treated with lumpectomy and whole-breast (but not axillary) RT (43,44). Among those randomized to ALND additional positive axillary nodes were found in 27% of patients, but the performance of ALND did not alter systemic therapy and at a median follow-up of 6.3 years there were no significant differences in disease free (82.8% vs. 83.8%) or overall survival (91.9% vs. 92.5%), or in regional node (0.5% vs. 0.9%), breast (3.6% vs. 1.9%), or overall locoregional recurrence (4.1% vs. 2.8%, $p = .53$). Whether these practice-changing results can be extrapolated to women outside the Z0011 entry criteria (for example, those having mastectomy without RT, those with more than 2 positive SLN, or those receving neoadjuvant chemotherapy) remains unproved. A parallel trial, EORTC AMAROS (45), randomized SLN-positive patients to ALND versus axillary RT; the investigators have reported no differences between arms in the usage of local or systemic adjuvant therapy, but have not yet reported longer-term outcomes.

Validation Trials of SLN Biopsy

SLN biopsy is a *diagnostic test* for the presence of axillary node metastases, and is measured by standard test characteristics: sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy. These do not

require a randomized trial, but do require that SLN biopsy be validated by an immediate planned "backup" ALND. In an overview (1) of 69 observational (nonrandomized) studies of SLN biopsy with planned ALND (comprising 8,059 patients), the success and false-negative rates were 96% and 7%, respectively. The UK ALMANAC trial (46) required each of its initial participant surgeons to do 40 SLN procedures validated by an ALND, with threshold success and false-negative rates of 95% and 5%, respectively, prior to entering the randomization phase; they observed a shorter "learning curve" than expected, with most failed and false-negative results occurring in the very first procedure. This observation is supported by the NASBP B-32 trial (39), in which a false-negative rate of 9.7% did not significantly decline with increasing surgeon experience.

Failed SLN Biopsy

With increasing experience, the success rate of SLN biopsy approaches but does not equal 100%. For that small fraction of failed SLN biopsy procedures, or for an SLN procedure that is technically unsatisfactory in any other way, it is reasonable to perform ALND (47).

Clinically Suspicious Nodes at SLN Biopsy

During SLN biopsy, a small proportion of patients will have a marked reactive adenopathy that is grossly indistinguishable from cancer. In this setting, benign intraoperative assessment (frozen section or imprint cytology) may not be completely reassuring, and it is reasonable on the basis of clinical suspicion alone to proceed with ALND (47).

Neoadjuvant Chemotherapy for Inflammatory Cancer

The suitability of SLN biopsy for T2 and T3 breast cancers is well established, but an overview (48) of 21 small validation studies of SLN biopsy after neoadjuvant chemotherapy (given largely for noninflammatory cancers) observed success and false-negative rates (91% and 12%, respectively) somewhat inferior to those of SLN biopsy in general. In a separate study (49), 56 patients with axillary node metastases proven by FNA had neoadjuvant chemotherapy followed by SLN biopsy with a planned ALND; while 31% had a pathologic complete response, the false-negative rate of SLN biopsy in the remaining patients was unacceptably high (25%). A meta-analysis of 21 published studies, which included 1,273 patients who underwent SLN biopsy with subsequent ALND after preoperative chemotherapy, reports an SLN identification rate of 90% and a false-negative rate of 12% (50). Results from the ACOSOG trial Z1071 that investigated the role of SLN biopsy in clinically node-positive patients undergoing induction chemotherapy were recently published in abstract form (51). In this trial, women with T0-4, N1-2, M0 breast cancers receiving neoadjuvant chemotherapy were enrolled to undergo SLN biopsy followed by ALND at the time of surgery. The SLN correctly identified the nodal status of 84% of all patients and was associated with a false-negative rate of 12.8%. After neoadjuvant chemotherapy, SLN biopsy may be reasonable for patients with T2 and T3 tumors, but ALND should remain standard care for patients with T4 (inflammatory) cancers.

Unavailability of SLN Biopsy

SLN biopsy is not universally available, especially in developing nations where the added logistics and cost may prove to be excessive. Since the potential impact of SLN biopsy worldwide is substantial (a significant proportion of clinically diagnosed breast cancers are still node-negative), the challenge will be to find ways to minimize the cost of SLN biopsy while maintaining accuracy. Where SLN biopsy is not available, ALND should remain standard care.

Isolated Locoregional Recurrence

Axillary local recurrence after a negative SLN biopsy is rare and comparable to that after ALND, occurring in less than 1% of patients (52). Most axillary masses that appear after SLN biopsy are benign, but for those that are proven malignant ALND is indicated. ALND is also indicated for those patients who relapse in the contralateral axilla and do not have other distant sites of disease.

AXILLARY ANATOMY

The axillary contents lie within a complex space best described as an eccentrically shaped pyramid. Viewed through a transverse section (Fig. 38-1), the axilla is a triangular space, bounded by the chest wall medially, the subscapularis posteriorly, the latissimus posterolaterally, and the pectoralis major and minor muscles anteriorly. Viewed from the front through a coronal section (Fig. 38-2), the triangle is bounded by the axillary vein superiorly, the latissimus laterally, and the chest wall medially.

The axillary contents are arbitrarily divided into three "levels": level I lying lateral to, level II lying posterior to, and level III lying medial to the pectoralis minor muscle (Fig. 38-2). Level I comprises the largest volume of axillary tissue and the largest proportion of the axillary nodes (perhaps two-thirds), with level II comprising most of the remainder and level III 10% or less. The anatomic distinction between axillary levels I and II is somewhat arbitrary, while level III is more anatomically distinct. Historically, breast cancer prognosis was related to the "highest level" of axillary node involvement, but since about 1970 the *number* of positive nodes, and not the *level*, has emerged as the prognostically relevant variable.

The extent of ALND is formally classified as level I, level I to II, or level I to III ("complete ALND"); there is no evidence that the morbidity of ALND varies with the extent of the dissection. The historic justification for a complete ALND was the observation of "skip metastases" to levels II or III nodes with level I negative (53–55). Since most "skip metastases" were found in level II (isolated level III disease is rare), many authorities recommended a level I or II ALND as standard care. At present, "skip metastases" are best viewed as level II or III SLN which happen to receive lymphatic drainage *directly from the breast*. These nodes should be readily identified by lymphatic mapping and submitted for pathologic exam as SLN.

In our own practice, ALND is usually a level I to II dissection, but we perform a complete (level I to III) ALND in patients with high-risk (T3 to T4) tumors or with grossly suspicious nodes identified at surgery.

TECHNIQUE OF ALND

ALND is best done under general anesthesia, but for patients with comorbidity is feasible under local anesthesia with sedation. The incision is either separate from or contiguous with the incision used for the breast operation. Separate axillary and breast incisions are cosmetically superior to contiguous ones, but a contiguous incision is reasonable for patients either having mastectomy without reconstruction,

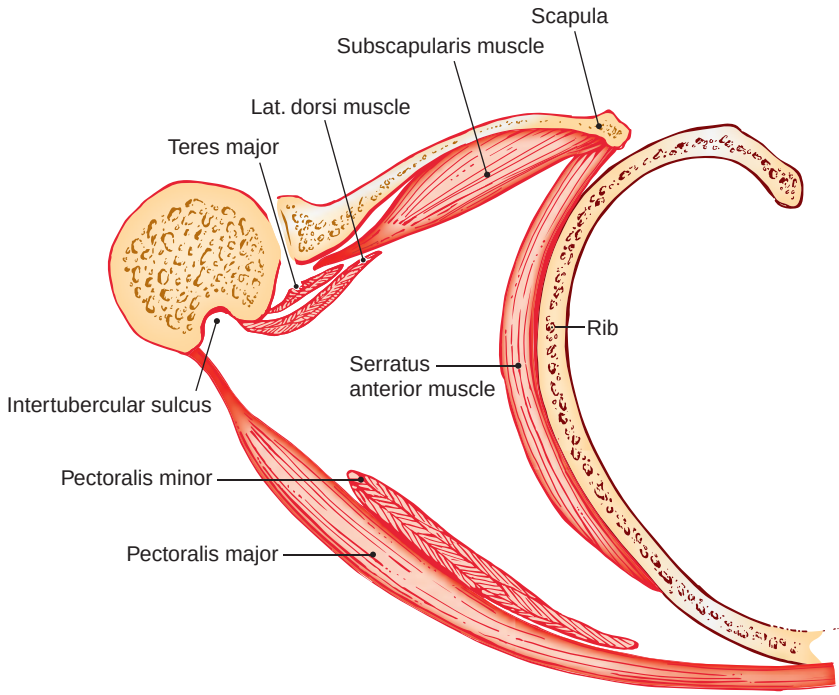

FIGURE 38-1 The anatomic boundaries of ALND, as seen in a transverse section through the midportion of the axilla, showing the pectoralis major and minor anteriorly, the serratus medially, and the latissimus and subscapularis posteriorly.

or having breast conservation for tumors very high in the axillary tail.

The foremost technical element of ALND is to fully dissect the skin flaps to their anatomic limits (the axillary vein superiorly, the pectoralis major superomedially, the serratus inferiorly, and the latissimus laterally) *prior* to entering the axilla; virtually all technical difficulties with ALND stem from inadequate flap elevation at the outset of the procedure. The dissection is carried around the lateral border of the pectoralis major, taking care to avoid injury to the medial pectoral nerve.

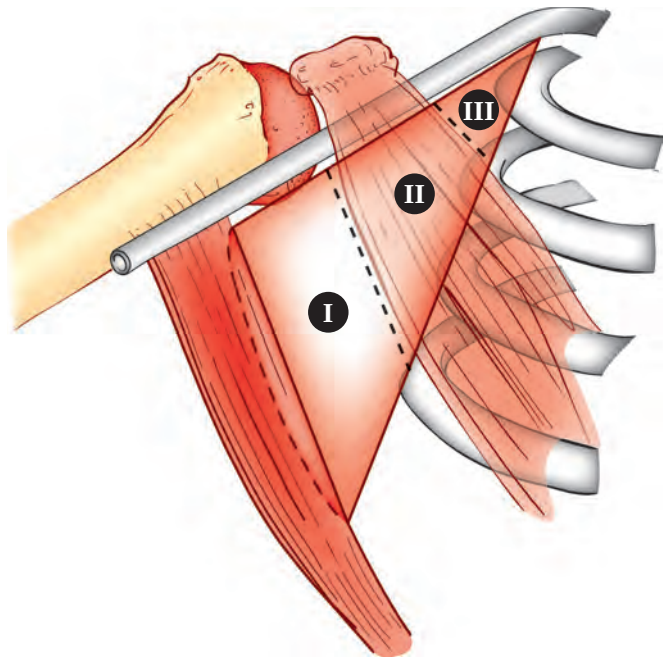

FIGURE 38-2 The anatomic extent of ALND, with "levels" I, II, and III designated as lying lateral to, behind, or medial to the pectoralis minor muscle.

The clavipectoral fascia is incised just anterior to the axillary vein and just lateral to the pectoralis minor, and with this step the axillary contents can be mobilized inferolaterally, completely exposing the axillary vein superiorly and the medial pectoral neurovascular bundle medially as it courses around the lateral border of the muscle. The arm is adducted and the major and minor are retracted medially, exposing level II. If gross axillary disease is palpable in levels II to III, the insertion of the pectoralis minor on the coracoid can be divided to fully expose level III.

The axillary contents are mobilized laterally off the chest wall, ligating side branches of the axillary vein as they are encountered. The long thoracic nerve (innervating the serratus anterior) and thoracodorsal nerve (innervating the latissimus dorsi) are identified and preserved, and the operation is completed by dissecting along the thoracodorsal neurovascular bundle and handing off the operative specimen. A closed suction drain is placed and the skin incision is closed.

Patients having ALND with breast conservation are normally discharged the day of surgery, and with mastectomy on the following day. All patients are instructed in wound care, given a log book to record their wound drainage (the drains are removed when 24-hour drainage is less than 30 cc), and given a program of postoperative shoulder exercises which they can usually begin immediately (except in the setting of breast reconstruction). Patients are encouraged to resume using their arm as soon, and as normally, as possible.

COMPLICATIONS OF ALND

Lymphedema

Lymphedema is the single complication of greatest concern to patients, and is the subject of an extensive but problematic literature. There are no large population-based studies that estimate the incidence of lymphedema, and across the literature there is wide variation in the definition of lymphedema, methods of assessment, patient characteristics,

extent of surgery, extent of RT, and length of follow-up. In a classic 1986 report, Kissin et al. (56) found that (i) lymphedema was more frequent when measured by arm volume (25.5%) than by patient self-assessment (14%); (ii) the frequency of subjective late lymphedema was similar for axillary RT alone (8.3%), axillary sampling plus RT (9.1%), and ALND (7.4%); and (iii) lymphedema occurred far more often after ALND plus RT (38%, $p < .001$). In a comprehensive 2001 overview, Erickson et al. (57) cite 10 more recent studies (1991–2000) in which the incidence of lymphedema ranged from 2% to 43%, and appeared to increase with patient age, body mass index, and length of follow-up.

The most useful current data regarding lymphedema will come from the four randomized trials that compare ALND with SLN biopsy, three of which report less arm swelling with SLN biopsy (38,39,58). In the ALMANAC trial (58), the patient-reported incidence at 12 months of moderate or severe lymphedema was less with SLN biopsy than with ALND (5% vs. 13%) and the relative risk of *any* lymphedema (for SLN biopsy relative to ALND) was 0.37 (95% CI 0.23–0.60). Regarding lymphedema and all of the other side effects of ALND, it is worth noting in the current era of SLN biopsy that the sequelae of ALND are not as severe as patients may expect, and that the sequelae of SLN biopsy may exceed expectations: in a recent report from the prospective ACOSOG Z0010 trial (59) (comprising 5,327 patients), lymphedema developed following SLN biopsy in 6.9% of patients at 6 months.

Standard recommendations to patients for the prevention of lymphedema include the avoidance of (i) trauma or injury, (ii) infection, (iii) arm constriction (especially by blood pressure cuffs), and (iv) heavy lifting or repetitive motions (57). These recommendations are deeply entrenched in the medical and nursing literature, but there is no evidence that any of them are effective in avoiding lymphedema, or that lymphedema *can* be avoided; they may even have the unintended consequence of making a patient feel that the lymphedema is *her fault*, rather than a known side effect of treatment.

Lymphedema cannot be cured but it can be treated. Using various combinations of elastic compression garments, compression pumps, bandaging, exercise, and complex physiotherapy, 15 studies (1989–1991) (57) have reported reductions of 15% to 75% in arm volume or circumference. Large randomized studies are needed to determine the relative efficacy of these treatments and the natural history of lymphedema posttreatment.

Axillary Web Syndrome

Axillary web syndrome (AWS) has been long observed by surgeons but only recently named and described by Moskovitz et al. (60). AWS is a characterized by the appearance 1 to 8 weeks after ALND (or SLN biopsy) of a network ("web") of tender subcutaneous cords running from the lateral axilla down the upper inner aspect of the arm, associated with pain and limitation of arm movement. Among 750 consecutive patients, they observed AWS in 6%. The presumed cause, surgical disruption of veins or lymphatics proximally at the level of the axilla, is supported by the observation of thrombosis in subcutaneous veins and/or lymphatics in four of their patients who underwent biopsy. AWS is a benign and self-limited condition that should not be confused with lymphedema, and which does not require treatment.

Sensory Morbidity

The sensory sequelae of ALND are largely related to the division of sensory nerves, most notably the intercostobrachial nerve (ICBN), a cutaneous sensory branch of T2 that innervates the upper inner arm, axilla, and superolateral breast. Technical modifications of ALND that allow preservation of the ICBN are the subject of an enthusiastic but anecdotal literature. In the single randomized trial comparing ICBN preservation versus division (61,62), ICBN preservation reduced the size of the sensory deficit, but there were otherwise no differences between groups in pain, shoulder movement, arm circumference or presence of neuromas, either at 3 months or at 3 years of follow-up.

Shoulder Function

Restriction in shoulder range of motion (ROM) is a side effect of ALND, and of the four randomized trials, two (38,58) report less limitation in ROM after SLN biopsy than after ALND. In the ALMANAC trial (58), this difference was significant at 1 month, but shoulder ROM (flexion and abduction) improved rapidly in both groups, and at longer follow-up the difference was no longer significant. Exercises to restore shoulder ROM are an essential element of postoperative care following ALND.

Infection

Cellulitis of the arm, chest wall, or breast is a well-recognized but relatively infrequent side effect of ALND and presumably reflects a localized immune impairment from the surgery. The incidence of cellulitis is unknown, but in a careful report by Roses et al. (63) of 200 patients followed 1 or more years after ALND, 5.5% developed cellulitis, and 2% had multiple episodes. Cellulitis can arise following a nonsterile skin break (cut, abrasion, or burn) but often appears without an obvious cause. Patients are routinely advised following ALND to avoid injections, venipunctures, or IVs in the ipsilateral arm, but there is no evidence whatever that *sterile* skin punctures cause cellulitis, or that avoidance prevents either infection or lymphedema (57). Repeated episodes of infection are thought to increase the risk of lymphedema (although it remains unclear in this setting whether infection is a cause or an effect of lymphedema) and prompt treatment with oral or IV antibiotics is recommended.

ALND: FUTURE DIRECTIONS

We have entered a dynamic new era in which genomic technologies (i) suggest a new classification of breast cancer (64); (ii) appear to improve prognostication (65); (iii) may better predict which patients will (or will not) benefit from adjuvant systemic therapy (66); and (iv) promise the identification of new therapeutic targets and more effective drugs. If the prognostic and predictive power of gene expression profiling prove superior to that of conventional histopathology *and* if new classes of drugs with curative potential emerge, then ALND, lymph node staging, and breast cancer surgery in general could become obsolete. The present reality is that surgery remains the single most effective treatment for breast cancer, lymph node staging remains essential for prognostication, and ALND still has a role in achieving local control for select node-positive patients.

MANAGEMENT SUMMARY

1. SLN biopsy has largely replaced ALND as the initial axillary staging procedure of choice for patients with cN0 breast cancers.
2. Staging accuracy, local control, and survival appear to be comparable between SLN biopsy and ALND.
3. ALND is indicated for
   a. SLN-positive patients outside the ACOSOG Z0011 entry criteria, specifically:
      i. T3 disease
      ii. A clinically positive axilla and biopsy-proven node metastasis
      iii. Positive SLN with disease requiring mastectomy
      iv. More than two positive SLN or matted axillary nodes
   b. A recent inadequate ALND
   c. Validation trials of SLN biopsy
   d. A failed SLN biopsy
   e. Clinically suspicious nodes identified at surgery
   f. T4 disease
   g. Unavailability of SLN biopsy
   h. Axillary local recurrence
4. A level I to II ALND is usually sufficient. A level I to III (complete) ALND is indicated for patients with gross axillary disease.
5. Postoperative care after ALND should include shoulder exercises to maintain ROM.
6. There is no evidence post-ALND that other standard recommendations (including the avoidance of trauma or injury, blood pressure cuffs, heavy lifting or repetitive motion) are effective in preventing lymphedema.
7. There is no evidence post-ALND that the avoidance of venipuncture, injections, or IVs in the ipsilateral arm is effective in preventing either infection or lymphedema.

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CHAPTER 39

Preserving and Restoring Function after Local Treatment

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CHAPTER CONTENTS

INTRODUCTION

Primary breast cancer treatment is associated with long-term musculoskeletal problems in up to one third of patients. This is significant because of the favorable survival enjoyed by the majority of women diagnosed with breast cancer. Current estimates suggest that there are 2.9 million breast cancer survivors alive in the United States, and millions more worldwide (1). Physical impairments develop secondary to normal tissue damage inflicted through cancer removal and staging procedures. Nerves, muscles, stroma, and lymphatics fall within surgical and radiation treatment fields leaving them vulnerable to inadvertent injury. Musculoskeletal problems may develop within, adjacent to, or distant from treatment fields, manifesting as impairments in strength, flexibility, and integrated movement patterns (2). Table 39-1 lists impairments associated with breast cancer treatments, some of which may persist for decades following treatment. At all time points, impairments may be associated with disability and diminished health related quality of life (HRQOL) (3–7). The likelihood of long-term disability correlates directly with the intensity and extent of breast cancer treatment. More surgery (e.g., axillary lymph node dissection [ALND] versus sentinel lymph node biopsy [SLNB]) and more radiation (e.g., four-field versus tangent beam configurations) increase the probability that patients will develop musculoskeletal problems (3,8,9).

Empirical data now reinforce theoretical concerns that musculoskeletal pathology at surgical and radiation sites will not spontaneously resolve independent of treatment. (10). Ninety percent of breast cancer survivors report one or more adverse treatment effects 6 months following their diagnoses, with 60% endorsing multiple problems (11). Unfortunately, such problems persist for the 30% of survivors who continue to report adverse sequelae 6 years after their diagnoses (11). Elderly patients and those with elevated body mass indices are at increased risk of developing lasting functional deficits following their breast cancer treatment (12).

Despite the clear correlation between breast cancer treatment and musculoskeletal problems, tissue-level changes remain ill defined. Radiation-induced fibrosis has been implicated on the basis of long-term follow-up studies (13,14). Additional radiation-related problems include shoulder capsule and epimesial contractures, brachial plexopathies, lymphostasis leading to accumulation of inflammatory mediators (15), and muscle hypertonicity secondary to direct or neural irritation. However, no empirical links yet implicate these processes in the development of treatment-related impairments. Surgical procedures, even when limited to local tumor excision and SLNB, can produce maladaptive changes in posture and upper quadrant movement patterns. These changes are thought to be mediated through pain, scarring, and adaptive positioning in the postoperative period. Adjuvant chemotherapy may also contribute to musculoskeletal problems by reducing muscle mass (16) and oxidative capacity (17). The relative contributions of different cancer treatments and pathological processes to functional problems remain poorly characterized despite a growing understanding of treatment-related late toxicities. Manual treatments and therapeutic exercises may effectively address most problems (18), although systematic reviews, noting a paucity of rigorous randomized trials, have remarked the persistent need for better quality evidence (19).

Successful management of musculoskeletal problems depends on a patients' willingness to perform therapeutic exercises. Because treatments are active and must often be continued for extended intervals, its success requires a high level of adherence. Patient "buy in" can be substantially enhanced by the strong endorsement of the entire breast

TABLE 39-1

Physical Impairments Affecting the Shoulder, Cervical Spine, and Thoracic Spine Following Primary Breast Cancer Treatment

Shoulder Complex
Restricted scapulothoracic motion
Glenohumeral joint contracture
Pectoralis major and minor muscle shortening
Muscle weakness
Serratus anterior
Middle trapezius
Rhomboids
Hand intrinsics
Myofascial dysfunction
Middle trapezius muscle
Rhomboid muscle
Maladaptive neuromuscular recruitment patterns
Cervical Spine
Exaggerated lordosis
Myofascial dysfunction
Upper trapezius muscle
Levator scapulae muscle
Restricted range of motion
Lateral rotation
Lateral bending
Thoracic Spine
Exaggerated kyphosis
Intercostal muscle contracture

cancer treatment team. With increasing appreciation of latent treatment toxicities, prophylactic stretching and strengthening activities are now accepted as integral components of comprehensive survivorship care. In the absence of such preventative activities, breast cancer survivors, treated years previously, may become uniquely vulnerable to delayed morbidities that manifest when the musculoskeletal and other systems senesce (20). This chapter will outline the evidence base regarding the epidemiology and management of breast cancer treatment-related musculoskeletal morbidity.

EPIDEMIOLOGY

Upper quadrant disability following breast cancer treatment is primarily due to restricted range of motion (ROM), persistent pain and diminished strength. Reported incidences of these problems vary widely depending on the type of breast cancer treatment, measurement technique, and duration of follow-up. Systematic reviews consistently comment on the heterogeneity of measurement and reporting strategies that characterize the literature on treatment-related morbidity (14,21,22). None-the-less, all concur that late musculoskeletal effects are potentially prevalent and problematic among breast cancer survivors.

Loss of Range of Motion

Survivors who develop ROM deficits are more likely to report pain, reduced HRQOL and difficulty performing activities of daily living (23). Table 39-2 lists shoulder ROM deficits reported at different time points following surgery. Most patients experience an abrupt transient reduction in shoulder ROM after breast cancer surgeries (3,24). Two weeks postoperatively, incidences of restricted ROM as high as 86% have been reported following ALND, and 45% following SLNB (25). However, it should be noted that some surgeons, to reduce the risk of seroma formation, restrict active shoulder abduction to 90° until drain removal which may occur as late as 3 to 4 weeks postoperatively (26).

By 6 weeks the postoperative incidence of restricted shoulder abduction is substantially lessened to 26.5% after ALND, and 24.8% after SLNB (27). Longitudinal studies suggest that restrictions in shoulder ROM gradually resolve to near baseline in a majority of patients (5,28). However, a significant minority of patients do not recover normal shoulder ROM in abduction, forward flexion, and/or external rotation. A history of ALND, modified radical mastectomy, and radiation therapy are associated with more significant and lasting limitations (5,27,29–31). Older age and elevated BMI also increase the risk of persistent ROM deficits (30).

Pain

Recent reports have highlighted the potential for persistent and severe upper quadrant pain following breast cancer treatment (32). The presence of moderate or worse pain among breast cancer survivors is strongly associated with poor mental and physical functioning (29,33). Pain is more common after ALND and axillary/supraclavicular radiation (4,32). Few studies differentiate musculoskeletal pain from neurogenic or lymphedema-related pain. Table 39-3 lists reported pain prevalence. Reports neither specify pain etiologies, nor report consistent outcome measures (e.g., presence/absence of pain versus visual analogue scores [VAS]). The data are therefore challenging to synthesize. However, the table clearly demonstrates that a significant percentage of patients experience persistent pain in the shoulder or arm. A unique study that integrated pain maps from 343 breast cancer survivors established that post-treatment pain may affect the entirety of the upper quadrant, but occurs most commonly in the axilla (34).

Loss of Strength

Strength deficits are less prevalent immediately following breast surgery but become increasingly problematic with time. This pattern has been appreciated for grip strength. In a longitudinal cohort, mean grip strength decreased by 16.9 Nm at 6 weeks and by 41.3 Nm at 24 months after ALND, relative to preoperative values (5,27). A similar pattern was noted after SLNB though the reduction was less pronounced, 5.8 Nm at 6 weeks and 17.2 Nm at 24 months. These reductions agree with high reported prevalence of impaired grip strength, which range from 16% to 40% (23,35). The influence of Lymphedema (LE) on grip strength remain inadequately characterized but may be an important mediating factor (36). Prevalence of reduced shoulder and arm strength are also high with self-reported limitations affecting up to 69% of patients (37). Objective reductions of 10 nM in shoulder abduction strength have been detected at 12 and 24 months following treatment (5,23). Shoulder strength deficits are more common following modified radical mastectomy (38).

Musculoskeletal Syndromes

Axillary web syndrome, Figure 39-1, manifests as taut cords that extend distally along the medial arm from the treated axilla to the cubit and, at times, as far as the wrist. Incidence estimates range from 5.2% to 72%, with completion axillary dissection being a potential inciting factor (25,39,40,41,42). Retrospective studies produced lower incidence estimates (41). Pathological analyses suggest that superficial lymphatic

TABLE 39-2

Prevalence and Severity of Shoulder Range of Motion Deficits at Different Time Points Following Breast Cancer Surgery

Outcome Measure	*Author (Reference)*	*Elapsed Time after Breast Cancer Surgery*[a]											
		6 wks		*3 mos*		*6 mos*		*9–12 mos*		*18–24 mo*		*>2 yrs*	
		ALND	*SLNB*	*ALND*	*SLNB*	*ALND*	*SLNB*	*ALND*	*SLNB*	*ALND*	*SLNB*	*ALND*	*SLNB*
Mean decrease from ipsilateral baseline AB	Rietman et al. 2003, 2006 (27,5)	26.4°	24.7°							21.0°	5.5°		
	Purushotham et al. 2005 (60)							6.3°	3.1°				
	Mansel et al. 2006 (28)			4.2°	1.9°	2.3°	1.5°	1.9°	2.5°				
	Husted Madsen et al. 2008 (61)					11.0°	5.0°			9.0°	4.0°		
Mean difference in AB relative to untreated shoulder	Hack et al. 1999 (35)											6.4°	
	Kaya et al. 2010 (33)							14.4°					
ROM <160° AB	Ernst et al. 2002 (38)							14.0%				8.0%	
ROM <20° normal value ≥1 plane	Langer et al. 2007 (62)											11.3%	3.5%
Self-reported limitation ROM	Leidenius et al. 2005 (63)											34.0%	16.0%
	Warmuth et al. 1998 (64)											8.0%	
	Veronesi et al. 2003 (65)					27.0%	0.0%			21.0%	0.0%		
	Land et al. 2010 (66)					3.0%	2.0%	3.0%	1.0%	1.0%	1.0%	1.0%	2.0%
Decrease in lateral AB	Gill 2009 (67)							4.4%	2.8%				
ROM <normative values any plane	Lauridsen et al. 2008 (9)											35%	
Mean ROM (normal = 180°)	Rietman et al. 2004 (68)											156.6° AB	
	Gosselink et al. 2003 (3)			FF 126° MRM 150° BCT									
	Peintinger et al. 2003 (24)							143.8° AB	158.9° AB				
Lateral AB <140°	Kopec et al. 2012 (69)					8.30%							
140°–159°						21.20%							
160°–179°						44%							
Lateral AB (ipsilateral–contralateral)/(contralateral) × 100% 5–10%	Ashikaga et al. 2010 (70)					13.1%	10.1%						
≥10%						9.0%	5.70%						

[a]For studies that did not collect data at specified intervals, the elapsed time after surgery is the cohort average.
ALND, axillary lymph node dissection; SLNB, sentinel lymph node biopsy; FF, forward flexion; AB, abduction; BCT, Breast-conservation therapy; MRM, modified radical mastectomy.

TABLE 39-3

Reported Pain Prevalences and Intensities Following at Different Time Points Following Breast Cancer Surgeries

Outcome Measure	*Author (Reference)*	*Elapsed Time from Breast Cancer Surgery*[a]									
		<6 wks		*6–8 mos*		*9–12 mos*		*24 mos*		*>2 yrs*	
		ALND	*SLNB*	*ALND*	*SLNB*	*ALND*	*SLNB*	*ALND*	*SLNB*	*ALND*	*SLNB*
Mean change in EORTC QLQ-C30 Pain Scale Score	Peintinger et al. 2003 (24)	20.2	–2			7.2	0.1				
VAS (0–100) change from preoperative baseline	Rietman et al. 2003, 2006 (27,5)	1.3	1.1					8.7	0.6		
VAS >0	Ernst et al. 2002 (38)									50.7%[b]	
Mild, moderate, or severe pain per Likert scale	Gartner et al. 2009 (32)									54.0%	41.0%
	Levy et al. 2012 (30)					49.0%					
Mean VAS score (0–100)	Peintinger et al. 2003 (24)					11.3	6.8				
	Hack et al. 1999 (35)									17.3	
	Rietman et al. 2004 (68)									25.0[b]	
	Kaya et al. 2010 (33)					Arm—at rest 1.7; on motion 3.0; Chest wall—2.0					
Pain in neck, arm, or shoulder ≥2×/week	Lauridsen et al. 2008 (9)									31.0%	
Severe or very severe axillary aching	Temple et al. 2002 (71)					19%	11%				
Sporadic or continuous axillary pain	Veronesi et al. 2003 (65)			91%	16%			39%	8%		
	Warmuth et al. 1998 (64)									30.0%	
	Hack et al. 1999 (35)									31.1%	
Chest, axillar, or shoulder pain (including hyperesthesia, phantom breast, Tinel +)	Alves Nogueira Fabro et al. 2012 (72)			53%							
Shoulder/arm pain	Langer et al. 2007 (62)									21.2%	8.1%
	Voogd et al. 2003 (73)									28.3%[b]	
Arm pain	Leidenius et al. 2005 (63)									30.0%	12.0%
	Ahmed et al. 2008 (74)									21.3%	

[a]For studies that did not collect data at specified intervals, the elapsed time after surgery is the cohort average.
[b]No distinction made between ALND and SLNB.
ALND axillary lymph node dissection, SLNB sentinel lymph node biopsy.

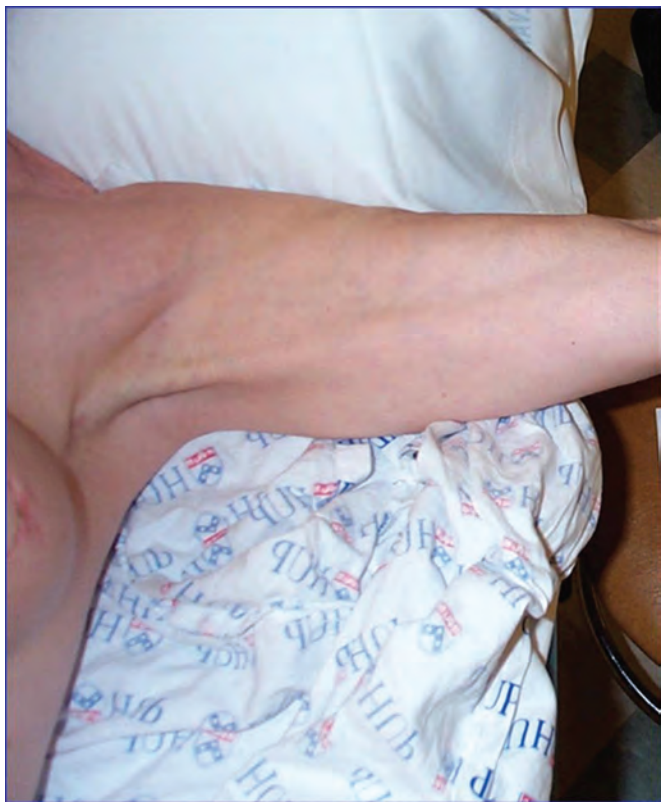

FIGURE 39-1 Axillary web syndrome.

vessels and veins, together with their surrounding connective tissue, comprise the cords (41). The natural history of axillary web syndrome is self-limited with gradual resolution over the first year following surgery without residua (41). However, the cords can be quite painful and may discourage patients from performing needed shoulder ROM activities, thereby contributing to long-term ROM deficits (42).

Since breast cancer treatments may destabilize the balance of shoulder muscles, patients are placed at theoretical risk of secondary musculoskeletal problems (e.g., rotator cuff pathology, premature degenerative disease of the acromioclavicular and glenohumeral joints, and myofascial pain). A prospective cohort study found the incidence of myofascial pain syndrome after ALND to be 44.8% (43), and a second study noted the pectoralis major muscle to be the most commonly affected (44). An additional cohort study serially screened patients for a range of discreet impairments and found that the point prevalence of myofascial pain remained stable at roughly 6.3% over the 12 months following breast cancer treatment, while that of rotator cuff pathology increased from 2.1% at 3 months to 7.1% at 12 months (45). The extent to that breast cancer treatment engenders these common problems must remain speculative until comparisons with age-matched, non-breast cancer populations permit estimation of the attributable risks.

TREATMENT

Shoulder function depends on the coordinated recruitment of multiple muscle groups to perform even basic activities. For this reason, although deficits may initially be discreet, few problems remain isolated. The onset of secondary problems occurs when patients lose flexibility due to pectoral muscle, or generalized shoulder, tightness which causes secondary strength and biomechanical deficits in uninvolved muscles. The anterior deltoid and coracobrachialis muscles, for example, may adopt dysfunctional length-tension relationships and firing patterns which cause weakness and further deviation from normal biomechanics (46). Over time, clusters of related impairments may develop and produce global shoulder dysfunction (47). Addressing problems in isolation will be, at best, limitedly successful. It is more clinically useful and practically relevant to examine generalized shoulder disability arising from multiple, inter-related impairments.

Many exercise and manual treatments benefit musculoskeletal problems provided they are administered in a structured and monitored fashion (6,8,48–50). Regimens tested with randomized, controlled study designs are consistently superior to the common practice of providing patients with illustrated exercise sheets after surgery without formal follow-up. The fact that a variety of therapeutic techniques offer benefit reflects the straightforward treatment goals of restoring normal flexibility, strength, postural alignment, and muscle recruitment patterns to the upper truncal quadrant. Positive results have been reported with therapist-directed programs emphasizing disparate approaches such as general biomechanics and pectoral muscle stretches (49). Although a wide range of structured regimens yield benefit, all therapy programs should have several essential elements that are listed in Table 39-4 and described below.

ROM Activities

ROM activities restore normal flexibility and influence scar formation to prevent restrictions. Distractive forces influence collagen deposition such that fibers align in parallel, rendering the resultant scar supple, distensible, and able to support normal musculoskeletal function. Muscles within surgical and radiation fields are of greatest concern; however, adjacent and even remote muscle groups can also become hypertonic and develop flexibility deficits. Therefore, comprehensive ROM activities should incorporate both treated and "at risk" muscle groups such as the scapular stabilizers (e.g., upper and middle trapezius and rhomboid muscles).

Stretching can be performed in a variety of ways and controlled studies have yet to shed light on which techniques are most effective in breast cancer populations. Several general caveats apply:

1. ROM activities should never be pulsatile, painful, or overly aggressive.
2. Pain or swelling following ROM activities mandates revision of the program.
3. Patients should breath steadily and consciously during ROM activities.
4. ROM activities should continue in an abbreviated fashion long after normal flexibility has been restored to prevent latent fascia contractures.

Active ROM activities can begin 7 days after breast cancer surgeries provided patients have not undergone breast reconstruction. In the latter case, patients should clear all physical rehabilitation activities with their plastic surgeons. Initial stretches include shoulder shrugs; shoulder retraction; wall walking; rowing motions; cervical rotation, extension, and lateral bending; and cane-based overhead stretches. Most institutions have printed sheets illustrating these activities which are provided to patients on hospital dismissal.

For patients who have undergone ALND, once their drains have been removed, a formal physical therapy evaluation will ensure that patients are performing ROM activities correctly and that their recovery is following a

TABLE 39-4

Essential Elements of All Comprehensive Rehabilitation Programs Following Primary Breast Cancer Treatment

Flexibility/range of motion exercises	
Shoulder:	Forward flexion
	Scaption (plane of the scapula; ~20° of cross-abduction)
	Abduction
	Extension at 0° and 90° of abduction
	Internal/external rotation
Thorax:	Abdominal muscles: rectus and obliques
	Pectoral muscles
	Intercostal muscles
Cervical spine	Lateral rotation
	Lateral bending
	Extension
Progressive resistive/strengthening exercises	
Shoulder:	Scapular retractor muscles
Thorax:	Spinal extensor muscles
Cervical spine:	Spinal extensor muscles
Activities for posture and biomechanics	
Education	
Rationale for exercises (e.g., need for continued stretching activities)	
Precautions (e.g., lymphedema)	
Signs of complications strain, infection, seroma	
Tailored home program	
Instructions for tapering over time	
Indefinite maintenance activities as needed	
Emphasis on limited, "essential" exercises	

normal trajectory. The physical therapy visit can be used to demonstrate how patients should advance their ROM activities, to educate patients in the long term protective benefits of regular stretching, and to provide instruction in breathing techniques (e.g., breath stacking to enhance intercostal muscle excursion). Patients should also be alerted to contact a health care provider if they have not recovered full, painless shoulder ROM one month prior to the start of radiation.

The major and minor pectoral muscles merit special attention as they are in proximity to breast surgeries, receive up to 60 Gy with conventional breast tangent beams (51) and may be affected by implant-based breast reconstruction. Pectoral stretching should be a central therapeutic focus since tightness produces well-characterized, maladaptive changes in shoulder biomechanics that may increase survivors' risk of secondary problems (46). Several approaches to pectoral stretching are illustrated in Figures 39-2 through 39-4. The standing corner stretch in (see Figs. 39-2A,B) should be held for at least five deep breaths with the patient leaning forward and allowing her body weight to gently carry her into the stretch. The abdominal muscles should be lightly engaged tilting the pelvis forward to protect the lower back as illustrated by the curved arrow. The positions in Figure 39-3A–D should be passively maintained for as long as 15 minutes on a firm surface. The progression from A to D illustrates increasing shoulder external rotation which places greater traction on the pectoral muscles and intensifies the stretch. At no time should patients experience discomfort. The pectoral stretch can also be increased by placing a pillow, rolled towel or bolster between the scapulae, Figure 39-4, ensuring that the head is adequately supported with a pillow to avoid anterior cervical muscle strain.

Strengthening

Resistive exercises normalize focal strength deficits, ensure adequate strength for normal activities, and prevent periscapular muscle strain. Strength deficits are rarely immediately apparent after surgery in the absence of long thoracic nerve injury. More commonly, evaluations for pain reveal weakness or myofascial dysfunction of the muscles that act on the scapula and upper arm. Strength deficits generally respond to incremental, isotonic resistive activities in all but the rare cases of significant axonal damage. Muscle spasm and pain must be addressed before initiating treatment. A "no pain no gain" approach simply aggravates the problem and may aversively condition the patient. Resistance can be offered by elastic bands, light weights, circuit training equipment, or even soup cans. Activities should target the scapular retractor (middle trapezius, rhomboids), scapular elevator (upper trapezius, levator scapulae), and thoracic spinal extensor muscles. The risk of inciting lymphedema mandates that resistive exercises be initiated at a low level and increased gradually with an emphasis on stamina rather than strength. Patients considered at risk of developing lymphedema should inspect their arms following sessions and consider use of a prophylactic garment. The choice to use a garment should be discussed and supervised by a health care professional familiar with lymphedema.

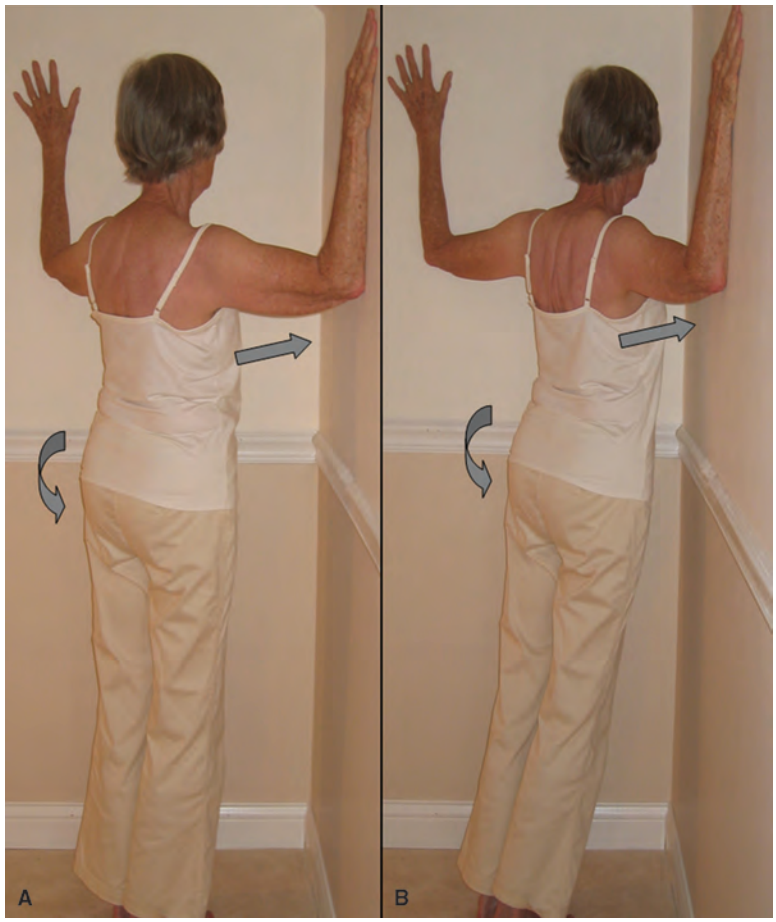

FIGURE 39-2 Wall stretches for pectoralis major and minor muscles should be performed with the abdominal muscles engaged to protect the low back as indicated by the arrow.

Posture

Effective postural therapy requires restoration of adequate strength and flexibility. Once this essential foundation has been laid, patients can progress to activities designed to enhance truncal and scapular alignment. In the discussion that follows, posture and alignment are used interchangeably. Postural work following breast cancer treatment strives to eliminate exaggerated thoracic kyphosis, scapular protraction, compensatory cervical lordosis, and asymmetry in the shoulder girdle. Postural work can be deceptively subtle and, although not inherently difficult, may be more challenging than ROM and strength-building activities. Most patients recognize "good" posture and can adopt it with little concentrated effort provided they have the requisite strength and flexibility. However, many patients are unable to maintain it once their concentration drifts, as it eventually must, to an alternate focus.

A host of factors operating within muscles and at different levels of the peripheral and central nervous systems determine patients' alignment. Several important factors may be influenced by breast cancer treatment: muscle length–tension relationships, muscle spindle and Golgi tendon organ sensitivity, and afferent proprioceptive input. The dorsal horn of the spinal cord, thalamus and cerebellum receive and process afferent signals to generate efferent signals that maintain patients' default alignment. When an individual deviates too far from her default posture, afferent input triggers subconscious, autorighting mechanisms that restore the default.

Postural therapies refine patients' default alignment to avoid secondary musculoskeletal problems, reduce stress on osseous and articular structures, and support normal biomechanics. Effective therapies spare patients future difficulties including premature osteoarthritis, neural impingement, and rotator cuff dysfunction. Fortunately, the physiological determinants of posture respond predictably to therapies. Once flexibility and strength have been normalized, postural work begins by bringing patients passively into proper alignment. Therapists then work through active assistive techniques to teach patients selective recruitment and relaxation of discrete muscles in order to maintain proper alignment. Work is ideally performed in front of mirrors that provide visual feedback from several planes (e.g., frontal, oblique, etc.). In this way patients can begin to appreciate when they are properly aligned and self-correct when out of alignment. Therapy's ultimate goal is automatic self-correction independent of visual feedback. With due diligence, patients internalize a more functional default alignment sustained through subconscious, autorighting mechanisms. It should be noted that many patients have poor posture when diagnosed with breast cancer and it is not the medical profession's responsibility to eradicate poor posture. However, attention to treatment-related problems that increase patients' vulnerability to future morbidities is an integral part of comprehensive cancer care.

Biomechanics

Biomechanics can be thought of as dynamic posture, or the interrelationship of body parts as patients engage in integrated, multiplanar movements. Restoration of normal upper quadrant biomechanics represents the culmination of successful therapy. Treatments attempt to preserve the

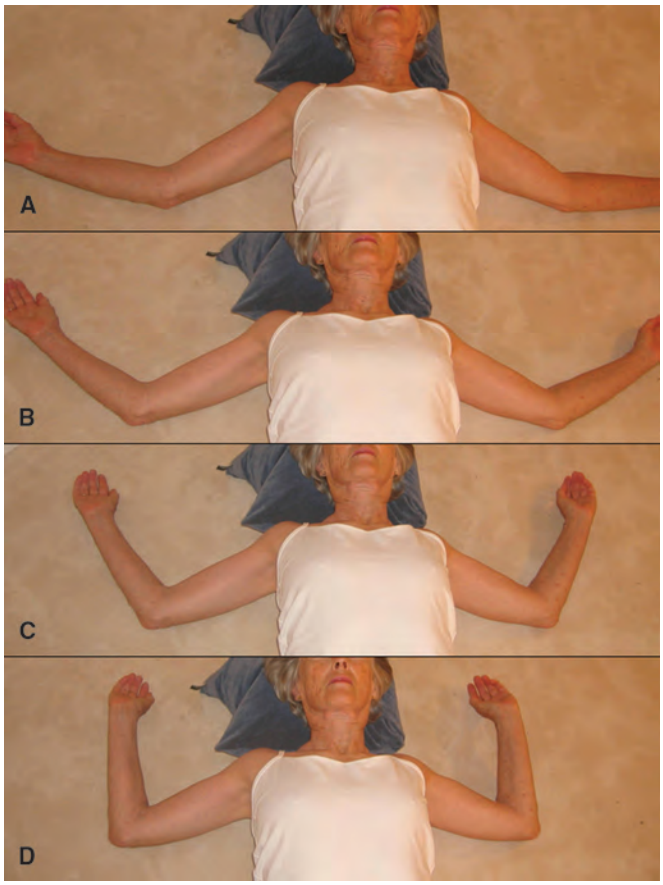

FIGURE 39-3 Sustained anterior chest wall stretch.

optimized static relationships achieved through postural therapies. Initially therapists provide active assistance and tactile cuing to optimize patients' performance of simple motions such as shoulder abduction. Once patients can perform these motions with proper biomechanics, they are encouraged to do so repeatedly with visual feedback from mirrors and verbal cuing. Eventually patients are taught to self-correct independent of feedback while performing increasingly complex activities in multiple planes.

FIGURE 39-4 A rolled pillow, towel or bolster can be placed between the shoulder blades to achieve a more intense pectoral stretch.

Timing

Much research has examined the timing of mobilization and exercise therapies following breast cancer surgery. Early shoulder mobilization within the first week after surgery increases wound drainage and the risk of seroma formation; however, delayed mobilization is associated with decreased shoulder range of motion for 6 months (10,50). By 2 years after surgery, no appreciable difference in flexibility persists between patients undergoing delayed versus early (≤7 days) mobilization (50). A robust evidence base supports the safety and efficacy of gentle postoperative shoulder, neck, and truncal mobilization provided that shoulder forward flexion and abduction are restricted to 90° for the first postoperative week (52). Thereafter, stretching and strengthening activities can be advanced as tolerated, although some surgeons continue to limit abduction and forward flexion until drain removal.

The literature provides far less guidance with respect to the optimal type, intensity, and timing of therapy after the subacute postoperative period. Continuous physiotherapy for 3 months following surgery is beneficial (8) but challenging to justify for all patients in the current era of medical cost containment. A majority of patients remain free of long-term musculoskeletal problems after limited physical therapy visits following removal of their surgical drains (52). Patients with advanced age or lymphedema and those who undergo ALND; chest wall or supraclavicular radiation treatments; or breast reconstruction are at up to 10 times greater risk of developing shoulder disability (3,4,8,9,36,37,48). Empirical data support more extended physical therapy for these patients with the goals of detecting incipient problems, education in self-diagnosis and referral, and provision with long-term prophylactic ROM and strengthening programs (53).

POTENTIAL CONCERNS

Several clinical finding should alert physicians to the possibility that patients require additional attention and care. Lymphedema remains a concern when patients exercise, particularly if they have undergone ALND with or without axillary or supraclavicular irradiation. Patients who have undergone these treatments will generally benefit from a visit with a lymphedema therapist certified by the Lymphology Association of North America (LANA) to review precautions and formulate a safe yet effective rehabilitation program. LANA-certified therapists can be located at http://www.clt-lana.org. The Physical Activity in Lymphedema (PAL) trial established that breast cancer survivors with, and at risk, for lymphedema can safely perform an incremental, resistive exercise program when gradually and systematically initiated and advanced (54,55).

Particular concern attends the rehabilitation of patients who have undergone breast reconstruction with autologous tissues. The range of harvesting and reconstruction techniques coupled with practitioner variability makes it difficult to accurately predict the locations and fragility of vascular anastomoses. Referral to a cancer rehabilitation specialist, or conferral with the plastic surgeon, is advisable prior to initiating physical activity, particularly if reconstruction involved muscle flaps. A comprehensive rehabilitation plan should address potential donor site morbidity, as well as the affected upper quadrant.

INTEGRATED EXERCISE APPROACHES

An ever-expanding array of fitness approaches is available to breast cancer survivors at health clubs and, increasingly, cancer centers. Some approaches such as Feldenkrais movement therapy are long established traditions utilized routinely by physical therapists. Other approaches have only become widely available within the past decade. To name but a few, patients may encounter Pilates, yoga, Alexander technique, Mensendieck exercise therapy, and tai chi. Each approach has unique emphases with the potential to benefit breast cancer survivors beyond enhancing general fitness and body awareness. For example, the Alexander technique focuses on craniocervical alignment, a critical dimension of postural therapy, and tai chi enhances physical functioning in breast cancer survivors (56). Patients should be encouraged to explore different approaches with several caveats. First, most fitness instructors are unaware of lymphedema precautions, hence patients must function as their own self-advocates to protect against inadvertent lymphatic overload. A recent pilot study detected increased arm volumes in breast cancer survivors performing a home-based Pilates program (57). Second, breast cancer patients' fitness regimens should include pectoral muscle stretching, strengthening of scapular retractors, and postural exercises as discussed above. If an integrated exercise approach does not include these elements, patients will need to independently supplement with guidance from a health professional.

A number of exercise regimens have been tailored to breast cancer survivors and marketed through video classes, books, and weekend workshops. The developers of such approaches may or may not have formal clinical training and familiarity with the unique physical vulnerabilities associated with breast cancer treatment. No empiric data supports the efficacy or safety of these tailored approaches. In the authors' opinion, the worth of such media derives from patients' enhanced comfort levels and enthusiasm.

A PROSPECTIVE SURVEILLANCE MODEL

The growing recognition that breast cancer treatments produce adverse upper quadrant sequelae that are common, morbid, and undertreated, particularly among ethnic minorities, has spurred the development of proactive approaches to detect and treat physical impairments. Among these, the prospective surveillance model (PSM) for breast cancer rehabilitation has been most extensively elaborated and studied (58). This model involves a preoperative physical therapy evaluation to characterize patients' baseline status, followed by physical therapy visits at 3, 6, 9, and 12 months post-surgery. The PSM's implementation among a survivor cohort reduced incident lymphedema and improved shoulder function over the first year following diagnosis. A bold initiative, supported by the American Cancer Society, has promoted the adoption of the PSM as a new of standard care (58). However, concern has been raised regarding the PSM's lack of level I supportive evidence, the formidable cost of implementation, and the potential for diverting resources away from the minority of survivors who develop severe and refractory problems (59).

CONCLUSIONS

Musculoskeletal problems involving the shoulder and upper truncal quadrant are common following primary breast cancer treatment, associated with disability, and a source of degraded HRQOL. Many patients recover normal strength and ROM after recovering from transient postoperative deficits, however, a significant proportion develop chronic problems. Modified radical mastectomy (MRM), ALND, breast reconstruction, and axillary or supraclavicular irradiation increase the likelihood that a survivor will develop long-term problems.

All breast cancer patients should receive formal instruction in gentle progressive shoulder and arm ROM following surgery. Forward flexion and abduction should be restricted to 90° until the seventh postoperative day. Patients at increased risk of long-term musculoskeletal problems should receive additional physical therapy with the goal of prevention and education in long-term risk reduction and self-advocacy. Irrespective of risk, all exercise programs should include several essential elements including: anterior chest wall stretching, strengthening of scapular retractor muscles, as well as activities to foster optimal posture and biomechanics. Patients treated with radiation therapy should indefinitely continue a limited ROM program targeting the anterior chest wall and shoulder muscles.

Empiric evidence suggests that musculoskeletal problems can be prevented with routine rehabilitative interventions after primary breast cancer treatment. Simple stretching, strengthening and postural activities may have the capacity to improve breast cancer survivors' HRQOL and represent an integral part of comprehensive care.

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CHAPTER 40

Lymphedema

Sarah A. McLaughlin

CHAPTER CONTENTS

Breast cancer–related lymphedema remains a feared complication following breast cancer treatment (1) because it is a chronic process that cannot reliably be prevented. Dramatic modifications to surgical approaches, including less radical breast surgery and widespread adoption of sentinel lymph node biopsy (SLNB) as the standard of care for axillary staging, have contributed to significant decreases in the incidence of lymphedema. However, despite these changes, there remains approximately a 20% risk of lymphedema after axillary dissection (ALND) and a 0% to 7% risk after SLNB. Persistent risk and patient worry result in almost uniform adoption of lifestyle modifications (1). Unfortunately, it is unclear if these modifications reduce the risk for lymphedema, and it is further unclear how these changes impact overall quality of life (QOL).

Women affected by lymphedema have historically had an overall poorer QOL (2). Lymphedema can contribute to musculoskeletal pain and reductions in shoulder range of motion, limiting performance of activities of daily living. Unattended severely lymphedematous limbs can lead to elephantiasis and, in a few cases, to Stewart-Treves Syndrome, a rare but deadly angiosarcoma arising from the lymphedematous tissues. Despite these limitations, most patients with lymphedema do not consider themselves as disabled (3). They do, however, suffer from decreased body image and loss of self-esteem, but further refinement in assessment of all QOL measures has been lacking. Emerging interest supports standardization of QOL assessment in lymphedema patients as a recent meta-analysis demonstrated significant heterogeneity with 17 different instruments used (only two of which were specific to lymphedema patients) in 39 studies to assess health-related QOL outcomes in breast cancer–related lymphedema patients (4). The authors encourage future studies to use high quality lymphedema-specific patient-reported outcome instruments such as the Upper Limb Lymphedema 27 (ULL 27), which had the strongest psychometric properties.

The medical community has devoted little time and attention to lymphedema research and the resources necessary for successful lymphedema treatment. The financial burden placed on patients is frequently a source of anxiety. While Medicare supports consultation and treatment by trained lymphedema specialists, treatment coverage is frequently limited to diagnosis, acute intervention, and establishment of the treatment plan with visits and services covered only as patients demonstrate improvement. Interestingly, federal guidelines exist supporting the coverage of postmastectomy bras and prostheses; however, coverage for lymphedema compression garments and short stretch bandages, both mainstays for in-home maintenance therapy, varies among private insurers and Medicare. Advocating for equality in patient rights, the National Lymphedema Network (NLN) supports the Lymphedema Treatment Act (5,6), a bill before Congress that would help establish and standardize treatment coverage, patient education, development of self-treatment plans, and, ultimately, would reduce healthcare costs. As of July 2011, this bill was referred to the House of Representatives subcommittee on Health and has not been discussed again.

ANATOMY AND PATHOPHYSIOLOGY

The lymphatic system is composed of lymphatic capillaries, transporting vessels, and lymph nodes. The lymphatic system has a low oncotic pressure, allowing diffusion of protein-rich interstitial fluid into lymphatic vessels, which transport it to the venous system. In the upper extremities, the superficial lymphatic system is composed of valveless capillaries located at the dermal–subcutaneous

level that communicate directly with collecting lymphatic vessels coursing through subcutaneous tissues with superficial veins. These collecting vessels, or secondary lymphatics, drain into tertiary lymphatics, which progressively network and ascend to the axilla. On the left, these lymphatic vessels join other thoracic and intercostal lymphatic channels, draining into the thoracic duct, which empties into the left subclavian vein. A smaller right lymphatic duct drains the right upper extremity and neck and enters the right subclavian vein. Secondary and tertiary lymphatic vessels have valves to aid in the unidirectional propulsion of lymph fluid. Lymphatic flow is encouraged by active skeletal muscle contraction, causing intermittent compression of the subcutaneous compartment, and by nearby arterial pulsations. The lymph nodes act as points of filtration throughout the lymphatic drainage process and serve a primarily immunologic function. The vessels of the deep lymphatic system run beneath the muscular fascia near neurovascular bundles. Little communication exists between the superficial and deep systems, and lymphedema generally spares the deep component.

The etiology of lymphedema is incompletely understood, but it likely results from (1) lymphatic obstruction due to obliteration of the lymphatic pathways or removal of the lymph nodes, (2) mechanical insufficiency due to faulty lymphatic pumping or malfunction of the lymphatic valves, or (3) loss of lymphatic vessel integrity. The quantity of fluid within the interstitial space is determined by the delicate balance of hydrostatic and oncotic pressures between the vascular capillaries and the interstitial space. More than 90% of fluid within the interstitial space is removed by the venous capillaries; what remains is normally returned to the vascular system by lymphatics. The combination of the negative oncotic pressure of the lymphatic vessels and their indistinct, virtually nonexistent basement membranes allows larger proteins and macromolecules, such as bacteria and cellular debris, to passively diffuse from the interstitium into the lymphatic system. When the lymphatic system is dysfunctional, fluid transport is disrupted, and interstitial protein accumulates, increasing its oncotic pressure. This draws more fluid into the interstitium. Excessive accumulation of interstitial fluid due to impaired lymphatic transport is called *lymphedema*.

The cycle of lymphedema self-perpetuates as increased lymphatic fluid volume causes stretch in lymphatic vessels, leading to incompetent valves and further failure of lymph transport. Additionally, the stagnant bacteria ignites a chronic inflammatory cascade, recruiting macrophages and neutrophils to the interstitium for wound healing, and leading to collagen deposition and fibrosis, hindering lymphatic contraction. Furthermore, the severity of edema can be exacerbated by episodes of lymphangitis, chronic inflammation, or recurrent cellulitis. It is hoped that the recent development of lymphatic endothelial markers such as LYVE-1, Prox1, and podoplanin will help the study of lymphangiogenesis and regeneration.

CLINICAL EVALUATION OF UPPER EXTREMITY LYMPHEDEMA

To evaluate for lymphedema, the patient sits with arms outstretched and then flexed and rested on the hips. The clinician should pay close attention to subtle differences in symmetry including loss of bony prominences, especially at the olecranon process, styloid process of the ulnar head, and over the extensor tendons of the hand. Other subjective signs of swelling include imprints from tight-fitting shirt sleeves, watches, or jewelry. The physical exam also includes evaluation of skin turgor, firmness, and the presence of pitting or nonpitting edema. Lymphedematous changes may involve the entire upper extremity but can also be isolated to the hand in 61%, the lower arm in 55%, and the upper arm in 72% of patients (7). Table 40-1 lists the clinical stages of lymphedema.

TABLE 40-1

Clinical Stages of Lymphedema

Stage	*Clinical Findings*
0	Subclinical lymphedema Impaired lymphatic transport Swelling not visible by gross evaluation Can be latent for months to years
I	Visibly swollen limb Pitting edema Edema may resolve without treatment
II	Limb is visibly swollen but swelling is nonpitting Onset of tissue fibrosis Chronic condition
III	Lymphostatic elephantiasis Irreversible skin changes, fatty deposits, hyperpigmentation

Metrics

The diagnosis of lymphedema is confirmed by physical exam and a combination of subjective and objective measures (Table 40-2). Unfortunately, the most challenging problems in accurately determining the incidence of lymphedema remain poor standardization in defining lymphedema and the lack of robust data with long-term follow-up. Many studies diagnose lymphedema using subjective measures such as patient questionnaires or survey instruments to directly and indirectly assess symptoms of arm or breast swelling, tightness, tenderness, or edema (7–10). Little correlation between subjective assessment tools and arm measurement changes constituting lymphedema exist; however, it could be argued that it is the patient's perception of lymphedema, not the presence or absence of objective measurement changes, that negatively impacts QOL and contributes to adoption of risk reducing behaviors. A recent study found that, in patients having SLNB, perceptions of lymphedema appear to decline significantly over the first year; however, among ALND patients, perceptions of lymphedema increase between 6 and 12 months after surgery (1). At 5 years' follow-up, a large prospective study found perceived rates of lymphedema to be less than measured after SLNB (3% vs. 5%), while patients undergoing ALND perceived more swelling than was measured (27% vs. 16%) (11). More recently, a retrospective study with 10 years of follow-up documented subjective lymphedema in 10% of SLNB patients and 33% of ALND patients (12). This study did not obtain baseline assessments. Well-documented sensory changes occurring after axillary surgery and the inconsistent practice of sparing the intercostal brachial nerve likely explain the differences between perceptions and measurements of lymphedema (12).

The objective measures of lymphedema that quantify volume differences and volume displacement using water remain the gold standard in assessing lymphedema despite multiple limitations (see Table 40-2). Circumferential arm

TABLE 40-2

Advantages and Disadvantages of Common Lymphedema Diagnostic Tools

Method	*Advantages*	*Limitations*
Patient report (subjective assessment)	• Patient perception of symptoms and their impact on function • Detection of prodromal symptoms of heaviness or subtle arm changes undetected by objective measures	• Recall bias of risk factors • Unclear influence of postoperative sensation sequelae • No standardization in subjective assessment or QOL tools
Water displacement	• Gold standard • Volume calculation of entire limb	• Cumbersome • Infection control limitations (water must be changed between each patient use) • Cannot isolate location of lymphedema (i.e., to hand, forearm, or upper arm)
Circumferential tape measurements	• Portable • Easy to learn • Noninvasive • Cost efficient • Relatively quick to perform	• Intra-rater and inter-rater variability • Nonstandardized process (i.e., inconsistent measurement intervals and diagnostic thresholds) • Requires baseline and bilateral arm measurements
Perometry	• Standardized process • Multiple measurement intervals • Reproducible • Sensitive	• Not portable • Expensive equipment • Cannot reliably measure the upper arm or hand
Bioimpedance spectroscopy (BIS)	• Measures only extracellular fluid compartment • May detect subtle volume changes of <150 mL (prodromal or Stage 0 lymphedema) • Portable • Cost effective • Standardized • FDA approved	• Variable reimbursement • Recommended at baseline and every 3 mo after surgery

measurements with a non-elastic tape measure remain the most commonly reported method for objectively assessing lymphedema. Implementation in clinical practice is relatively straightforward; however, a few guidelines should be followed. First, baseline measurements of the ipsilateral and contralateral arm are essential to control for normal variations between the dominant and nondominant arms at baseline and for any weight gain during follow-up. Second, to minimize intra-rater and inter-rater circumferential arm measurement variability, patients should be measured by the same healthcare professional at all visits and ideally measured multiple times at each point to ensure the most accurate results. Unfortunately, the number of anatomic locations and the number of measurements obtained vary between studies. Some investigators measure at only two points while others obtain 10 to 15 measurements at 3 or 4 cm increments from the nail bed to the axillary fold and then calculate the arm volume according to the volume of a frustrum or truncated cone. When compared to water displacement, multiple measures used to calculate arm volume and patient self-report had the highest specificities (90% and 89%, respectively), while measurement of arm circumferences at 2 points alone had the lowest specificity (73%) (13). Finally, the measurement change constituting lymphedema is not standardized; some consider lymphedema a 2-cm increase in circumference (9), while others consider a volume increase of less than 10% as minimal lymphedema, 10% to 20% moderate, and greater than 20% severe when compared to the baseline (14). The clinician should decide the diagnostic thresholds prior to commencement of screening to ensure consistency in measurements. Figures 40-1 through 40-4 demonstrate mild, moderate, severe, and isolated hand lymphedema. Regardless of the implementation strategy, arm measurements cannot determine the actual volume of extra lymphatic fluid.

Perometry or opto-electric volumetry uses a perometer to emit infrared light beams and to measure changes in the beam angles caused by the shadows of the limb. The frame moves at 3-mm increments along the length of the limb, obtaining circular cross-sectional measures, and then calculates overall total limb volume. The advantages and limitations are listed in Table 40-2. When perometry is used, clinicians consider a change of 3% over baseline measurements to be diagnostic for lymphedema (15).

Another noninvasive measurement option is bioimpedance spectroscopy (BIS), previously known as multifrequency bioelectrical impedance (Table 40-2). BIS uses resistance to electrical current to compare the composition of extracellular fluid compartments within the body and specifically between the affected and unaffected limbs (16). An increase in extracellular fluid results in a decrease in impedance of the affected limb. The most popular device available is the L-Dex marketed by Impedimed. Exploratory studies suggest an increase of 10 L-Dex units from the baseline or

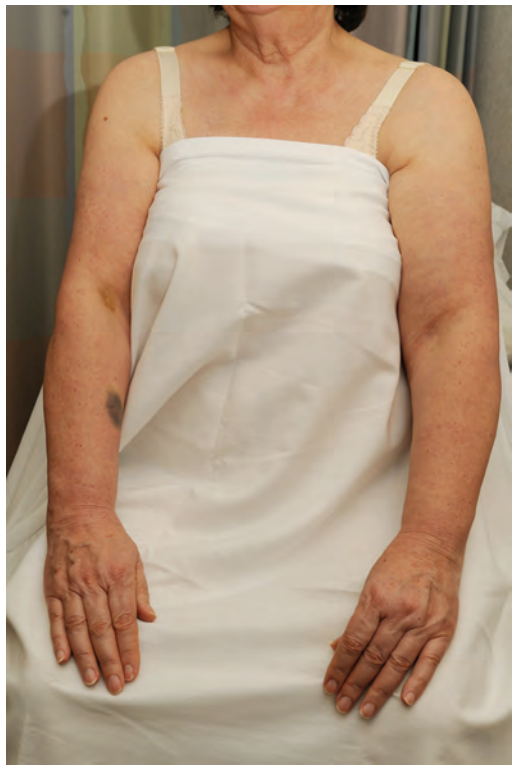

FIGURE 40-1 Mild lymphedema in the left arm.

a value outside of the normal range may aid in the clinical assessment of unilateral arm lymphedema when compared to matched normal controls (17). Smoot et al. compared BIS to circumferential arm measures and found BIS to have the highest Area Under the Curve (AUC) value of 0.88, while using the 2-cm diagnostic cutoff option had an AUC of approximately only 0.60 (18). BIS may be best suited to identify the prodromal early stage of lymphedema as circumferential arm measures or volume calculations may fail to capture subclinical fluid accumulations of less than 150 mL (14). The device is portable and easy to use; however, reimbursement for the procedure varies by state across private insurers and Medicare. Taking all measurement options into account, the NLN recommends circumferential tape measurements made with a flexible non-elastic tape measure at a minimum of six anatomical locations per arm, infrared perometry, or BIS (5); the National Accreditation Program for Breast Centers (NAPBC) strongly recommends the use of BIS or perometry, given their high correlation of results in the assessment of stage 0 lymphedema. The dilemma in

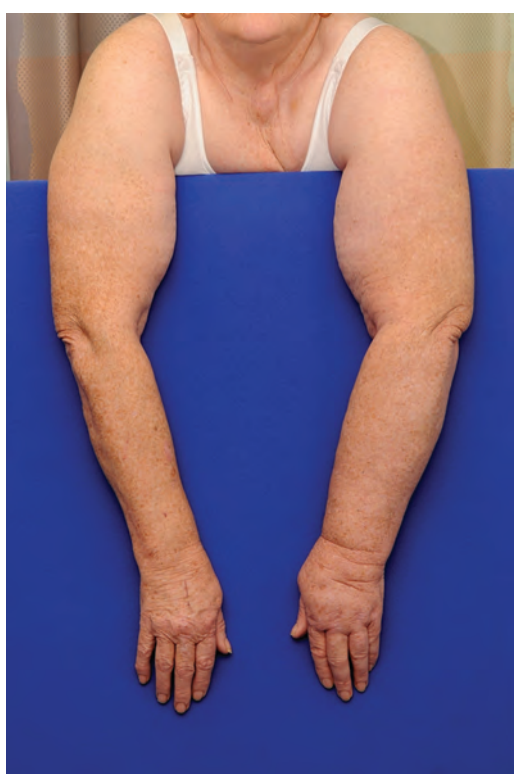

FIGURE 40-2 Moderate lymphedema in the left arm.

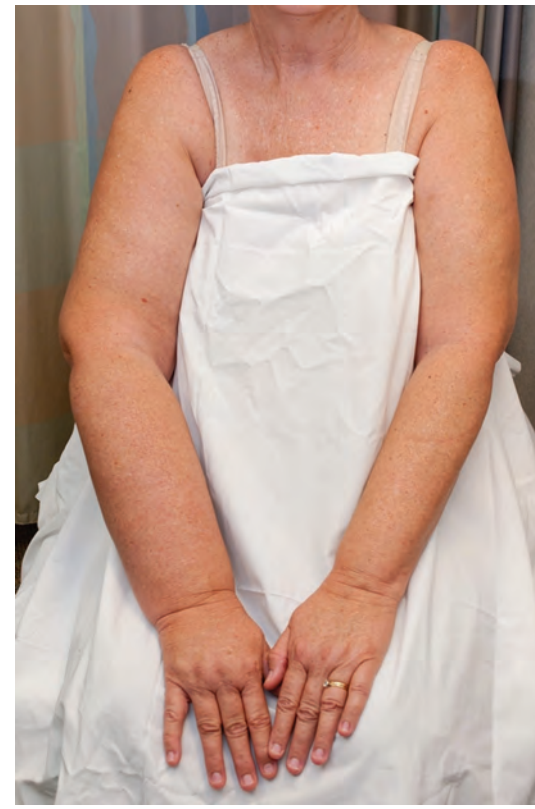

FIGURE 40-3 Severe lymphedema in the right arm.

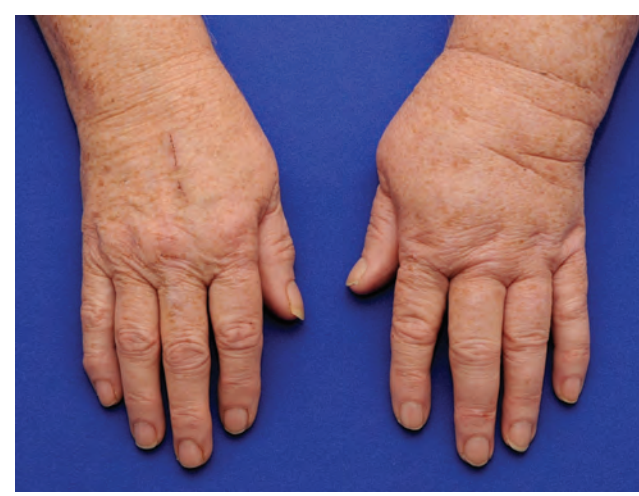

FIGURE 40-4 Moderate lymphedema in the left hand.

diagnosing lymphedema remains that measurement changes alone may not find all patients who are suffering from clinically significant lymphedema and may overdiagnose those who are unaffected by their measurement changes. Imaging techniques including lymphoscintigraphy, CT, and MRI are occasionally discussed to image a lymphedematous limb; however, these imaging techniques are predominantly limited to research, not clinical use.

Early Detection and Progression

An emerging body of literature supports the early detection of breast cancer–related lymphedema. These data cite improvements in functional outcome, resolution of prodromal symptoms, and decreased cost as reasons to support aggressive early detection practices (19). Stout presented data (15) supporting early detection and found intervention at this early stage can reduce or resolve the progression of lymphedema. This study prospectively followed 196 women, measuring arm volumes by perometer at baseline and every three months postoperatively. They controlled interventions, prescribing compression sleeves for 4 weeks to all women with a 3% change from baseline in perometer measurements. After intervention, the investigators found a mean arm volume decrease of 58% that was maintained for nearly 5 months after the compression sleeve was discontinued. Torres-Lacomba also highlights the importance of early intervention and conducted a prospective randomized trial to assess the role of early physical therapy, including manual lymphatic drainage, scar massage, and progressive active shoulder range of motion, on the incidence of lymphedema. After one year of follow-up, those in the intervention group demonstrated significantly less lymphedema (7% vs. 25%, $p = .01$) (20).

Luckily, contemporary estimates find that, among those with lymphedema, the majority have only a mild form (7). However, women with mild lymphedema are more than three times more likely to develop moderate or severe lymphedema compared to women with no lymphedema. Bar et al. reinforces these findings, documenting that 48% of mild lymphedema patients progressed to more severe lymphedema by 5 years follow-up (21). Risk factors for the progression of lymphedema included age more than 65 at diagnosis, morbid obesity, and regional nodal irradiation including posterior axillary boost (22). While studies agree on the importance of early identification and intervention, there is less agreement on what type of intervention should be pursued. Regardless, prospective evaluation and intervention for lymphedema is associated with significant cost savings with a recent study finding the cost to manage early-stage breast cancer–related lymphedema to be $636 annually, while the cost to manage late-stage lymphedema (traditional model) is $3,124 (23).

Risk Factors

Many retrospective studies have reported risk factors for lymphedema, including the extent of axillary surgery, mastectomy, obesity, patient age, radiation, and infection or injury in the ispilateral upper extremity. The strength of association between these treatment and epidemiologic risk factors and lymphedema is inconsistent across studies (24). A meta-analysis reviewed lymphedema risk factors from 98 studies and found a significantly increased incidence of lymphedema after mastectomy compared to lumpectomy (RR, 1.42; CI, 1.15–1.76), ALND compared to no dissection (RR, 3.47; CI, 2.34–5.15), ALND compared to SLNB (RR, 3.07; CI, 2.20–4.29), radiation versus no radiation therapy (RR, 1.92; CI, 1.61–2.28), and for positive versus negative axillary lymph nodes (RR, 1.54; CI, 1.32–1.80). While these data represent a comprehensive, contemporary review of potential risk factors, it should be acknowledged that the 98 studies used 11 different definitions for lymphedema and follow-up ranged between 1 month and 30 years. Finally, the influence of infection and injury must be tempered, as most accounts documenting these occurrences are obtained by patient recall and are therefore subject to significant bias as those affected by lymphedema are more likely to recall infection or injury (1).

The number of nodes removed or the extent of axillary surgery is the most commonly cited risk for lymphedema. However, the relationship between the number of lymph nodes removed and lymphedema risk is unclear, as some retrospective studies find no correlation and others find an increasing risk with more lymph nodes removed (25–29). The prospective randomized trials establishing SLNB as the standard of care for axillary staging support the theory that lymphedema is proportional to the number of nodes removed. They also document the small but definitive risk of lymphedema after SLNB. Although follow-up ranges from 6 to 60 months, these prospective randomized trials comparing SLNB and ALND find SLNB reduces rates of lymphedema to 0% to 7% after SLNB compared to 12–16% after ALND (30–32).

Goldberg et al. questions the role of the number of lymph nodes removed as the sole cause of lymphedema and proposes instead that it may be the relative degree of lymphatic destruction (33). They demonstrated no difference in lymphedema rates among 600 SLNB patients when stratifying the data according to the mean, median, or range of number of nodes excised ($p = .93$). They also found no lymphedema in women having more than 10 lymph nodes excised at SLNB. When this subset was compared to women having 10–17 nodes removed at ALND, they discovered 11% of the ALND patients had lymphedema ($p = .04$) and suggested the etiology of lymphedema is multifactorial and perhaps relative to the amount of lymphatic destruction. In contrast, while patient objective measurements of lymphedema were not correlated with the number of nodes removed, patient perceptions of lymphedema did increase as more nodes were removed (34).

Axillary radiation can also contribute to lymphatic dysfunction. Shah et al. recently retrospectively reviewed 1,861 patients with breast cancer treated by breast conservation surgery and whole breast irradiation. When stratified by regional nodal irradiation technique, they found lymphedema occurred in 9.9% of patients receiving a supraclavicular field, in 14.7% in those receiving a posterior axillary boost, and in 8.3% of patients receiving internal mammary irradiation (35). Bar et al. found similar results, noting that 54% of patients having supraclavicular radiation and posterior axillary boost developed lymphedema within 5 years of treatment compared to 27% of patients with breast irradiation only (22). Additionally, a recent meta-analysis by Shah and Vicini found lymphedema in 9% to 65% of patients after lumpectomy alone (no nodal surgery) and regional nodal radiation and in 58% to 65% of women after mastectomy alone and regional nodal radiation (36). The synergistic effect of surgery and radiation is well documented to result in a 3.5- to 10-fold higher risk of lymphedema when compared with surgery alone (36–38). Although axillary radiation may cause less acute morbidity, long-term complications (such as brachial plexopathy) and decreases in motor and sensory function can occur. The prospective randomized AMAROS (After Mapping of the Axilla: Radiotherapy or Surgery?) trial was presented at the Annual American Society of Clinical Oncology meeting in June 2013. This trial randomized women with clinical T1-2 N0 breast cancer found to have a positive sentinel node to either axillary radiation or ALND. After 5 years of follow up, the investigators reported axillary recurrence rates of less than 1% and found lymphedema to be less after axillary radiation when compared to ALND (14% vs. 28%). As of the completion of this chapter, the final AMAROS manuscript has yet to be published.

Finally, adjuvant chemotherapy, especially anthracycline-based regimens, may also affect lymphatic destruction. Norman et al. (39) conducted a prospective study that followed 631 breast cancer survivors for 5 years and found a hazard ratio of 1.46 (95% CI, 1.04–2.04) for lymphedema among breast cancer patients receiving anthracycline chemotherapy versus no chemotherapy even when the data were controlled for stage at diagnosis or number of positive nodes. Additionally, they found treatment combinations involving ALND or chemotherapy led to four- to fivefold increases in hazard ratios for lymphedema [HR of 4.16 (95% CI, 1.32–12.45) for SLNB/chemotherapy/no radiation] compared with no treatment. Further validation of these findings is needed.

While clinicians widely acknowledge all the risk factors listed above, little effort has been put forth to estimate individual patient risk for developing lymphedema. Prevention and treatment efforts have been historically uniformly applied to all patients at risk. Ideally patient, tumor, and treatment characteristics could be individually weighted to risk stratify each patient. With this goal, Bevilacqua et al. (40) retrospectively evaluated 1,054 women undergoing ALND for breast cancer. Then, using lymphedema risk factors such as age, body mass index, ipsilateral arm chemotherapy infusions, level of ALND, radiation fields, seroma, infection, and early edema, they created a nomogram to predict the risk of lymphedema. The nomogram (available at www.lyphedemarisk.com) was modeled to run at baseline, postoperatively within 6 months of surgery, and postoperatively after 6 months of surgery. The nomogram performed with reasonable certainty in validation with concordance indices of 0.706, 0.729, and 0.736 at each time point, respectively. The authors concluded that the model can help clinicians predict lymphedema and therefore risk stratify patients accordingly.

Incidence

The true incidence of lymphedema has been difficult to determine, and, therefore, wide ranges in incidence are reported from 0% to 75%. The wide ranges may reflect the differences in measurement techniques and the lack of a standardized definition of lymphedema. For example, some studies measure any lymphedema while others measure only moderate or severe lymphedema. Furthermore, the relatively short follow-up of most contemporary studies suggests that the incidence of lymphedema is likely underreported. Although it is clear that 80% to 90% of women who will develop lymphedema do so within 3 years of treatment (7,9), women remain at risk for many years later, as approximately 1% per year will develop lymphedema between years 4 to 20 of follow-up. A recent meta-analysis documents that lymphedema ranges from 0% to 3% after lumpectomy alone to as high as 65% after modified radical mastectomy with radiation to the chest wall and regional lymphatics (41). Otherwise, contemporary estimates of lymphedema appear to range from 0% to 7% after SLNB and 15% to 20% after ALND.

Changes in the surgical management of the axilla, including the adoption of SLNB, limiting ALND even after a positive SLNB, and even questioning the need for SLNB in all patients, aim to further reduce the incidence of lymphedema. In addition, changes in surgical techniques, such as Axillary Reverse Mapping (ARM), have been proposed. Proponents hypothesize that breast and upper extremity lymphatic pathways to the axilla may be separate. ARM uses a combination of blue dye injected into the arm to map the lymphatic channels draining the upper extremity and technetium injected into the breast to map the lymphatic channels draining the breast. The goal is to identify and protect the blue lymphatics during axillary surgery, therefore preventing lymphatic damage and, ultimately, lymphedema. So far, limited data have demonstrated wide variations in ARM identification rates ranging from 40%–90%, salvage of the ARM nodal pathway of approximately only 50%, overlap in the ARM and breast drainage pathways in 20% of patients, especially those with heavy axillary disease burden, and cancer in the ARM node in 9% to 43% of cases (42–45). Most studies have limited follow-up, and the risk of lymphedema after the procedure is unknown.

TREATMENT

The treatment of lymphedema focuses on the chronic nature of the disease and aims to prevent lymphedema progression and recurrent infection and to facilitate return to normal function. Patients and family members must understand the physiologic process of lymphedema and the rationale behind the treatment process. They must also accept life-long active participation in treatment regimens. Certified physical or occupational therapists, physicians, nurses, and even massage therapists can help develop care plans to reduce and maintain fluid volume and provide compression garments and supplies. Early education and intervention remain vital to limiting tissue fibrosis, pain, and decreased function.

Risk-Reducing Strategies

For decades, clinicians have recommended risk-reducing behaviors to prevent lymphedema. Unfortunately, as noted in the risk-reduction guidelines published by the NLN, there remains "little evidence-based literature regarding many of these practices, [as such] the majority of the recommendations must at this time be based on the knowledge of pathophysiology and decades of clinical experience by experts in the field" (5). The overall lack of robust data surrounding this topic has led to the perpetuation of many myths about lymphedema. The primary goals of the risk-reducing practices are to prevent further lymphatic destruction by limiting increases in lymphatic flow, metabolic waste products, and infection, and to avoid lymphatic obstruction. Table 40-3 organizes the commonly recommended behaviors according to the physiologic process they are intended to prevent. In general, many inconsistencies in the application of these behaviors exist, as application of these practices is not differentiated between at-risk and affected individuals nor are at-risk patients stratified by their individual risk. In fact, prospective studies find that most patients having axillary surgery adopt four or five risk reducing behaviors without regard to the type of axillary surgery performed (1,10).

Avoidance of venipuncture, injection, or blood pressure measurement in the ipsilateral arm are the most widely recognized risk-reducing measures. Review of the available literature identifies only one study supporting avoidance of venipuncture or IV catheters as they found skin puncture for intravenous catheter insertion, venipuncture for blood draw, or finger stick for blood glucose testing were associated with an increased risk for lymphedema (RR 2.44, 95% CI 1.33–4.47). However, this was based on only 18 patients recalling skin puncture, of whom 8 had lymphedema at 3 years follow-up, suggesting the possibility that patients with lymphedema are more likely to recall a previous skin puncture (46). Interestingly though, surveys of orthopedic surgeons demonstrate low rates of lymphedema in at-risk patients and nonstatistical rates of infection or progression of lymphedema symptoms in affected patients among women needing carpel tunnel or other ipsilateral orthopedic surgery after breast cancer treatment (47–49). These studies may also be the best assessment of the outcome after planned lymphatic obstruction as surgeons reported

TABLE 40-3

Summary of Frequently Recommended Precautionary Behaviors Categorized by Physiologic Principles and the Cited Evidence Supporting or Refuting the Practice

Supporting Evidence	*Physiologic Principle and Precautionary Behavior*	*Refuting Evidence*
Expert opinion	**Increase lymphatic load** Overuse Trauma Hot weather and sunburn Heating pads Vigorous massage	Showalter (53)—prospective secondary analysis of RCT
Showalter (53)—prospective secondary analysis of RCT	**Increase lymphatic load** Sauna use	none
Casley-Smith (50)—retrospective survey	**Increase lymphatic load** High altitudes	Graham (51)—retrospective survey Kilbreath (52)—prospective but short follow-up
Clarke (46)—retrospective review	**Cause infection** Venipuncture Injections or intravenous catheter placement Acupuncture Cuts and scrapes from gardening Cuticle cutting Shaving with a straight razor	Showalter (53)—prospective secondary analysis of RCT Dawson (47), Hershko (48), Gharbaoui (49); all retrospective, survey, or opinion-based
Expert opinion	**Cause lymphatic obstruction** Blood pressure measurement Tight clothing on upper arm or wrist Tight jewelry Carrying a purse Crossing legs	Showalter (53)—prospective secondary analysis of RCT Dawson (47), Hershko (48), Gharbaoui (49); all retrospective, survey, or opinion-based
Expert opinion	**Increase metabolic waste products** Exercise	Kwan (58), Schmitz (59), Schmitz (60), and Courneya (61): meta-analysis and RCTs
Expert opinion	**Increase metabolic waste products** Heavy lifting Racquet sports	Showalter (53)—prospective secondary analysis of RCT

using tourniquets for exsanguination without evidence of lymphedema postoperatively. This finding may negate the recommendation of avoiding blood pressure measurements as taking a blood pressure requires significantly less time (or lymphatic obstruction) than a surgical tourniquet. These data, however, are anecdotal at best as they are all retrospective with small numbers, complicated by recall bias, and lack any objective measurements.

Another commonly recommended risk-reducing behavior is the use of compression sleeves for air travel. Three studies find conflicting data with one supporting compression garments, citing lowered cabin pressure as the inciting cause for lymphedema (50), while the other two find no difference in lymphedema rates between fliers and non-fliers and no difference according to the length of flight (51,52). In fact, one study found the practice of precautionary behaviors, including using a compression garment when flying, to be associated with an increased risk of lymphedema (OR 6.2, 95% CI 1.2–20.8, $p < .04$). Interestingly, further analysis also found patient use of compression garments did not correlate with other suspected lymphedema risk factors such as nodal disease, number of nodes removed, or radiation (51). Showalter et al. recently reviewed 30 risk-reducing practices with the goal of quantifying the association between these suspected risk factors and the occurrence of incident arm swelling among at-risk breast cancer survivors (53). Overall, 9% of 295 patients developed lymphedema, and sauna use was the only factor predictive of swelling (OR 6.67, 95% CI 1.36–32.56) by multivariate analysis. These findings underscore the discordance in clinician lack of knowledge regarding lymphedema prevention and recommendations made everyday to breast cancer survivors.

TREATMENT COMPONENTS

Complex decongestive therapy (CDT) remains the standard of care for long-term lymphedema treatment. There remain no effective medications to treat or prevent lymphedema. CDT is provided in two phases, the Reductive (Phase I) and the Maintenance (Phase II), and their components are outlined in Table 40-4. Clinicians providing CDT should be certified. Phase I CDT is performed 5 days per week until the reduction in fluid volume plateaus, at which point Phase II begins and a home regimen plan for maintenance therapy is established. Certified therapists also train caregivers to

TABLE 40-4

Goals and Components of Complex or Complete Decongestive Therapy (CDT)

Goals	
• Decrease swelling • Increase lymphatic drainage • Reduce skin fibrosis • Relieve discomfort • Reduce risk of cellulitis • Improve functional status	
Treatment Components	
Phase I: Reductive • Education in self-management • Skin care • Manual Lymphatic Drainage (MLD) • Short stretch bandaging • Lymphatic exercise	*Phase II: Maintenance* • Daily use of compression garments • Custom nighttime compression garments or alternative compression device • Periodic Manual Lymphatic Drainage (MLD), self massage, and lymphatic exercise

assist with the maintenance phase. Individual treatment recommendations and plans may vary according to the expertise of the treating clinician, insurance coverage and patient resources, complexity and duration of the therapy, patient motivation, and ability of patient to perform her own home care. Furthermore, regimens may be modified throughout the treatment process depending on the patient's response to treatment and exacerbations.

Skin Care

Methodical skin care is imperative to prevent infection. Therapists educate patients on daily cleansing routines, cuticle care, shaving, and hydration to minimize skin tears. Patients are also taught to recognize early signs of infection, especially erythematous streaks or increased swelling or fever, and to treat minor wounds with antibiotic ointment and dry gauze. Patients prone to recurrent bouts of cellulitis may carry antibiotics with them for use in case of rapid onset of cellulitis.

Manual Lymphatic Drainage (MLD)

Manual Lymphatic Drainage (MLD) is gentle massage designed to encourage natural drainage of lymphatic fluid away from a blocked lymphatic drainage area toward nearby functioning lymphatic vessels, usually toward the contralateral axilla or inguinal areas. MLD uses light massage strokes in a rhythmic circular fashion distally to proximally to stimulate lymphatic flow. Success of MLD is based on the physiologic principle that massage strokes apply tension to the skin which stimulates peristalsis of the smooth muscle cells in the walls of the superficial lymphatics. In phase I CDT, MLD is provided daily by a trained therapist; in Phase II, the patient practices MLD themselves on an as-needed basis to maintain volume reductions in conjunction with daily daytime and nighttime compression garment regimens.

Several prospective studies have demonstrated MLD to successfully reduce limb volume. Mondry et al. demonstrated a median girth reduction of 1.5 cm (54), while others found a limb reduction of 50% to 60% after MLD and compression bandaging (55,56). In the maintenance phase, increases in limb volume were associated with noncompliance with the bandages and compression garments (RR 1.55, 95% CI 1.3–1.76; and RR1.61, 95% CI 1.25–1.82) but not associated with MLD noncompliance (RR 0.99, 95% CI 0.77–1.2), suggesting the greatest benefit of MLD is seen in the reductive phase of CDT (57). Younger age, greater weight, and higher BMI also contributed to CDT maintenance failure (55).

Multilayer Short Stretch Compression Bandaging

Multilayer short stretch compression bandaging employs multiple layers of material to create low resting pressure but high working pressure gradient compression. Bandages are placed with the limb at rest; muscular contraction within the limited space of the short-stretch bandages creates high working pressure and therefore aids in fluid propulsion from the congested lymphatics to the venous circulation when the arm is in use. Bandage application begins with a bandage lining followed by digital bandage wraps, padding (polyester, cotton, or foam) to protect the fibrotic portions of the limb, then multiple layers of short-stretch bandages with 50% overlap and 50% stretch to cover the entire limb (Fig. 40-5). The goal of these bandages is to promote lymphatic and venous flow return and reduce limb fibrosis. These bandages differ from high-stretch bandages, such as Ace bandages, that can stretch to greater than 100% of their resting length. Compression bandaging is always a part of reductive CDT, and patients with severe forms may require continuation in the maintenance phase. However, success in this phase is variable as the bandages can be difficult for patients to apply and can take up to an hour twice daily to apply and remove. Additionally, insurance coverage is not standardized and bandages must be replaced every 4 to 6 months to maintain optimal stretch. Finally, compliance wanes in warmer climates as these bandages can be bulky and hot.

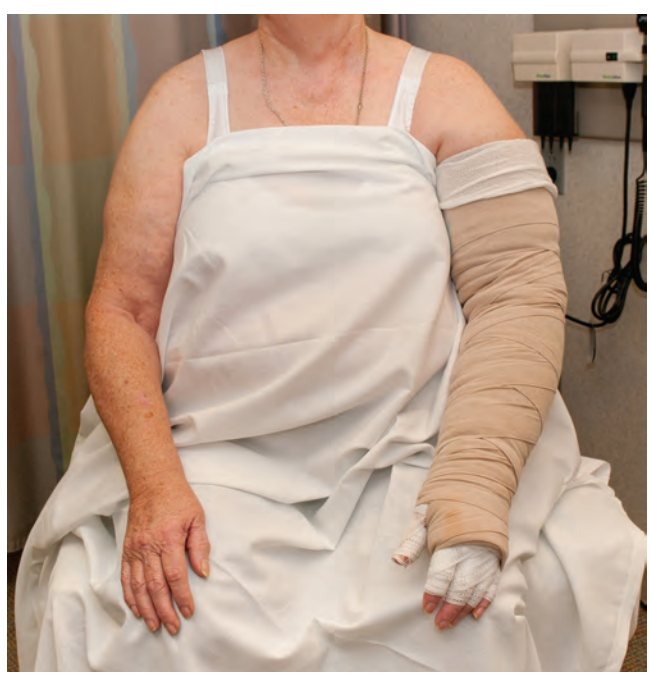

FIGURE 40-5 Multilayer short stretch compression bandaging.

Exercise

Remedial or lymphatic exercise to reduce arm swelling and promote mobility during lymphedema treatment is beneficial for all patients at risk for and affected by lymphedema. However, aerobic exercise and resistance exercise or weight training have long been discouraged for breast cancer survivors based on the physiologic theory that strenuous exercise would increase metabolic waste products and extracellular fluid causing lymphedema. Recently, these recommendations have been challenged.

Between 2006 and 2010, five randomized control trials found weight lifting is associated with minimal risk of developing or exacerbating lymphedema (58). The physical activity and lymphedema trial (PAL) was the largest study with the longest follow-up; it followed 141 women afflicted with breast cancer–related lymphedema. Patients were randomized to supervised twice weekly weight training wearing a compression sleeve or to the control group who were asked not to alter their exercise level. The authors found no increase in lymphedema in the intervention group and found fewer and less severe lymphedema exacerbations in the weight training group at one year follow-up (59). The researchers then studied weight training in at-risk survivors and similarly found no difference in lymphedema rates between the control and intervention groups (60). Interestingly, at-risk women with more than 5 nodes removed randomized to the intervention weight training group were significantly less likely to develop lymphedema than those in the control (7% vs. 22%, $p = .003$) (60). Based on these data, the NLN guidelines have been modified to reflect the positive benefits of resistance exercise in a controlled fashion, but these guidelines emphasize that patients should start with low weight and a low number of repetitions and progress gradually (5). In general, it is recommended that women wear compression garments during exercise if they are affected by lymphedema and should be considered on an individual basis if they are at-risk for lymphedema.

Less robust data exists on the influence of aerobic exercise; however, it appears to be safe. Kwan et al. reviewed seven studies evaluating aerobic exercise in lymphedema (58). Only three of the trials were randomized, but none found aerobic exercise or the combination of resistance and aerobic exercise to trigger or increase lymphedema. Despite the relative agreement between the studies, the authors expressed caution about the safety of aerobic exercise as the trials were limited by small numbers or poor trial adherence rates (61).

Compression Garments and Alternative Compression Devices

Compression garments are the mainstay of lymphedema maintenance therapy. They effectively reduce edema and can be easier to apply than bandages although their exact mechanism of action is unclear. Some hypothesize that the garments help augment interstitial pressure to maintain interstitial fluid homeostasis and prevent stretching of the patient's skin (62). Once garments are fitted properly, patients may choose fabric, style, and color. Improperly fitting garments lead to noncompliance and decreased efficacy. In general, upper limb garments should be worn with a gauntlet (hand compression glove) to prevent distal limb constriction and fluid build up in the hand. Upper extremity lymphedema compression garments are classified according to the pressure transmitted: class I (20 to 30 mm Hg), class II (30 to 40 mm Hg), or class III (40 to 50 mm Hg). At-risk patients are recommended to start with class I garments.

Compression garments are worn for 12 hours during the day and removed at night as they have higher resting pressures than the multilayer short stretch bandages. Given the difficulties and time needed to correctly place multilayer short stretch compression bandages, custom-made compression sleeves with properties similar to compression bandages (i.e., low resting pressures) have been designed as an alternative. Unfortunately, the cost for some of these custom overnight compression garments can exceed $1,000 and may not be covered by insurance.

Intermittent Pneumatic Compression

Intermittent pneumatic compression pumps (IPC) represent an alternative to multilayer short stretch compression bandaging; however, their incorporation into treatment regimens has been controversial. IPC are made to fit the upper or lower extremity and come equipped with a truncal attachment or vest if necessary (Fig. 40-6). They work

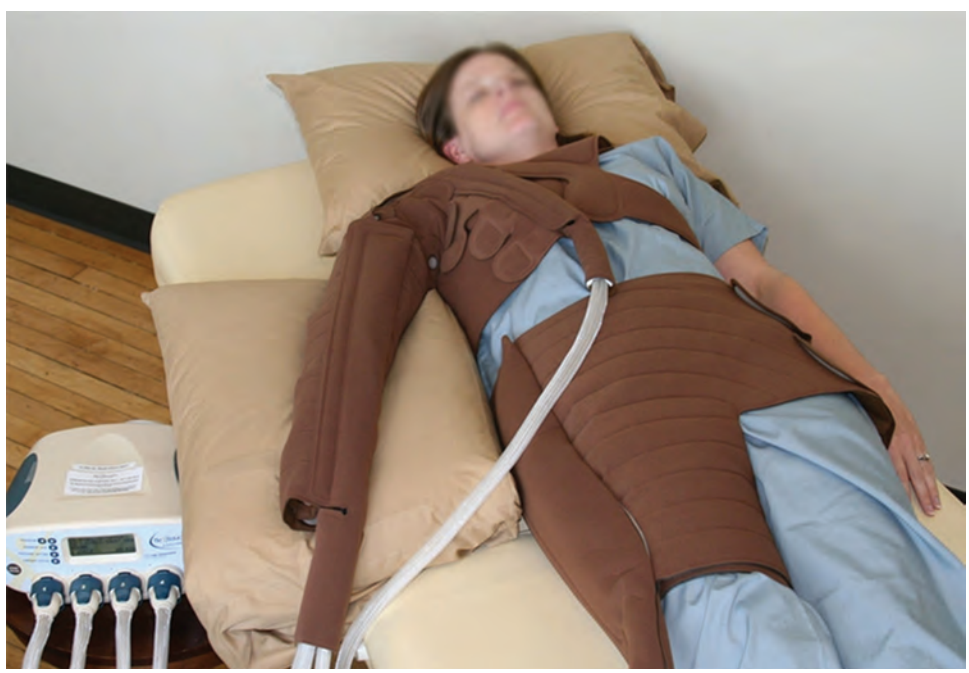

FIGURE 40-6 Intermittent pneumatic compression device.

by delivering sequential pressure through the multiple chambers to force fluid to return to the central venous system in a unidirectional fashion. The primary concern about these devices relates to the potential high pressure applied to the skin, which, in turn, may further damage the subcutaneous tissues and superficial lymphatics (63). However, data suggests IPC may provide better maintenance edema control than self-administered massage and may be a helpful adjunct in maintenance phase treatments (64). Also, Ridner et al. (65) found patients report high satisfaction with the IPC devices and feel they are beneficial to their lymphedema management. The compression process generally takes about an hour and may be used once or twice a day. After IPC, standard compression garments or multilayer short stretch bandages should be applied to maintain the edema reductions. Additional data regarding the role of IPC is needed, as recent studies continue to disagree on how it should be incorporated into treatment regimens (66,67).

Surgery

With advancements in microsurgical techniques, there has been a significant resurgence in the idea of surgery as a treatment for lymphedema. It excites clinicians and patients because it offers a potential cure for an otherwise chronic, incurable condition. In contemporary practice, surgery for lymphedema is either reconstructive—lymphovenous anastomosis (LVA) or free lymph node transfer (FLTS)—or reductive—liposuction.

With modern LVA, the surgeon performs multiple microsurgical anastomoses between 0.3–0.8 mm venules and lymphatics. Although the largest series supporting LVA (68) reports elimination of compression garments in 85% of patients, the data lacks any real patient details, objective measures of subjective improvement, and fails to clearly identify the number of patients with 10 year follow-up. Other series reporting no more than 19 patients find conflicting results of the procedure's benefit, with Lee (69) finding that 47% of patients had worse edema 4 years postoperatively. FLTS harvests healthy lymph nodes from a separate nodal basin (inguinal or contralateral axilla) and transplants them into the affected lymphedematous nodal basin. It fosters lymphatic collateral growth but has the potential risks of donor site morbidity. Overall, studies find only 37% of patients achieved >50% volume reduction, 47% eliminated compression garments, and 0% to 23% experienced donor site morbidity, specifically lymphedema. While these cases of lymphedema were reported as transient, none of the studies have sufficient follow-up or power to detect a small but albeit significant detrimental risk of donor site issues (69,70). Both LVA and FLTS physiologically seem to be more effective in early stages of lymphedema before significant tissue fibrosis exists. Liposuction is the contemporary volume reductive surgery for lymphedema. All series demonstrate >100% limb edema reduction but require lifelong strict adherence to compression garment therapy for maintenance of reduction (71). This technique in no way cures the underlying physiologic process causing lymphedema. Above all else, LVA and FLTS lack data supporting their beneficial impact on overall QOL or improvement in functional capacity. Only Brorson (72) explores these outcomes after liposuction, finding improvement in arm swelling, activities of daily living, and pain but without an improvement in overall QOL. Finally, these highly specialized surgical techniques require significant experience and a dedicated multidisciplinary team. Ideally, lymphedema surgeons would understand and be competent in all techniques for the best results. Until clinicians can assure patients of these standards with rigorously tested data, surgery for lymphedema should be viewed with guarded optimism.

Laser

Low-level laser therapy (LLLT) is a noninvasive laser treatment of damaged tissues. LLLT uses very low-intensity single-wavelength pure light to reduce limb volumes, break down fibrous tissue, and increase range of motion. Theoretically, laser increases lymph flow while reducing the amount of excess tissue fluid protein. LLLT is likely most effective in advanced lymphedema with significant tissue fibrosis, though indications for use are not standardized. A recent meta-analysis reviewed 230 patients in 8 studies and found moderate to strong evidence supporting LLLT but notes further well-designed studies are needed to determine the precise effectiveness (73).

MANAGEMENT SUMMARY

- Lymphedema occurs in 15% to 25% of ALND and 0–7% of SLNB patients.
- There are four stages of lymphedema. Physical exam and a consistent method of arm measurement should be performed on the ipsilateral and contralateral limbs at baseline and in follow-up to accurately diagnose and follow lymphedema.
- Identification of lymphedema at stage 0 and early intervention are the keys to preventing lymphedema progression.
- Common risk factors for lymphedema include ALND, axillary radiation, obesity, and injury or infection in the ipsilateral arm since surgery.
- Treatment focuses on risk reduction, skin care, manual lymphatic drainage, compression garments and devices, and exercise. Surgery remains controversial.
- Compression garments remain essential to lymphedema therapy and represent the most widely used form of compression. Both garments and bandages reduce edema.

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CHAPTER 41

Local Management of the Axilla

Monica Morrow and Jay R. Harris

CHAPTER CONTENTS

MANAGEMENT SUMMARY: AXILLA

The management of the axillary lymph nodes changed dramatically with the introduction of sentinel lymph node biopsy (SLNB), and has continued to evolve in parallel with changes in our understanding of breast cancer biology and improvements in systemic therapy. SLNB is now a well-established technique. A sentinel lymph node can be detected in more than 95% of women with breast cancer and predicts the status of the remaining axillary nodes with greater than 90% accuracy, and after a negative SLNB, first failure in the axilla is seen in fewer than 1% of patients. With experience, it has become apparent that there are relatively few contraindications to SLNB. The procedure is contraindicated in inflammatory breast cancer and other T4 tumors. Isosulfan blue dye is not known to be safe in pregnant women, and although the fetal dose with radioisotope mapping is estimated to be safe (1), the procedure has not been widely adopted in pregnant women. With these few exceptions, SLNB is the axillary staging procedure of choice in clinically node-negative women.

In women with clinically positive nodes, a needle biopsy diagnosis of metastases prior to surgery avoids the need for sentinel node biopsy and frozen section, saving OR time and costs by proceeding directly to axillary dissection. Axillary dissection should not be performed without histologic confirmation of nodal metastases because physical exam has a false-positive rate of approximately 20%. If the diagnosis of metastases is not confirmed with a needle biopsy, SLNB is appropriate, but care must be taken to remove any palpably abnormal nodes at surgery even if they are not radioactive or blue, since lymphatics that are blocked with tumor cells may not take up the mapping agents.

Axillary lymph node dissection (ALND) remains standard management for patients with clinical N1 disease, after histologic confirmation, regardless of whether they are undergoing mastectomy or breast-conserving surgery (BCS). ALND also remains standard management for clinically node-negative women found to have sentinel node macrometastases who are undergoing mastectomy.

There is more controversy regarding the management of clinically node-negative women having BCS with whole breast irradiation. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial (2) indicates that women with metastases in one or two sentinel nodes can be managed with no further axillary treatment after SLNB with no decrease in survival and a rate of first failure in the axilla of less than 1% at 6 years follow-up. SLNB alone is associated with significantly fewer side effects than ALND (3). However, there were concerns that patients randomized into ACOSOG Z0011 were an extremely favorable, highly selected subset of women undergoing BCS, and the results of this study were not generally applicable. This concern was addressed in a study at Memorial Sloan-Kettering Cancer Center which prospectively examined an unselected series of patients meeting ACOSOG Z0011 eligibility criteria to determine how often ALND could be avoided. Of 2,157 T1 and T2, clinically node-negative women undergoing BCS between August 2010 and November 2012, 381 (18%) were found to have hematoxylin and eosin detected sentinel node metastases, and 287 met ACOSOG Z0011 eligibility criteria. ALND was performed for metastases in three or more sentinel nodes or for gross extracapsular extension. Only 45 patients (16%) had such criteria for ALND. Patients requiring ALND did not differ significantly from those who did not by median age, nuclear grade, or estrogen receptor (ER) and HER2 status of the tumor. Tumors were significantly larger in the ALND group (2.2 cm vs. 1.6 cm; $p > .001$) (4). These results indicate that most women undergoing BCS who have metastases to the sentinel nodes have involvement of a limited number of nodes and are candidates for management without ALND. Further follow-up is necessary to determine the incidence of axillary recurrence. However, 72% of women selected for ALND on the basis of involvement of more than two sentinel nodes or the presence of gross extracapsular extension had additional involved lymph nodes, while the Memorial Sloan-Kettering Cancer Center nomogram for predicting the likelihood of additional nodal metastases in breast cancer patients with a positive sentinel node biopsy predicted additional positive nodes in only 34% of patients treated with sentinel node biopsy only, suggesting that the selection criteria used for ALND identifies a population of women at risk for a heavier burden of nodal disease. The findings of the ACOSOG Z0011 trial are supported by the results of the International Breast Cancer Study Group (IBCSG) 23-01 trial, which addressed the need for ALND when micrometastases were present in the sentinel node. In spite of 13% of patients in the ALND arm having additional nodal disease, the 5-year rate of the regional recurrence in this study was 1%, although not all patients received whole breast radiation therapy (RT) (5).

An alternative approach to the patient with positive sentinel nodes was raised in the After Mapping of the Axilla: Radiotherapy or Surgery? (AMAROS) trial, which randomized clinically node-negative, sentinel node–positive patients to ALND or axillary irradiation. At a median follow-up of 6.1 years, 5-year rates of regional control did not differ between the two arms (99.5% vs. 99.0%), but fewer side effects were seen in the RT arm, with 28% of ALND patients having lymphedema compared to 14% in the RT arm ($p < .0001$) (6). However, significant side effects of RT, such as brachial plexopathy, evolve over a more prolonged time course than surgical side effects. Therefore, it is uncertain whether this advantage for RT will persist over time, and provides a note of caution for the widespread adoption of this approach.

In aggregate, ACOSOG Z0011 (2), IBCSG 23-01 (5), and AMAROS (6) all suggest that, in the setting of systemic therapy and limited RT, ALND can be avoided in many patients, decreasing morbidity, and with no decrease in survival. In contrast to these results are the findings of the MA.20 trial (7), which indicate that maximal treatment to the regional nodal areas improves disease-free survival (DFS). In this study, clinically node-negative patients with T1 and T2 tumors undergoing BCS and whole breast irradiation were randomized to ALND or ALND plus RT to the axillary apex, supraclavicular, and internal mammary nodes. Eighty-five percent of patients had one to three positive nodes. After a median follow-up of 5 years, both local-regional and distant metastatic recurrences were significantly reduced from 5.5% to 3.2% ($p = .02$), and from 13.0% to 7.6% ($p = .002$), respectively, with nodal RT, and DFS was significantly improved. A trend toward improved overall survival was also observed. These findings were somewhat surprising because in contrast to findings in the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview, the absolute reduction in distant metastases seen with RT was greater than the reduction in local-regional recurrence, and it occurred in the same 5-year time interval. (A similar trial conducted by the EORTC should have results in the near future and will help to clarify the MA.20 results.) How to integrate the findings of these somewhat contradictory trials into a unified approach to the axilla and, more generally, to the regional nodes remains a work in progress. At present, it appears that women with sentinel node micrometastases do not require ALND for local control or survival benefit, although caution should be used in patients having mastectomy who are found to have micrometastases in multiple nodes, as data addressing this scenario are limited. Defining which patients with macrometastases can be managed with no ALND and tangent field RT, and which require both ALND and node field RT, is the challenge for the future, but it is unlikely that a single approach will be appropriate for all node-positive patients.

MANAGEMENT SUMMARY

- Sentinel node biopsy is the axillary staging procedure of choice for clinically node-negative breast cancer patients.
- The only contraindications to sentinel node biopsy are inflammatory and other T4 tumors, and pregnancy.
- In patients with clinically positive nodes, needle biopsy should be used to establish a preoperative diagnosis of metastases. If metastases are not confirmed, sentinel node biopsy is appropriate as long as palpably abnormal nodes are removed.
- ALND remains standard management for clinically node-positive women undergoing mastectomy or BCS, and for clinically node-negative women with sentinel node macrometastases having mastectomy.
- Micrometastases in the sentinel node are not an indication for ALND if BCS and RT are being performed, and evidence is accumulating that ALND is not necessary for micrometastases in the setting of mastectomy.
- At least some patients with macrometastases in one or two sentinel nodes undergoing treatment with BCS and whole breast RT do not require ALND. The largest experience with this approach is in ER-positive, HER2-negative women.
- Subsets of women with one to three positive nodes treated with BCS and whole breast RT requiring nodal field irradiation remain to be defined. Consideration of this approach should be given to women with heavier tumor burdens and high-risk features.

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CHAPTER 42

Postmastectomy Radiation Therapy

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CHAPTER CONTENTS

INTRODUCTION

The use of postmastectomy radiation therapy (PMRT) is perhaps one of the most intensively studied topics in oncology and yet continues to be a cause of considerable debate. Indeed, some of the first ever prospective randomized trials to be conducted addressed the utility of PMRT. This area has attracted robust scientific inquiry since the initial efforts, and has been the subject of over 20 randomized prospective trials. Despite the scientific scrutiny this area has attracted, important questions still remain to be answered.

This chapter will focus on the topic of PMRT and is divided into four sections:

1. In the section on the Rationale for PMRT, we will review the data supporting the efficacy of PMRT as well as the risks and sequelae of PMRT.
2. Patient selection.
3. Reconstruction and PMRT.
4. Technique of PMRT.

The role of PMRT after neoadjuvant chemotherapy and in locally advanced and inflammatory breast cancer is discussed in Chapters 57, 58, and 59, respectively.

RATIONALE FOR PMRT

The principle that irradiating the chest wall and regional lymph nodes after mastectomy can reduce subsequent local-regional recurrences (LRRs) has been well documented by multiple older trials comparing mastectomy alone to mastectomy with postoperative radiation. These trials typically used unsophisticated radiation techniques coupled with outdated radiation treatment machines that produced orthovoltage x-rays, resulting in less precise delivery of radiation to target tissues and increased doses to nontarget normal structures. Naturally, the relevance of these older trials is limited in the context of modern radiation therapy, but they adequately demonstrated two important facts: first, PMRT can effectively reduce the burden of residual local-regional disease, and second, radiation therapy is more comprehensive and more "radical," in terms of treatment volume, than even the most radical surgery. These trials did not demonstrate improvements in survival; benefits in breast cancer mortality may have been offset by nonbreast cancer–related morbidity and mortality associated with the radiation techniques employed (1).

The potential improvement in local-regional control resulting from adjuvant systemic therapy alone can be studied through the numerous trials of systemic therapy versus nil that have reported patterns of failure (2). Data demonstrating a benefit of systemic cytotoxic chemotherapy on local-regional control are somewhat inconsistent, which may be related to the confounding effects of patient selection, surgery and radiation delivery. However, the most recent Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis of systemic therapy trials reported statistically fewer isolated local relapses in patients receiving polychemotherapy (recurrence rate ratio of 0.63 and 0.70 for women younger than 50 and 50–69, respectively) (3). Similarly, adjuvant tamoxifen seems to improve local-regional control as corroborated by the last fully reported EBCTCG meta-analysis, which demonstrated an isolated local recurrence rate ratio of 0.47 with tamoxifen versus without (3). These observations, along with the demonstrable improvement in survival with systemic agents, raise the obvious question of the relative additional benefit of PMRT in patients receiving systemic therapy.

Randomized Trials of Adjuvant Systemic Therapy Alone or in Addition to PMRT

Several trials have studied the efficacy and incremental benefit of PMRT in the presence of systemic therapy (2). The most significant contributions have come from the Danish Breast Cancer Cooperative Group (4,5) and the British Columbia Cancer Agency (BCCA) (6). The trials conducted

by these two groups, together with the updated findings of the EBCTCG meta-analysis of radiation trials discussed later (7), have decisively altered practice and reaffirmed the role of PMRT in current breast oncology.

In protocol 82b, the Danish Breast Cancer Cooperative Group randomized premenopausal women with high-risk breast cancer after modified radical mastectomy (total mastectomy and level I and II axillary dissection) to either nine cycles of cyclophosphamide-methotrexate-fluorouracil (CMF) chemotherapy or to eight cycles of CMF chemotherapy and radiation therapy to the chest wall and regional nodes between the first and second cycles of chemotherapy (4). High-risk status was defined as positive lymph nodes, tumor size greater than 5 cm, or invasion of the skin or pectoralis fascia. Radiation therapy was delivered to a total dose of 50 Gy in 25 fractions or 48 Gy in 22 fractions using anterior electron fields to treat the chest wall and internal mammary nodes (IMNs) and a matched anterior photon field to treat the supraclavicular, infraclavicular, and axillary lymph nodes. A posterior axillary photon field was used in patients with a large anterior-posterior (AP) separation. Over 92% of all patients were treated with megavoltage equipment. The study enrolled 1,708 patients between 1982 and 1989. With a median follow-up of 114 months, the irradiated group demonstrated statistically significant improvements in LRR (32% vs. 9%), disease-free survival (3% vs. 48% at 10 years), and overall survival (45% vs. 54% at 10 years). Over half of all LRRs were on the chest wall.

In the companion trial, protocol 82c (5), postmenopausal women younger than 70 with high-risk breast cancer (defined as in 82b) were randomized after modified radical mastectomy to receive either 30 mg of tamoxifen daily for 1 year beginning 2 to 4 weeks after surgery alone or with concurrent radiation therapy delivered to the chest wall and draining lymph nodes. A total of 1,375 patients were recruited between 1982 and 1990 and followed for a median time of 10 years. As in the 82b study, the irradiated group demonstrated statistically significant improvements in LRR (35% vs. 8%), disease-free survival (24% vs. 36%) and overall survival (36% vs. 45%). As in the 82b study, recurrence at all local-regional subsites was lower with PMRT than without. Although these well-designed efforts by the Danish group are not without flaw (as discussed below) they nonetheless strengthened the theory that, in certain patient subsets, aggressive local-regional control could result in improvements in survival end points.

The smaller British Columbia trial enrolled 318 node-positive premenopausal breast cancer patients and randomized them after modified radical mastectomy to either radiation therapy or no additional local-regional therapy (6). Both groups received adjuvant CMF chemotherapy for 12 (first 80 patients) or 6 months. Radiation therapy was delivered to the chest wall to a dose of 37.5 Gy in 16 daily fractions through opposed tangential photon fields. The supraclavicular and axilla nodes were treated with an AP field and a posterior axillary field, with a target midaxilla dose of 35 Gy. Bilateral IMNs were treated with an additional anterior field to a dose of 37.5 Gy in 16 fractions. All treatments were delivered with cobalt machines, between cycle four and five of chemotherapy. After a median follow-up of 20 years, the 20-year survival free of local-regional disease developing before systemic was 61% in the chemotherapy alone arm and 87% in the irradiated group. The irradiated group had statistically significant improvements in 20-year event-free survival (25% vs. 38%), systemic disease-free survival (31% vs. 48%), breast-cancer specific survival (38% vs. 53%), and overall survival (37% vs. 47%). There were slightly more nonbreast cancer deaths in the irradiated group (9% vs. 4%, $p = 0.11$). There were three cardiac deaths (2%) in the irradiated group versus one (0.6%) in the control group ($p = .62$), and 9% of patients in the irradiated group developed arm edema compared with 3% in the control group ($p = .035$). This study corroborated the Danish experience and again demonstrated some of the most remarkable improvements in survival end points ever reported for any adjuvant therapy.

Taken together, these studies demonstrated that certain patient cohorts have a high risk for LRR that is inadequately addressed by systemic therapy alone. Furthermore, reducing the likelihood of LRR can result in improved survival; presumably, persistent or recurrent local-regional disease can be a source of distant metastases and subsequent death. These studies imply that the benefit of systemic therapy is primarily to lower the competing risk of distant micrometastases, and that adjuvant local-regional therapy and adjuvant systemic therapy independently benefit these patients on the principle of spatial cooperation. There is no definitive randomized data supporting any specific sequencing of systemic therapy and radiation in the postmastectomy setting; for patients receiving both cytotoxic chemotherapy and postmastectomy radiation, the prevailing practice typically sequences the cytotoxic chemotherapy first, followed by radiation. Hormonal therapy, if indicated, may be given concurrently with radiation or following radiation, though some clinicians prefer to sequence tamoxifen after the radiation. Although there is little in the way of long-term follow-up data and additional studies will likely be forthcoming in the next few years, adjuvant systemic therapy with trastuzumab (typically administered for up to 1 year following chemotherapy) appears to be safe and effective given concurrently with radiation (8).

EBCTCG Meta-Analysis

The EBCTCG has collected primary data from every randomized trial of adjuvant radiotherapy in breast cancer and periodically reports the ongoing analyses on the benefits and risks of radiation therapy in these patients. The most recent full report from 2005 reviewed data on 9,933 patients enrolled in 25 trials of PMRT, all of which were unconfounded by the use of systemic therapy (7). Node-positive patients who had axillary clearance and received radiation therapy after mastectomy had a 5-year LRR rate of 6%, compared to 23% for unirradiated controls (15-year rates were 8% vs. 29%). In every large trial of PMRT in node-positive women, radiation therapy produced a similar proportional reduction in local recurrence, powerfully demonstrating the comparable efficacy of radiotherapy in achieving local control across all time periods. Even more significantly, PMRT also produced comparable proportional reductions in local recurrence in all women irrespective of age or tumor characteristics.

Absolute reductions in local recurrence were dependent on the absolute risk in the control arm (i.e., larger reductions were seen in subsets with greater risk). For patients with a control risk of local recurrence greater than 10%, the addition of radiation therapy (RT) improved local recurrence irrespective of systemic therapy. For women with node-positive disease who were irradiated after mastectomy and axillary clearance, a 17% absolute improvement in 5-year local control translated into a highly statistically significant 5.4% absolute improvement in 15-year breast cancer mortality (60.1% vs. 54.7%, $2p = 0.0002$, Fig. 42-1) (7), and a 4.4% absolute improvement in 15-year all-cause mortality (64.2% vs. 59.8%, $2p = 0.0009$) over unirradiated controls.

There was an excess cancer incidence in women studied in the EBCTCG report (including women treated with an intact breast), mainly in contralateral breast cancer and lung

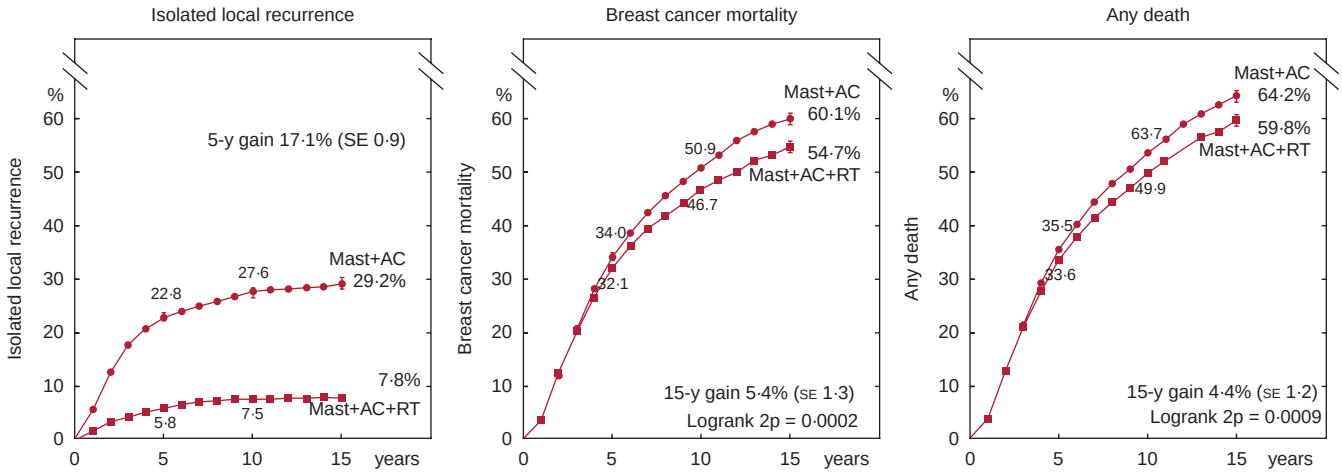

FIGURE 42-1 Probabilities for isolated local recurrence, breast cancer mortality, and any death in node-positive patients treated with postmastectomy radiation therapy after mastectomy and axillary clearance. (Reproduced with permission from Early Breast Cancer Trialists' Collaborative Group. Effects of radiotherapy and differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomized trials. *Lancet* 2005;366:2087–2106.)

cancer, and an excess mortality from heart disease and lung cancer. The averaged detrimental effects were modest, with 15-year absolute loss of 1.8% for contralateral breast cancer and 1.3% for nonbreast cancer mortality. Importantly, the proportional excess of nonbreast cancer deaths was greatest 5 to 14 years and more than 15 years after randomization, and the mean dates of randomization for these two groups was 1975 and 1970, respectively. The authors of the EBCTCG correctly point out that the late hazards evident in their report could well be substantially lower for modern radiation therapy technique and regimens.

The EBCTCG data were presented at the 2007 annual meeting of the American Society of Clinical Oncology (9). Since then further analyses have been carried out and prepared for publication (Sarah Darby, personal communication). Although the data are still preliminary, they represent the first detailed analysis of patients stratified both by extent of axillary dissection (at least level II vs. less extensive and by degree of nodal involvement (1–3 vs. 4+), and several pertinent and new findings have been described.

Among women with node positive disease, radiotherapy reduced the rate of any recurrence both for women who had undergone axillary dissection to at least level II (recurrence rate ratio: 0.75, $2p < 0.00001$), and for women who had undergone less extensive axillary dissection (0.59, $2p < 0.00001$), although the proportional reduction was larger in the women who had less extensive axillary dissection ($2p$ for difference = 0.003). In addition, the subgroup of patients with axillary dissection to at least level II and one to three positive lymph nodes had a statistically significant improvement in 15-year breast cancer mortality (death rate ratio irradiated vs. unirradiated: 0.80, 15-year gain 7.9%, 50.2 vs. 42.3%, $2p = 0.01$) with PMRT. This proportional reduction did not differ significantly according to whether or not the trial policy was to give systemic therapy (usually cmf or, for ER+, tamoxifen) in both trial arms.

The cohort of women with axillary dissection to at least level II and four or more positive nodes also enjoyed significant benefits from PMRT in their risk of any recurrence (recurrence rate ratio: 0.79, $2p = 0.0003$) and breast cancer mortality (death rate ratio: 0.87, $2p = 0.04$). In contrast to women with node positive disease, women with node negative disease had no benefit from PMRT either in terms of recurrence (rate ratio: 1.06, $2p > 0.1$) or breast cancer mortality (rate ratio: 1.18 $2p > 0.1$). In summary, the EBCTCG update appears to suggest that women with node positive disease are likely to benefit from PMRT, even when they have had axillary dissection to at least level II and probably also in the presence of systemic therapy.

The EBCTCG overview represents one of the most significant contributions to the study of PMRT. However, the relevance of its findings may be limited by the inclusion of older trials that used fractionation schemes, treatment machines, and treatment volumes that are antiquated by current standards, as well as by the usual limitations of meta-analyses. To address these issues, Van de Steene et al. (10) re-examined the EBCTCG data and identified four factors which selected for significant improvement in the odds ratio (OR) for survival in the irradiated versus control populations: start date of the trial (after 1970 [OR 0.935]), number of patients (>600 patients [OR 0.932]), fractionation (conventional [OR 0.896]), and crude survival on the trial (at least 80% [OR 0.799]). Excluding trials that began before 1970 and trials with small sample sizes produced a significant odds reduction of 12.3% ± 4.3% with irradiation (10). Gebski et al. performed a meta-analysis in which they carefully attempted to control for the quality of radiation delivery in PMRT trials. The authors defined optimal dose as being between 40 and 60 Gy delivered in 2 Gy fractions (nonconventional fractionation schemes were converted to 2-Gy equivalents using bioeffective dose calculations) and appropriate treatment volumes as both chest wall and regional lymphatics (11). The authors reanalyzed data from the EBCTCG applying these criteria. The proportional reduction in local-regional recurrence was greater for trials with optimal dose and volume (80%), compared to those with suboptimal dose (70%) or field design (64%). An improvement in breast cancer mortality was restricted to those trials that used appropriate doses and fields for irradiation (6.4% absolute increase in survival, $p < .001$).

The most concerning risk of PMRT for radiation oncologists is the risk of radiation induced cardiac morbidity. As described above, the EBCTCG meta-analysis as well as other registry data have detected increased risks of cardiac

mortality in irradiated patients (7,12,13). In contrast, an analysis of the Danish postmastectomy trials patients by Hojris et al. (14) found, using a technique of RT that avoided cardiac irradiation, equal rates of ischemic heart disease and acute myocardial infarction in the irradiated and unirradiated group. Approximately 3% of patients in both groups had ischemia-related morbidity at a median follow-up of 117 months and less than 1% of patients in both arms had death due to cardiac causes. There was no difference in this study when comparing left- versus right-sided irradiation. However, these numbers may underestimate the true burden of radiation-related cardiac morbidity due to the competing risk of breast-cancer death in this high-risk population, and also because this study was an unplanned retrospective report on a prospectively studied patient cohort.

Gyenes et al. (15) reviewed 960 patients treated on the first Stockholm Breast Cancer trial (modified radical mastectomy alone vs. preoperative vs. postoperative RT accrued 1971–1976) and reported 58 acute myocardial infarctions (MI) in the study population for a crude rate of 6%. There were no differences in acute MI or death due to cardiovascular disease (n = 63/960) between irradiated and unirradiated patients. Importantly, the authors showed that only patients in the high-dose–volume group had an excess hazard ratio (HR) of cardiovascular death (HR 2, 95% CI, 1.0–3.9, p = .04). A retrospective study by Harris et al. (16) examined cardiac events in a series of 961 women irradiated to the intact breast and reported no interaction between left-sided versus right-sided RT on cardiac mortality or congestive heart disease. A significant interaction was noted between left-sided RT in the subsequent development of coronary artery disease (20-year actuarial risk 25% vs. 10% for right-sided, p <.001) and MI (15% vs. 5%, p <.002). Coexistent hypertension was an independent hazard for the development of coronary artery disease.

A study of the Surveillance, Epidemiology and End Results (SEER) database conducted by Giordano et al. (17) compared 15-year cardiac mortality rates in left- versus right-sided breast cancer as a function of the year of diagnosis in patients who received RT. Presumably, patients with left-sided lesions received more heart irradiation than those with right-sided lesions. Although the authors demonstrated excess cardiac mortality in left-sided breast cancer patients diagnosed between 1973 and 1979 (13% vs. 10%, p = .02), they found no significant difference in patients irradiated in the most recent time periods (~9% for both groups in the 1980–1984 cohort, and 5% to 6% in the 1985–1989 cohort). Beginning in 1979, the hazard of death from ischemic heart disease in left-sided breast cancer patients (vs. right-sided) declined by an average of 6% per year.

In a similar study, Henson et al. (18) evaluated the relative risk (RR) of cardiac disease in women irradiated for left- versus right-sided breast cancer and the relative risk of lung cancer in the ipsilateral versus contralateral lung in women irradiated for breast cancer using the SEER public-use data set. They found that the RR of breast cancer continued to increase, reaching 1.9 (1.52–2.37) 20 years after diagnosis. Similarly, the RR of lung cancer increased continuously in time, peaking at 3.87 (2.19–6.82) for women 20 years after diagnosis. As noted by the study authors, many women in this analysis were treated during an age in which IMN nodal RT was much more common, thus, potentially increasing the toxicity risks compared to contemporary treatment cohorts. Furthermore, current techniques that enhance treatment conformity probably decrease cardiac and lung doses compared to the study cohorts, even when the IMs are treated.

Darby et al. (19) reported a well-executed population-based case-control study of the risks of cardiac irradiation in patients treated for breast cancer. The mean dose to the whole heart was 5 Gy in the control cohort, and each excess Gy in mean dose conferred a 7% RR decrement. Importantly, no threshold dose for risk was detected. Taken together, these data stress the potential for cardiac morbidity and mortality with breast irradiation but are reassuring that routine contouring of the heart and improvements in image-based simulation and treatment delivery can substantially reduce these risks.

Little data exists on the cumulative effects of anthracyclines and radiation therapy on cardiac morbidity and function. Perhaps the best data on this topic comes from Fumoleau et al. (20) who reported long-term cardiac function in 3,577 assessable patients randomized on eight French trials of adjuvant therapy, 2,553 of whom received epirubicin-based chemotherapy. Ninety-seven percent of women on the epirubicin cohort had adjuvant radiation (to the intact breast or postmastectomy) and 94% on the nonepirubicin cohort received RT (with about two-thirds of these receiving RT to the IMNs). The 7-year risk of left-ventricular dysfunction was 1.36% in the epirubicin arm and 0.2% in the nonanthracycline patients. Age 65 or greater and body mass index > 27 kg/m^2 were additional significant risk factors.

Additional nonlife-threatening late risks of postmastectomy irradiation can include arm edema, fibrosis, shoulder stiffness, and brachial plexopathy. In an instructive report, the Danish postmastectomy investigators invited patients irradiated at Aarhus University Hospital who were alive and without evidence of disease to participate in a study of the late effects of PMRT (21). Eighty-four patients accepted the invitation and were eligible for analysis, and these patients were carefully assessed for late toxicity based primarily on LENT-SOMA criteria. More women in the irradiated group had lymphedema (17% vs. 9%) and impaired shoulder movement (16% vs. 2%) that interfered with work or daily activities. Irradiated patients also had more arm parasthesias (21% vs. 7%) and more arm weakness (14% vs. 2%). Only the shoulder function comparison was statistically significant. Symptomatic pulmonary complications were equal in irradiated and unirradiated patients. In a separate report of 161 patients with neurological follow-up who were irradiated on the Danish 82 protocols, 5% of patients had disabling and 8% had mild radiation-induced brachial plexopathies (22). Kuhnt et al. (23) reported acute and chronic reactions in 194 patients receiving PMRT. Twenty-two percent of patients had any incidence of chronic effects, mostly from arm edema (28 of 43). Five patients had telangiectasia and one patient had plexopathy.

In conclusion, randomized trials as well as data from meta-analyses provide a strong rationale for PMRT in patients with a high likelihood of local-regional residual disease, despite the use of systemic therapy in these patients. Additional local-regional therapy in the form of RT reduces LRR rates by a factor of approximately two-thirds, and one breast-cancer death is averted for every four LRR prevented by RT. The risks of PMRT are modest but demonstrable, and cardiac effects may largely be attributable to older technique. The cardiac and pulmonary toxicities of modern day PMRT continue to be evaluated and are likely minimal with careful three-dimensional planning and treatment techniques.

PATIENT SELECTION FOR PMRT

Node-Positive Patients

Node positivity in the axilla is the most significant predictor of LRR after mastectomy. It should be borne in mind, however, that approximately two-third of LRR occur on the

chest wall, and that axillary failures are far less common (24–27). Accordingly, the degree of node positivity should be viewed as an adverse feature that confers a higher risk for overall LRR (i.e., not limited to failure at regional sites).

The Danish and Canadian PMRT trials demonstrated stable relative risk reductions for all events in all groups of node-positive patients. However, the conclusion that all node-positive patients warrant PMRT has been challenged. There are two general criticisms of these studies which limit the generalizing of these findings to all node-positive patients: first, the adequacy of the systemic therapy in the control arms of these studies; and second, the issue of the "background risk" in the relevant study populations.

The most recent EBCTCG meta-analysis of systemic therapy showed a significant but minor improvement for anthracycline containing polychemotherapy regimens over CMF regimens (3). Whether this incremental benefit improves local-regional control as well is unknown and is probably unlikely in patients with high risk for local-regional microscopic residual. Furthermore, neither the addition of taxanes nor increases in the intensity or density of chemotherapy have had demonstrable impacts on local-regional control in node-positive patients, although they do improve survival end points presumably by addressing micrometases (28–33). In sum, it seems unlikely that present-day chemotherapy regimens would significantly alter the findings of the postmastectomy trials. In contrast, the Danish 82c trial treated postmenopausal patients (untested for estrogen-receptor/progesterone-receptor [ER/PR] status) with 1 year of tamoxifen (5), and it is unknown how a longer duration of hormonal therapy in a population known to be hormone-receptor positive would modulate the risk of LRR and thus the benefit of PMRT.

A more significant factor that limits interpretation of the Danish and British Columbia trials is that node-positive patients on the control arm of these trials had higher LRR rates than commonly reported for patients treated in the United States and elsewhere (4–6,24). This difference is especially obvious in patients with one to three positive lymph nodes, who represented about 60% of patients on these studies. In the unirradiated Danish population, the 18-year probability of local-regional recurrence (as first site of failure) was 59% for patients with four or more positive nodes, and 37% for those with one to three positive nodes (34). In the unirradiated Canadian population, the 20-year isolated LRR rate was 41% for patients with four or more positive nodes, and 21% for patients with one to three positive nodes (6). LRR developing any time before distant failure (i.e., cumulative LRR as first failure) was not reported as a function of the number of positive lymph nodes, but was 39% for the entire unirradiated group. In contrast, several large series of patients treated in the United States and elsewhere have reported LRR rates in the range of 6% to 13% for patients with one to three positive nodes (25,26,35,36) (Table 42-1). This seems to indicate that the background risk for LRR in the Danish and BC trials was higher than average, and this may have exaggerated the benefit of PMRT in this population.

Differences in the extent of axillary surgery may partially explain the differences in the risk of LRR in patients with one to three positive nodes. Full level I and II axillary dissections were not performed; a median of seven lymph nodes were removed in the Danish studies and a median of 11 lymph nodes were examined in patients on the Canadian trial (4–6). As such, many of the patients scored as having one to three positive lymph nodes may have actually had four or more positive nodes had full axillary dissections been performed. Tellingly, failure in the axilla either alone or as a component of LRR represented 43% of all LRR in the Danish studies (24), compared to 14% in the data cited above (25).

TABLE 42-1

LRR Rates in Patients Not Treated with Radiation after Mastectomy in Randomized Clinical Trials

Patterns-of-Failure Studies (Reference)	*No. of Patients*	*LRR Rates at 10 Years (%)*
ECOG (26)		
1–3 +LN	1,018	13
≥4 +LN	998	29
MD Anderson (27)		
1–3 +LN	437	13
≥ 4 +LN	373	25
NSABP (35)		
1–3 +LN	2,957	13
≥4 +LN	2,784	27
IBCSG (38)		
1–3 +LN	2,402	17
≥4 +LN	1,670	31

ECOG, Eastern Cooperative Oncology Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; IBCSG, International Breast Cancer Study Group.

However, it is important to note that the reports cited above and in Table 42-1 have reported 10-year local-regional control rates. The Danish studies report 18-year recurrence rates, and also document a consistent LRR of about 1% per year between follow-up years 10 and 25 (24). Similarly, in the British Columbia (BC) trial, which has reported 20-year recurrence rates, approximately 20% of LRRs occurred after follow-up year 10 (6). In addition, other identified and unidentified risk factors, such as T4 tumors or pectoral fascia invasion, may have been over-represented in the postmastectomy trials (24), increasing the background risk for local-regional failure. For example, in a combined report of patients with one to three positive axillary nodes treated on the control arm of the British Columbia postmastectomy trial (n = 82) and similar patients treated on prospective systemic therapy trials at the MD Anderson Cancer Center (MDACC) (n = 462), statistically significant differences were detected in patients on the BC trial who were younger (median age 43 vs. 48) and had more lymphovascular invasion (LVI) (52% vs. 33%), in addition to fewer examined nodes (median 10 vs. 16) (37). The resultant 10-year Kaplan-Meier estimates of LRR were 21.5% and 12.6% for the BC and MDACC patients, respectively.

Nonetheless, several reports have demonstrated the prognostic impact of total dissected nodes, nodal ratio (number of involved to uninvolved nodes), and number of total uninvolved nodes on LRR and even overall survival (25,26,35–40). Attempts by Danish investigators to reanalyze their patients to include only those with adequate dissections are limited by the fact that these patients were not stratified by this important risk factor at randomization (41). This issue remains unclear and, because it has complicated the interpretation of the existing postmastectomy trials, can only be addressed in the context of additional large, randomized trials.

Recent reports have demonstrated rather low rates of LRR in patient populations treated with mastectomy and highly active systemic agents alone. These reports challenge the current interpretation of both the PMRT trials and the EBCTCG meta-analysis on the basis of current

improvements in detection, surgical technique, pathological review, and adjuvant therapies. Could the "control" risk for local-regional failure in currently treated patients be much lower than expected from a review of patient data collected decades ago? Sharma et al. (42) at the MDACC reported outcomes in a contemporary cohort of women with T1-2 breast cancer and node-negative or one to three node-positive disease, 1,019 women were treated between 1997 and 2002; 77% of women had adjuvant systemic therapy with a median follow-up of 7.5 years. The local-regional relapse rate was exceptionally low—2.3%. Young age was a significant covariate for LRR on multivariate regression analysis. As with any retrospective analysis, selection biases may have been operant and contributing the low rate of LRR. As pointed out by the study authors, there were few women with three positive lymph nodes in their analysis (<2%) and many women with T1-2N0-1a with adverse features on pathology were likely treated with PMRT, thus selecting for a low-risk group. Nonetheless, the Sharma report offers a tantalizing prospect—perhaps current cumulative improvements in screening, surgery, pathological assessment, and adjuvant systemic therapy combine to significantly reduce the background risk of LR failure. Pointedly, a similar report on identical stage patients treated at MDACC during an earlier time period (1975–1994) had a 10-year LRR of 14% (25).

Still, there is recent evidence that supports an aggressive treatment approach in patients with intermediate-risk presentations. Abdulkarim et al. (43) reported results on a retrospective cohort of triple-negative breast cancer patients (n = 768) and compared outcomes stratified by type of local-regional therapy. Patients who received breast-conserving therapy (BCT) had better local-regional control and better survival than patients who received modified radical mastectomy (MRM) on univariate analysis. On multivariate analysis, initial BCT continued to predict for improved LRR but not overall survival (OS). Interestingly, in the subset of women with T1-T2N0 disease, patients who received BCT had better 5-year local-regional control compared to women who had MRM. Local treatment strategy remained a predictor of LRR on multivariate analysis in this group. One possible explanation is the larger, more comprehensive treatment volume associated with standard radiation fields compared to mastectomy alone. Similarly, Canadian trials have reported preliminary MA.20 results in abstract form. In this trial, high-risk node-negative or node-positive patients were randomly assigned to whole breast irradiation alone or including regional draining lymph nodes after breast-conserving surgery. Results on 1,832 randomized patients were presented at the 2011 annual American Society of Clinical Oncology (ASCO) meeting (44). With a median follow-up of 62 months, the addition of regional nodal RT improved 5-year local-regional control, distant disease control (92.4% vs. 87%, p = .002), and overall survival (92.3% vs. 90.7%, p = .07). Given these data, it appears that a serious discussion of PMRT is *still* warranted in the majority of women with one to three positive lymph nodes on mastectomy.

Both the American Society of Therapeutic Radiology and Oncology (ASTRO) and the ASCO as well as other advisory organizations have endorsed the routine use of PMRT in women with four or more involved nodes and node-positive women with tumors greater than 5 cm, who have a high (>20% to 25%) risk of LRR without RT. Both societies recognize the uncertain benefit of PMRT in patients with T1 or T2 primaries with one to three positive nodes (stage II) in whom the risk of LRR is intermediate (around 10% to 20%) (45,46). The European SUPREMO trial (Selective Use of Postoperative Radiotherapy after Mastectomy) is currently open and will attempt to answer this question. This trial randomizes intermediate risk operable breast cancer (node-positive stage II tumors and node-negative tumors larger than 2 cm with adverse features [high grade or LVI]) to chest wall irradiation or observation after mastectomy.

Several groups have attempted to identify high-risk patients within the one to three positive lymph node group (Table 42-2). Clearly, this group of patients is heterogeneous in terms of various potential clinicopathological factors that may allow differentiation into low- and high-risk cohorts. One of the most significant efforts attempting to identify these risk factors comes from Wallgren et al. (36) who reviewed data on over 5,300 patients enrolled on the first seven trials of the International Breast Cancer Study Group (IBCSG). These trials of systemic therapy required a minimum of eight dissected lymph nodes and negative margins. In patients with one to three involved lymph nodes, premenopausal patients with LVI and grade 3 tumors had cumulative incidence functions (CIFs) exceeding 20% for any LRR. Postmenopausal women with grade 3 tumors and tumors larger than 2 cm had correspondingly high risk. Collapsing this information, premenopausal women with one to three positive lymph nodes had LRR risks ranging from 19% to 27% if they had grade 2 or 3 disease with vascular invasion, but that risk was less than 15% if they had grade 1 disease with no vascular invasion. In a subsequent report, the same group reported results from IBCSG trials 1 through 9 and demonstrated the significant independent impact, in a multivariate model, of the number of uninvolved lymph nodes (38). More specifically, in the group of patients with one to three lymph nodes (n = 2,402), factors that independently predicted a CIF for LRR exceeding 20% included age younger than 40, fewer than 10 uninvolved lymph nodes, and LVI.

The investigators at MDACC have reported results from their cohort of 1,031 patients treated with mastectomy and doxorubicin-based chemotherapy without subsequent radiation therapy on five prospective trials between 1975 and 1994 (25,39,47). Three factors were significant for isolated and total LRR on multivariate analysis of the entire group: T stage, number of involved nodes, and extranodal extension 2 mm or more. Restricting the analysis to patients with T1or T2 disease and one to three axillary nodes (n = 404, overall isolated 10-year LRR risk of 10%), multivariate predictors of LRR were fewer examined nodes, higher T stage, and extracapsular extension (ECE), with isolated 10-year LRR in excess of 25% for patients with gross ECE (33%) and tumor size greater than 4 cm (26%) (25). In a more detailed study of pathologic factors in the same group of patients, Katz et al. (47) reported that close or positive margins and gross multicentric disease were also predictive of LRR on multivariable. However, in the subgroup of patients with one to three positive nodes, invasion of skin and nipple, pectoral fascia invasion, and close or positive margins, but not multicentricity, were significant predictors of higher LRR. In a similar group of patients, Fowble et al. (48) reported that patients with multicentric disease without other strong risk factors for postmastectomy chest wall relapse had a 5-year actuarial risk of an isolated local-regional recurrence of only 8%.

Truong et al. (40) reported on 821 women with T1 and T2 primary lesions with 1 to 3 positive lymph nodes treated with mastectomy and systemic therapy (in 94%) within the BCCA. Twelve putative clinicopathologic factors were examined for their effect on LRR in a multivariate model. Age less than 45, nodal ratio greater than 25%, ER negative status, and medial location independently predicted for isolated and any LRR, with age having the greatest effect (HR = 3.44). The authors suggested using age and nodal ratio as first line discriminants of risk and medial location and ER negative status as secondary factors.

TABLE 42-2

Cofactors Associated with a Greater than 15% LRR after Mastectomy and Chemotherapy in Patients with One to Three Positive Lymph Nodes

Study	*Number of Patients*	*Cofactors*	*End Point*
Wallgren et al. (36)	2,404	• Premenopausal, G2 or G3, LVSI • Postmenopausal, G3 • Postmenopausal, G2, T2 disease	• 10-year LRF ± DF (isolated LRF or with simultaneous DF)
Taghian et al. (35)	2,403	• Age <50, T2 disease	• 10-year LRF ± DF
Recht et al. (26)	1,018	• Premenopausal, T1 disease	• 10-year LRF ± DF (isolated LRF or with simultaneous DF)
Truong et al. (40)	821	• Age <45[a] • 25% of lymph nodes involved[a] • ER negative disease[a] • G3 disease • T2 disease • LVSI • Medial tumor location[a]	• 10-year LRF ± DF (isolated LRF or with simultaneous DF)
Katz et al. (47)	466	• Tumor size >4 cm • Invasion of skin/nipple • Invasion of pectoralis fascia • Close or positive margins	• 10-year LRF ± DF
Cheng et al. (49)	110	• Age <40 • Tumor size ≥3 cm • Presence of LVSI • Adjuvant hormonal therapy	• 4-year LRF ± DF (isolated LRF or with simultaneous DF)

LRF, local-regional failure; DF, distant failure; LVSI, lymphovascular space invasion; ER, estrogen receptor; G2 or 3, grade 2 or 3.
[a]Retain significance on multivariate analysis.

Recht et al. reported on the outcomes of over 2,000 patients enrolled on four randomized Eastern Cooperative Oncology Group (ECOG) studies of systemic therapy. Median follow-up of the entire group was 12 years and 983 patients had tumors 5 cm or less and one to three positive lymph nodes (LNs). In a multivariate analysis of all patients, increasing tumor size, increasing number of positive nodes, ER-negative status and decreasing number of examined nodes were significant independent predictors of LRR (26). Cheng et al. (49) identified 110 patients with one to three positive axillary nodes treated at their institution with modified radical mastectomy and systemic therapy but without radiation, (median number of nodes examined, 17). Sixty-nine patients received adjuvant chemotherapy and 84 received adjuvant hormonal therapy with tamoxifen. On multivariate analysis, only tumor size (<3 cm vs. greater) was significant for LRR. However, the authors found that the four most significant factors on univariate analysis (age < 40 years, tumor ≥ 3 cm, ER-negative disease, and LVI) could segregate patients into a high-risk group (with three or four factors) and a low-risk group (with two or fewer factors). This report had relatively small numbers and short median follow-up (54 months). In a similar Hungarian study, the authors reported on 249 patients with T1 and T2 tumors with one to three positive axillary nodes, half of whom were treated with PMRT (50). Several putative risk factors for LRR were examined in the unirradiated patients on multivariate analysis, and only age (≤ 45 years) and size (T2) emerged as independent predictors of LRR. Finally, Cheng et al. (51) have reported on gene expression profiles that are predictive of LRR after mastectomy, although the number of local-regional events in their patients with 1–3 positive nodes was small. This promising methodology may serve as a valuable tool of risk assessment in the future.

Node-Negative Patients

The most recent EBCTCG overview demonstrated a nominal 5-year local recurrence rate of 6% after mastectomy and axillary clearance in node-negative patients. The addition of PMRT reduced this rate to 2% ($2p = 0.0002$), producing a modest absolute 5-year gain of 4% (7). Given the low overall risk of LRR in node-negative patients, several investigators have attempted to identify subsets within this group with LRR risks high enough to warrant PMRT.

In a multivariate analysis of the IBCSG trial patients discussed above, LVI was a significant risk factor of LRR in node-negative patients, as was size greater than 2 cm in premenopausal node-negative patients (36). Jagsi et al. (52) reported a retrospective analysis of a cohort of 870 node-negative patients (excluding T4 patients) treated with modified radical mastectomy without RT at the Massachusetts General Hospital between 1980 and 2000. A multivariate analysis of several potential risk factors for total LRR revealed four significant independent predictors: margin status (<2 mm), premenopausal status, size (>2 cm), and LVI, with these latter two having the greater hazard ratios (3.8 and 3.2, respectively). Ten-year total LRR rates were approximately 20% with two adverse factors and 40% with three adverse factors. Approximately two-thirds of the patients in this cohort did not received systemic therapy.

Floyd et al. (53) published data on a multicenter effort of 70 patients treated with mastectomy, systemic therapy,

and no radiation for patients with pathological T3N0 disease and reported a 5-year LRR of only 8%. Those who had LVI had a 21% LRR compared to a 4% rate for those without LVI. Taghian et al. (54) reported results on 313 patients with pathological stage T3N0 disease who were treated with mastectomy, systemic treatment, and no radiation on National Surgical Adjuvant Breast and Bowel Project (NSABP) clinical trials. The 10-year LRR for this series was only 7%, with 24 of the 28 LRR developing only on the chest wall.

Truong et al. (55) focused exclusively on patients with T1or T2 node-negative breast cancer treated within the BCCA and extracted clinicopathological data on this cohort from their outcome database. They reported an actuarial 10-year LRR risk of 8% in 1,505 women treated with mastectomy without RT. On logistic regression analysis, grade, LVI, T stage and systemic therapy use were statistically significant independent predictors of LRR. On recursive partitioning analysis, the first split occurred at histologic grade 3 (actuarial 10-year rate of LRR 12% vs. 6%). The concomitant presence of LVI increased the Kaplan-Meier estimate for 10-year LRR to 21% compared to 9% for grade 3 alone. Similarly, Yildirim et al. (56) reported on 502 patients treated with MRM for T1 or T2 node-negative disease in their retrospective study from Ankara Oncology Hospital. With a median follow-up of 77 months, only 3% of patients had LRR. Within these small numbers, multivariate analysis revealed tumor size greater than 2 cm and LVI as predictors for high risk of LRR in women 40 years or younger and tumor size greater than 3 cm, LVI, grade, and HER2 status, and use of tamoxifen in the older women. Ten-year risks of LRR exceeded 30% for younger women with both risk factors, and older women with at least three risk factors.

Margin Status

Margin status is another potential risk factor for LRR in postmastectomy patients. However, information documenting and quantifying the risk of LRR in these patients is scarce because margin issues are uncommon after mastectomy. Furthermore, interpreting the available data is difficult due to the variable definitions of close or positive margins and the small denominators in the handful of existing reports. Perhaps the best effort comes from BCCA who identified 94 women with tumor at the inked margin of resection after mastectomy in their outcomes database (57). Forty-one of these patients received PMRT, while 53 did not, and cumulative crude LRR were 11.3% versus 4.9% in unirradiated and irradiated groups, respectively, with no significant difference between the two groups. Factors that resulted in a cumulative crude LRR of approximately 20% (17% to 23%) without RT were age 50 or younger, T2 tumor size, grade 3 histology, and LVI. The corresponding rates with RT were in the single digits (0% to 9%) but all comparisons were statistically nonsignificant. Also, with a median follow-up time of about 8 years, none of the 22 women with positive margins without these associated features had LRR.

Freedman et al. (58) reviewed 34 patients with close or positive margins after mastectomy whose primary tumor was smaller than 5 cm with zero to three positive axillary nodes and who received no postoperative radiation. Five chest wall recurrences appeared at a median interval of 26 months (range, 7–127 months), resulting in an 8-year cumulative incidence of a chest wall recurrence of 18%. The authors reported a relatively high risk of local relapse among younger women (age 50 or younger) compared to older women (28% vs. 0 at 8 years, $p = .04$). In a multivariable analysis by Katz et al. (47) of factors predictive of LRR in patients treated with mastectomy and chemotherapy without irradiation, close or positive margins were a significant independent predictor of LRR. Although there were only 29 patients available for this analysis, their 10-year LRR was 45%; the risk was 33% for those with pectoralis fascia invasion even when negative margins were achieved.

Childs et al. (59) retrospectively reviewed records on 397 women who were treated at Faulkner Hospital (a Dana Farber affiliate) with mastectomy but without prior induction chemotherapy or PMRT. Fifty-four (14%) of these had positive margins and 68 (17%) had close (<2 mm) margins. The median age was 55 years and the risk profile of the study cohort was quite low. With a median follow-up of 6.7 years, the 5- and 8-year rates of LRR were 2.4% and 4.5%, respectively. The 5-year risk of LRR with a positive margin was 6.2% compared to under 2% for both close and negative margin cases ($p = .04$). Positive-margin status appeared to confer higher risks when combined with other adverse predictors.

Biologic Classifiers and Risk of LRR

Mamounas et al. (60) explored the significance of the Oncotype Dx recurrence score on LRR risk in postlumpectomy and postmastectomy patients enrolled on the NSABP-B-14 and B-20 studies. The Oncotype-Dx assay is a 21-gene expression panel that is a validated discriminator of distant recurrence risk in tamoxifen treated patients. Of 895 tamoxifen treated patients analyzed, 505 were postmastectomy. The LRR rate was 15.8% in patients with a high recurrence score (RS) (95% CI, 10.4–21.2) compared to 4.3% (95% CI, 2.3–6.3). Similar results were noted in the placebo and chemotherapy+tamoxifen cohorts. Multivariate Cox regression analysis confirmed the independent significance of RS. In the subgroup of patients treated with mastectomy ($n = 505$), the LRR rates for low, intermediate and high RS were 2.3, 4.7, and 16.8%, respectively. The RS appeared to consistently discriminate risk in both older (≥50) and younger postmastectomy patients. This hypothesis-generating data is consistent with distant failure validation studies of Oncotype Dx in tamoxifen-treated patients, and demonstrates that LRR rates can even be high in biologically-selected node-negative populations.

Breast cancer can be classified into biologically distinct subtypes (based on gene expression patterns) with varying clinical potential (61). These subtypes can be approximated by assessing expression levels of a handful of markers; prognostic information on metastasis and death is conserved even with these subtype constructs (62). Several groups have examined LRR rates as a function of biologic subtype.

Kyndi et al. (63) retrieved paraffin-embedded tumor blocks for 1,078 patients enrolled on the Danish postmastectomy trials who had at least eight lymph nodes examined. Tissue microarrays were constructed from 1,000 of these patients and then stained with standard immunohistochemical methods for ER, PR, and HER2. Successful IHC for all three markers was achieved in 996 patients. The median follow-up of surviving patients was 17 years. In their multivariate analysis, triple-negative status, and receptor-negative or HER2 positive (HER2 driven) were prognostic for LRR and overall mortality. HER2 driven phenotype was outperformed only by nodal status as a risk for all end points (LRR, DM, and mortality). In the subgroup of patients randomized to observation after mastectomy ($n = 510$), triple-negative tumors were associated with inferior overall mortality, DM rate, and LRR probability. HER2 tumors were associated with mortality and DM but not LRR. In patients who received PMRT ($n = 486$), triple-negative status continued to be

associated with worse LRR, but not survival or metastasis rate. Indeed, in patients who received PMRT, triple-negative status, and HER2 enriched status were the strongest associations with LRR, exceeding even nodal status and tumor size. Perhaps most startlingly, PMRT only appeared to benefit patients with favorable biologic subtypes (constructed Luminal A) with no statistical improvement in mortality for patients with Luminal B, triple-negative, and HER2 subtypes. Although LRR was improved with PMRT in all subgroups, except the HER2 enriched subtype, the relative reductions were higher in the luminal subtypes (HR 0.06–0.09) than in triple-negative subtype (HR 0.33).

The Kyndi report is provocative and requires careful thought and interpretation. Foremost, the subset numbers are limited in their power to detect differences. For example, the Luminal B (HR+, HER2+) curves appear divergent and have an HR of 0.65 (0.40–1.04, $p = .07$). Still, the results of the paper are hard to ignore and counterintuitive—the benefit of PMRT appeared to be somewhat restricted to favorable subtypes. It is plausible that hormone-negative and HER2-driven tumors had preexisting micrometastases that were insufficiently treated with the available systemic therapy and the limitations of the study design (hormonal therapy with tamoxifen was guided by patient age rather than receptor status on trial 82c, trastuzumab was not available, etc.). Additional agents that can be delivered with PMRT may perhaps benefit some of these patients.

Voduc et al. (64) analyzed biologic subtype as a predictor of local-regional recurrence in a cohort of over 4,000 women treated in the BCCA system. Fifty-eight percent of these women (n = 1492) were postmastectomy patients. Basal and HER2 positive subtypes predicted for higher rates of local and regional failure in both postlumpectomy and postmastectomy cohorts. In the postmastectomy patients, all non-luminal A subtypes were found to be independent predictors of chest wall and regional nodal failure on Cox multivariate analysis. The 10-year local relapse-free survival for Luminal A patients was 92% while the regional relapse-free survival was 96%. The corresponding rates were 86% and 88% in Luminal B patients, 83 and 88% for HER2 enriched, and 80% and 81% for basal subtype.

Dominici et al. (65) reported on a cohort of 819 patients who underwent mastectomy at the MDACC. Most of these patients received systemic therapy at the discretion of their treating oncologists—none received PMRT. The majority of patients were either T1 (75%) or N0 (72%). Approximately 27% of patients (219 of 819) had one to three positive lymph nodes. With a median follow-up of 58 months, the 5-year risk of LRR was only 2.5%. Patients with triple-negative tumors had a 10.9% incidence of LRR, which was higher than other phenotype constructs ($p < .01$). On multivariate analysis, having four or more positive lymph nodes and triple-negative status were the strongest predictors of LRR. Triple-negative status and either lymph-vascular space invasion or lymph node positivity increased risk of LRR at 60 months to 30% and 23%, respectively.

Using a three-marker classification, Billar (66) retrospectively analyzed recurrence rates by constructed subtype in a cohort of 1,061 patients of whom 35% were mastectomy patients. Local or regional recurrence developed more frequently in patients with "triple negative" phenotype (5.7%) compared to HER2+ (2.9%) and ER+ (1%), $p = .001$.

Albert et al. (67) also used a three-marker system to assess the prognostic value of molecular subtype for local-regional control in a retrospective cohort of 756 patients treated at the MDACC. Notably, they restricted their cohort to patients with small, node-negative tumors (T1a-b, N0). Approximately 38% of these patients were treated with mastectomy. With a median follow-up of 6 years, the 8-year LRR rates were 5.8% for triple-negative, 3.5% for hormone+/HER2– (Luminal A), 13.4% for hormone+/HER2+ (Luminal B), and 29% for hormone–/HER2+ (HER2 enriched). There were only 26 patients at risk in the hormone–/HER2+ patients. Likewise, there were only eight events in the mastectomy group, making a subgroup analyses impossible.

Finally, Wang et al. (68) successfully completed a multicenter randomized trial in China evaluating the benefit of PMRT in triple-negative breast cancer patients. Six-hundred and eighty-one women were randomly assigned to receive either no further treatment or 50 Gy in 25 fractions to the chest wall or regional lymph nodes after a mastectomy and systemic chemotherapy. With a median follow-up of 86.5 months, patients who received PMRT fared much better than patients randomized to observation in both 5-year relapse-free (74.6% vs. 88.3%) and overall-survival rates (78.7% vs. 90.4%). The Wang trial is notable for its randomized design and its strict inclusion of stage I and II patients. All patients had tumors that were no larger than 5 cm, and over 60% were node negative. Sixty-two percent were 50 or younger.

Taken together, these data strongly suggest that PMRT can reasonably be considered for most women with triple-negative or basal subtype cancers. In our opinion, these data nonetheless do not warrant routine PMRT.

RECONSTRUCTION AND PMRT

Many women desire breast reconstruction after mastectomy, and this presents a commonly encountered challenge in the management of these women should they also require radiation therapy. A multidisciplinary collaboration is warranted in which the surgical oncologist, reconstructive surgeon, and radiation oncologist confer with each other and with the patient to ensure an optimal aesthetic outcome without compromising the proven benefits of timely PMRT.

Breast reconstruction efforts can generally be categorized as either implant-based or autologous tissue reconstructions. In addition, reconstructions can occur at the time of the mastectomy (immediate reconstructions) or at some time after mastectomy, usually after the completion of radiotherapy (delayed reconstructions). Implant-based approaches are simpler to perform, avoid the potential morbidities associated with the donor site, and can be offered to thin women who do not have adequate autologous tissue in potential donor sites. A tissue expander is placed between the chest wall musculature and serially inflated until an appropriate tissue envelope is created, at which time the expander is replaced with a permanent prosthesis. Typically, implant-based reconstructions occur immediately after mastectomy because normal tissues can become less compliant after radiation, making tissue expansion problematic.

Autologous reconstructions are commonly performed using a transverse rectus abdominus myocutaneous (TRAM) flap. Alternatively, a latissimus dorsi flap or a flap based on the deep inferior epigastric perforator (DIEP) artery or gluteal arteries can be used for the reconstruction. These reconstructions can be immediate or delayed. In general, immediate reconstructions are accompanied by a skin-sparing mastectomy, thus preserving sensate skin and a natural inframammary sulcus for the reconstruction. The important advantages of an immediate reconstruction are offset by the potential adverse effects of radiation therapy on the reconstruction, and the negative impact the reconstruction can have on the design and delivery of PMRT.

PMRT can result in high rates of contracture, fibrosis, and poor cosmesis in patients who have immediate implant-based reconstructions. Spear et al. (69) reviewed the data on 40 consecutive patients who had undergone a two-stage saline implant reconstruction followed by RT and compared their outcomes to 40 controls. Fifty-three percent of irradiated reconstructions had complications compared to 10% in controls, including a 33% capsular contracture rate in the irradiated patients compared to zero in the controls (p <.00005). Krueger et al. (70) reviewed data on 19 patients who had expander/implant (E/I) reconstructions and radiation therapy and found that 13 (68%) had complications, compared to 19 of 62 (31%) in unirradiated controls (p = .006). In contrast, the group at Memorial Sloan Kettering Cancer Center (MSKCC) has reported results for their patients treated on an institutional algorithm of E/I reconstructions followed by PMRT and reported excellent disease control, no delays, and good to excellent aesthetic results in 80% of cases (71). Ho et al. (72) recently updated results from 151 patients treated with PMRT at MSKCC after exchange of a tissue expander with a permanent prostheses. With a median follow-up of 86 months, the 7-year rates of implant replacement and removal were 17% and 13%, respectively. Disease-related outcomes were consistent with uncompromised control. Others have demonstrated that immediate autologous reconstructions are associated with somewhat lower complications rates compared to prosthetic reconstructions (73).

Tran et al. (74) compared complication rates in immediate versus delayed TRAM reconstructions in patients who received PMRT. Twenty-four of 32 patients in the immediate reconstruction group had contracture, compared to 0 of 70 in the delayed reconstruction group (p <.0001). Furthermore, 28% of the patients with immediate reconstruction required an additional flap or prosthesis to improve cosmesis. In an attempt to reconcile the benefits of immediate and delayed reconstructions, Kronowitz et al. (75) have published on the "delayed-immediate" breast reconstruction wherein patients have a skin-sparing mastectomy, with preservation of sensate skin, and subpectoral placement of a tissue expander (75). After final pathology is reviewed, those patients not requiring PMRT go on to have an "immediate" (within 2 weeks) autologous reconstruction, while the remainder have a delayed autologous reconstruction after RT. The expander is kept inflated throughout chemotherapy and then deflated before PMRT.

Breast reconstruction can alter the contour of the chest wall in a way that makes delivery of radiation to the necessary target volume much more challenging. In a recent report, Motwani et al. (76) reviewed 112 radiation plans designed to treat postmastectomy breast reconstructions and found that 52% of these required compromises in field design due to geometrical constraints imposed by the reconstruction (33% were scored as moderate compromises and 19% major compromises). Only 7% of similar plans in matched controls had compromises due to patient anatomy (p <.0001). In contrast, the group at MSKCC has demonstrated excellent coverage in a series of 40 patients with E/I reconstructions treated with intensity modulated radiation therapy (IMRT) (77).

TECHNIQUE OF PMRT

Treatment Volume, Dose and Prescription

The volumes at greatest risk for recurrence, the chest wall and the supraclavicular lymph nodes, should always be included. However, a case can be made for omitting the supraclavicular/high axilla lymph nodes in patients with high-risk node-negative breast cancer, due to the low risk of regional failure reported in these patients (52,54). The entire mastectomy flaps, inclusive of the mastectomy scar and drain sites, should be treated. Most commonly, a monoisocentric photon technique is used whereby opposed tangent split beams are employed for chest wall irradiation and are matched at isocenter to a superior AP supraclavicular field. The medial border is typically at midsternum and lateral border is at the mid- or posterior axillary line as clinically indicated. The inferior edge is 2 cm inferior to the level of where the inframammary fold existed. The contralateral breast (if it is intact), can be used to estimate the level of the inframammary fold. The superior border of the chest wall fields serves as the match plane and should be marked at the palpable inferior edge of the clavicular head. The gantry angles on the tangent fields are then designed as is done in conventional intact breast tangents, with half-beam or asymmetric-jaws technique to limit posterior divergence into the lungs. Ultimately, the isocenter should be at mid-separation (SAD technique) along a straight line connecting the medial and lateral wires through the central ray of the symmetrical tangents. Typically, 2 to 3 cm of lung in the tangents is required for adequate coverage of the chest wall. The isocenter is then translated cranially to the match plane, ensuring that the geometry of the tangents remains stable. Collimator rotations on the tangent fields (to correct for the slope of the chest wall) can be avoided by opening the jaws on the lung side of the tangents by 2 to 3 cm and adding a superior lung block to ensure 2 to 3 cm of lung throughout the long axis of the tangent beams-eye view. This eliminates the need to correct for the angulation of the cranial edge and simplifies the isocentric match with the supraclavicular field. If the length of a patient's torso makes coverage of the chest wall impossible with half of the available beam length, the tangent jaws can be opened (symmetrically or asymmetrically) and couch rotations can be performed for each tangent to create a straight nondivergent cranial edge for the tangent fields. Simple trigonometric calculations can be performed to calculate the required couch rotation, or the rod-and-chain technique can be used. All of these steps can be reproduced virtually on image data acquired at the time of a CT simulation, and fields designed as described above. Alternatively, the entire chest wall can be treated with electrons, but variations in patient thickness and slope can make optimal dosimetry difficult with this technique. In particular, transmission into lung has to be carefully accounted for. CT planning should be strongly considered for all left-sided lesions, and dose to the cardiac volume should be tracked and constrained. If the heart is placed anteriorly, the medial chest wall can be treated with an anterior electron field which is matched to shallower chest wall tangents. The target dose to the chest wall is 45 to 50 Gy in conventional 1.8- to 2-Gy fractions. Dose can be prescribed 1.5 cm from the posterior edge of the tangents at midseparation or at one-third of the distance from this point to the anterior skin. Alternatively, dose can be normalized to a treatment isodose line covering the target volume. Ideally, the treatment volume should be homogenous for dose, with acceptable ranges within 95% to 107% of prescription dose. Contributions from 15 MV photons should be minimized and bolus placement should be considered to ensure superficial coverage. Forward-planned IMRT, electronic compensation, and inverse-planned IMRT can be important tools for the radiation oncologist to consider in meeting treatment objectives if the conventional techniques described above result in suboptimal dosimetry. Notably, both the START A and B randomized trials of

hypofractionation allowed PMRT patients, and no special toxicity concerns were noted (including the risk of brachial plexopathy) (78,79). The Cancer Institute of New Jersey and the Huntsman Cancer Institute are accruing patients to a prospective phase II trial of hypofractionated PMRT that is expected to complete enrollment in 2014.

The supraclavicular field is typically an AP photon field with the upper border above the AC joint (or just flashing the skin), medial border at the vertebral pedicles and lateral border at the coracoid process in patients who have had complete axillary dissections. Alternatively, the lateral border can be placed to include the medial two-thirds of the humeral head if the axilla is undissected or inadequately dissected. Strom et al. (80) found that in their population of well-dissected axillae (median number = 17), failures in the low and midaxilla were uncommon (10-year actuarial rate 3%).The AP supraclavicular field is prescribed at a depth of 3 cm by convention, although in the age of the CT planning, an alternate anatomically defined depth can be used provided the superficial entrance dose remains acceptable. Six MV photons are typically used, although higher energies are reasonable to consider. A posterior axillary boost (PAB) can be designed to supplement dose to the axillary apex if the contribution from the AP supraclavicular field to the midplane is inadequate. The depth of the supraclavicular prescription point can be altered to increase the midplane dose; the depth of the supraclavicular and high axilla nodes are often similar (81). Many centers are now routinely contouring axillary nodal stations as well as the supraclavicular nodal target, and this practice can be very helpful in treatment planning. Commonly, 50 Gy prescribed to the supraclavicular volume will result in 40 to 45 Gy to the axillary apex without need for a PAB.

Inclusion of IMNs is widely variable because of the conflicting data on the benefits and risks of irradiating these nodes. Although microscopic involvement of IMNs can be high (82), especially in patients with positive axillary nodes and medial tumors, IMN failures are exceedingly unusual (0.1% in the ECOG experience) (26). Furthermore, the benefit of routinely irradiating (or dissecting) the IMNs has never been proven, although it has not been tested in well-controlled studies. Advocates of IMN irradiation correctly point out that the postmastectomy radiation trials discussed earlier did include the IMNs. This issue will not likely be settled at least until the results of ongoing randomized trials of regional nodal irradiation are mature. If the IMNs are to be included, several techniques have been described, and these were compared by Arthur et al. (83) in a dosimetric study (83) The partially-wide tangents technique, in which the tangents blocks are altered to deepen coverage in the upper three intercostal spaces (Fig. 42-2), resulted in the least amount of incidental heart and lung irradiation. A popular technique not compared in this study is a 5 to 6 cm wide electron patch matched to the entry point of the medial tangent and tilted to a gantry angle 5 to 15 degrees less than the medial tangent (Fig. 42-3). Nine or 12 MeV electrons can be employed to treat at the requisite CT defined depth. At 80 to 90% of prescribed dose, acute skin reactions may necessitate substituting the electron field with a photon field in the same geometry to allow skin sparing. The target dose is 45 to 50 Gy.

The area around the scar is commonly boosted with an additional 8 to 12 Gy with electrons. An electron "cut-out" can be created to treat a 2- to 3-cm margin around the mastectomy scar and/or drain sites. In patients with complex scar geometry or extensive chest wall curvature (especially after reconstruction) a creative way to avoid the uncertainty of matching electron fields is to create a customized thermoplastic surface applicator with embedded afterloading catheters for remote high-dose rate delivery of dose (84).

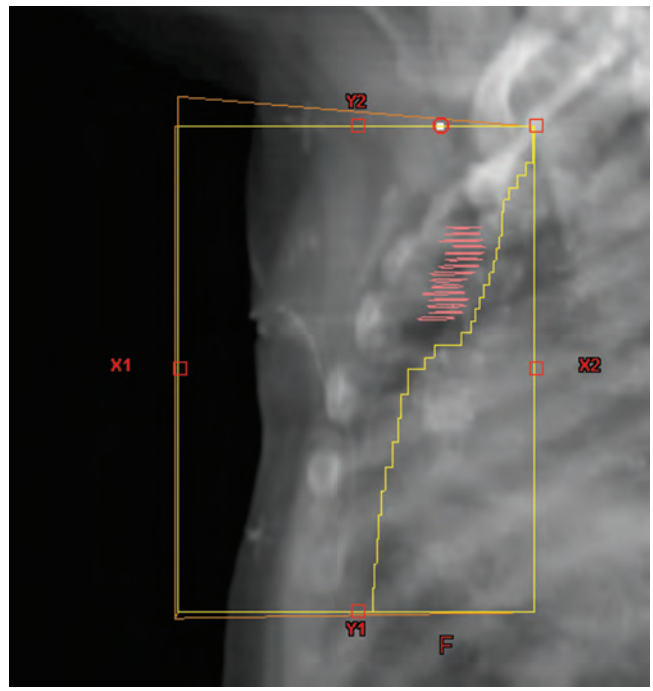

FIGURE 42-2 Beam's eye view reconstruction of a partially wide tangent field.

The quality of radiation treatment plans can be judged by prespecified dose-volume histogram parameters that correlate with disease control and/or tissue toxicity thresholds. The upcoming RTOG1304/NSABP-B51 randomized study of treatment volume after induction chemotherapy calls for 95% of the prescription dose delivered to 95% of the planning target volume (PTV), no greater than 30% of the lung receiving greater than 20 Gy, and no greater than 5% of the heart receiving greater than 25 Gy in left-sided cases. The mean heart dose should not exceed 4 Gy.

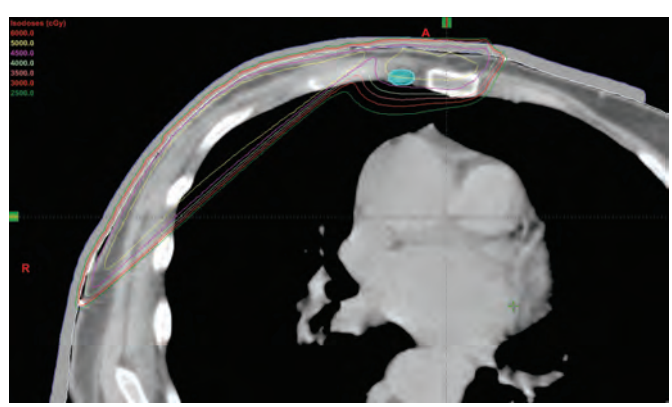

FIGURE 42-3 Axial view of isodose lines produced from a postmastectomy radiation treatment plan employing tangents and a matched electron strip angled toward the medial tangent.

MANAGEMENT SUMMARY

PMRT improves local-regional control, breast cancer-mortality, and all-cause mortality in appropriately selected patients.

In order to improve local-regional control, PMRT should be recommended for all patients who have a projected LRR rate of 20% or greater. This includes patients with four or more involved axillary nodes, patients with one to three involved nodes and a primary tumor larger than 5 cm, and patients with T4 disease (skin involvement, and/or involvement of the chest wall).

Patients with T1 or T2 disease and one to three involved nodes have an intermediate-risk of recurrence (10% to 20%) and should be considered for PMRT if they have less than 10 nodes removed, a nodal ratio greater than 0.20, age less than 45, positive margins, high grade tumors, or LVI. More recent data suggests that these patients might derive the most survival benefit from PMRT.

- Node-negative patients generally have low rates of LRR, including those with T3N0 LVI-negative disease. PMRT can be considered in patients who have at least three of these additional adverse features: young age, histologic grade 3, LVI, and T2 size.
- Adverse tumor biology as indicated by either triple-negative phenotype or high recurrence score on Oncotype Dx assay should be considered, along with other risk factors, as potential indications for PMRT.
- In assessing the survival benefit of PMRT, it is important to consider competing risks of mortality. Patients with a very high risk of DM and older patients derive less benefit from PMRT than patients with fewer competing risks.
- Adjuvant systemic therapy decreases LRR and efforts are underway to assess the survival benefit of PMRT in the context of increasingly-effective systemic therapy.
- In devising radiation fields, CT planning for left-sided cases is very important. The heart should be contoured and the mean cardiac dose limited.
- For patients desirous of reconstruction, a multidisciplinary collaboration is warranted in which the surgical oncologist, reconstructive surgeon, and radiation oncologist confer with each other and with the patient to ensure an optimal aesthetic outcome without compromising the proven benefits of timely PMRT.

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CHAPTER 43

Adjuvant Systemic Therapy: Endocrine Therapy

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CHAPTER CONTENTS

INTRODUCTION TO ADJUVANT ENDOCRINE THERAPY

Breast cancer causes death because of metastases in distant sites that gradually grow and cause organ dysfunction. In patients with early breast cancer these metastases are not clinically apparent (small numbers of individual or clumps of malignant cells can sometimes be found in the bone marrow or circulating in the blood by research techniques) and are referred to as micrometastases. Since clinicians cannot precisely identify which patients harbor micrometastases and which do not, decisions concerning the administration of systemic therapy, like endocrine therapy or chemotherapy, to kill these occult cells are difficult, and overtreatment with potentially toxic "micrometastatic eradication therapies" is therefore common. Nevertheless the conceptual change in the 1970s that micrometastases were present early on in many patients and that they were ultimately the cause of cancer death when treatment was confined to local treatment alone, led to a large number of clinical trials of adjuvant systemic therapy given either after (adjuvant) or before (neoadjuvant) local therapy. These trials confirmed the idea that micrometastases are present in many patients by the time of diagnosis and that systemic therapy to eradicate them markedly improves disease-free and overall survival of patients. Late recurrences do occur, sometimes decades after treatment of the primary tumor, particularly in patients with ER-positive breast cancer. These very late recurrences are not common but they raise questions about whether ER-positive breast cancer is ever really eradicated. Alternatively, micrometastases may lie dormant only to become reactivated later by some unknown factor(s) or they grow so slowly that it takes decades for them to become apparent.

Widespread use of systemic adjuvant chemotherapy, endocrine therapy, and, most recently, biological therapy has contributed to the continuing reduction in breast cancer mortality rates seen since 1990. Rates have declined 2% per year for the past 20 years and show no hint of stabilizing as further improvements are made in prevention, earlier diagnosis, and treatment.

The first randomized trials of breast cancer adjuvant endocrine therapy were initiated more than 50 years ago and investigated adjuvant ovarian ablation (1). Trials of the antiestrogen tamoxifen were initiated in the mid-1970s. In the late 1990s, trials of aromatase inhibitors were initiated

in postmenopausal patients since they had shown to be slightly more effective than tamoxifen in metastatic breast cancer. The current decade will be recognized for additional trials of aromatase inhibitors (AIs) and tamoxifen combined with other therapies designed to block alternative escape pathways that can cause resistance to ER-targeted therapy. An early example is the combined use of trastuzumab together with endocrine therapy in HER2 (*ERBB2*)-positive, ER-positive tumors. Other inhibitors of growth factor signal transduction molecules such as mTOR inhibitors are just entering adjuvant trials in patients with ER-positive tumors. Finally, this decade will enhance our ability to more accurately predict which patients have micrometastases and need systemic therapy and then to select the best therapy for such patients by comprehensive molecular profiling of both the patient and their tumor.

EARLY BREAST CANCER META-ANALYSES OF ADJUVANT THERAPY

Given the large number of randomized adjuvant therapy trials of different systemic therapies some are likely to be misleadingly promising whereas others misleadingly negative, solely by the play of chance, especially if they are small. One method of overcoming these pitfalls is the overview or meta-analysis technique. This combining of data from multiple trials enables meta-analyses to reliably detect modest advantages for one treatment over another and thereby correct false-negative results produced by small randomized trials. The meta-analyses, undertaken by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) use data from individual patients from all adjuvant trials, thereby allowing detailed and comprehensive analyses on tens of thousands of breast cancer patients.

BIOLOGY OF ENDOCRINE THERAPY

Endocrine therapy of breast cancer represents the first molecularly targeted therapy for cancer. The success of this approach provided a strong rationale for the development and testing of other targeted therapies. All endocrine therapies target the ER protein, which is present in 60% of premenopausal and 75% of postmenopausal breast cancers. The progesterone receptor (PR) has not been utilized as a treatment target itself, but a growing body of evidence suggests an important role for PR signaling in breast cancer development, implicating its potential as a target for prevention and treatment.

Estrogen receptor is a nuclear transcription factor (see Chapter 26). After the binding of estrogen, ER is phosphorylated, homodimerizes with another receptor molecule, recruits coregulatory proteins (CoA), and the receptor complex then binds to target genes at specific estrogen response elements (EREs) in their promoters (2). ER can also be phosphorylated and thereby activated by other signaling pathways in the absence of estrogen, a process called ligand-independent activation (2). Such tumors would not likely respond to estrogen deprivation therapy like aromatase inhibition. There are two estrogen receptors, alpha and beta (2). The function and role of ERβ in breast cancer is not totally defined, although several studies suggest that when it is present in abundance it may signal a tumor more likely to benefit from tamoxifen (3). When ERα (which will be called ER in this chapter) is bound by estrogen, it activates transcription of specific genes and inhibits transcription of others (genomic activity). Some of these induced genes encode proteins important for tumor cell growth and survival and, consequently, therapies designed to block this pathway have therapeutic benefit. Evidence also suggests that in some breast cancer cells, a small pool of ER is located outside the nucleus perhaps tethered to the cell membrane. This nonnuclear ER mediates the so-called nongenomic or rapid effects of estrogen to activate various growth factor pathways, among them epidermal growth factor receptor (EGFR), HER2, and insulin-like growth factor receptor (IGF1-R) (2). Receptor tyrosine kinase pathways, cellular stress, and the microenvironment can modulate ER activity and function by phosphorylation of the receptor and its coregulatory proteins. In this way ER itself can function as a coactivator by binding to other transcription factors such as AP-1 or NFkB or by binding to other sites on DNA to initiate transcription of a different set of genes.

All endocrine therapies target the classical ER pathway in one way or another. Ovarian ablation (surgical or medical) and AIs lower the level of estrogen, thereby reducing the ligand-dependent activation of ER signaling, both genomic and nongenomic. Selective ER modulators, such as tamoxifen and toremifene, bind ER just like estrogen, but they alter ER conformation in a slightly different way than estradiol (4). These drugs demonstrate dual estrogen agonist and antagonist activity depending on the tissue, cell or gene context. Thus, tamoxifen behaves as an estrogen in the endometrium, bone, liver, and even on some genes in the breast, whereas for other genes in the breast, tamoxifen functions as an antagonist to inhibit estrogen-dependent transcription. Growing evidence suggests that this intrinsic agonist activity of tamoxifen and other selective estrogen receptor modulators (SERM) may be higher in some patient's tumors than in others owing to activation of the ER and its coactivators by other cell survival pathways, potentially causing loss of tamoxifen's antagonist activity and resulting in *de novo* or acquired resistance (2,5). Additionally, tamoxifen acts as an agonist on nongenomic ER signaling, which may also be a cause of tamoxifen resistance in some patients.

Pure antagonists or ER downregulators (e.g., fulvestrant) bind ER, but have no intrinsic agonist activity. Furthermore, they induce degradation of ER and theoretically would be effective in tumors in which ligand-independent ER activation is present such as in tumors with active growth factor receptor signaling. This class of agents has not yet been studied in the adjuvant setting, although the steroidal antiestrogen, fulvestrant, when used at a dose of 500 mg monthly, is slightly more effective than the AI anastrozole in metastatic breast cancer (6). ER degraders like fulvestrant deserve clinical trials in the adjuvant setting.

ADJUVANT THERAPY WITH SELECTIVE ESTROGEN RECEPTOR MODULATORS

Tamoxifen is the most commonly prescribed SERM for the treatment of breast cancer. Toremifene, a drug with structural and functional similarities to tamoxifen, appears equally effective to tamoxifen but is prescribed far less frequently (7). Raloxifene is approved for the prevention but not for the treatment of breast cancer. These drugs are nonsteroidal compounds that bind to ER and display both estrogen antagonist and estrogen agonist properties. Although the agonist properties of this class of endocrine therapy may account for resistance in some patients (see above), they also account for the favorable effects in preserving bone mineral density in postmenopausal women and the favorable effect on blood lipid profiles (8,9), both attractive features in postmenopausal women for whom estrogen

replacement therapy is inappropriate. The net result of the binding of tamoxifen to ER in the cancer cell is a blockade of cell cycle transit in G1 phase and modest induction of apoptosis, thereby inhibiting tumor growth (10,11).

Because of its favorable toxicity profile and its activity in advanced breast cancer, tamoxifen entered clinical trials of adjuvant therapy in the mid to late 1970s. More than 70 randomized clinical trials of tamoxifen including 20 trials of 5 years of tamoxifen involving 21,457 patients were included in the most recent meta-analysis (12). The early trials focused on postmenopausal patients, although a few included some premenopausal patients. Most of these studies included both node-positive and node-negative patients, although a large trial from the National Surgical Adjuvant Breast and Bowel Project (NSABP) studied node-negative patients exclusively (13). Both ER-positive and ER-negative patients were included in many of the earlier studies because it was thought by some that tamoxifen might still have a beneficial effect even in tumors lacking ER expression. Nearly all of the early studies found a statistically significant disease-free survival (DFS) advantage for tamoxifen, but only two large studies, the NATO (Nolvadex Adjuvant Trial organization) Trial and the Scottish Trial, showed a significant overall survival (OS) advantage (14,15). A survival trend in favor of tamoxifen was found in most of the other trials.

The 2011 meta-analysis of tamoxifen confirms both a DFS and OS advantage for ER-positive patients treated with tamoxifen for 5 years (Table 43-1) (12). The recurrence rate ratio (RR) of tamoxifen versus control was 0.53 during the first 4 years and 0.68 during years 5 to 9 meaning that tamoxifen reduced the risk of recurrence by about half during the time the patient was taking the drug and by about a third during the first 5 years after stopping tamoxifen. There was no further reduction in recurrence during years 10 to 14. The RR for tamoxifen in patients also receiving chemotherapy was 0.67 while in those treated with tamoxifen alone it was 0.56. Thus, tamoxifen combined with chemotherapy offers significant benefit compared to chemotherapy alone. In contrast to recurrence, mortality was reduced by about a third in all time periods including years 10 to 14. This *carryover* effect of tamoxifen has not yet been explained, but there continues to be significant reductions in recurrence and death for many years after the drug is stopped. It has also been reported in trials of AIs as well and may be owing to a greater proportion of "cured" patients in the endocrine therapy groups. It should also be mentioned that the outcome data from these trials is an underestimate of the true benefit possible with these agents given the high nonadherence rates over the 5-year treatment durations reported in several studies.

Tamoxifen in Premenopausal and Postmenopausal Patients

Earlier meta-analyses suggested that tamoxifen had no benefit in women younger than age 50 (16,17). Because of the inclusion of women with ER-negative tumors, and because the duration of tamoxifen treatment was usually only 1 or 2 years in these early trials, definitive conclusions could not be drawn. Later meta-analyses indicated that more prolonged treatment (approximately 5 years) results in a significant benefit in women younger than 50 years, as well as in older women, so long as their tumors are ER positive (18). The recently updated meta-analyses confirm these results (Table 43-2) (12). Patients younger than 45 years of age, most of whom are premenopausal, benefit in terms of recurrence and mortality from 5 years of tamoxifen nearly as well as those 55 years of age and older. The benefits found with 5 years of tamoxifen in younger women, along with the lack of benefit with the shorter durations used in earlier studies, strongly suggest that longer treatment is very important in this age group. These data also indicate that the tamoxifen dose used in these studies can inhibit breast cancer cells even in the presence of the much higher than normal serum levels of estrogen typically found in premenopausal patients taking the drug.

Thus, with more than 30 years of follow-up from many studies involving thousands of patients, it is certain that if tamoxifen is given for 5 years to patients selected on the basis of ER status, it is effective in both younger and older women. It is also important to emphasize that the differences in outcome between tamoxifen and no tamoxifen observed after 5 years of follow-up grow even larger during the next 5 years, indicating that the benefits of tamoxifen are very durable over time (12).

Tamoxifen in Node-Negative and Node-Positive Patients

No biological reason exists for women with axillary node-negative ER-positive breast cancer to benefit differently from adjuvant tamoxifen therapy than those with positive nodes, and many trials of adjuvant tamoxifen included both node-negative and node-positive patients. Fewer recurrences and deaths overall in the node-negative subset make it more difficult to show significant reductions with tamoxifen, but strong trends were evident early on in the larger studies (14,19). NSABP trial B-14 is by far the largest of the initial

TABLE 43-1

Results of Five Years of Tamoxifen in Patients with ER-Positive Tumors by Years of Follow-Up

Ratios (treatment vs. control) of the Annual Event Rates		
Years	*Recurrence (p-value)*	*Mortality (p-value)*
0–4	0.53 ± 0.03 (<.00001)	0.71 ± 0.05 (<.0001)
5–9	0.68 ± 0.06 (<.00001)	0.66 ± 0.05 (<.0001)
10–14	0.97 ± 0.10 (NS)	0.68 ± 0.08 (<.0001)

Adapted from Early Breast Cancer Trialists' Collaborative Group. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomized trials. *Lancet* 2011;378:771–784.

TABLE 43-2

Results of Five Years of Tamoxifen by Patient Age

	Ratio of Annual Event Rate ± SE	
Age	*Recurrence*	*Mortality*
<45	0.63 ± 0.05	0.71 ± 0.07
45–54	0.72 ± 0.05	0.82 ± 0.07
55–69	0.54 ± 0.04	0.63 ± 0.05
≥70	0.50 ± 0.15	0.64 ± 0.18

Adapted from Early Breast Cancer Trialists' Collaborative Group. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomized trials. *Lancet* 2011;378:771–784.

trials of adjuvant tamoxifen (2,644 patients), and it focused on patients with histologically negative axillary nodes (19). Both patients younger than 50 years of age (820 patients) and older patients (1,824 patients) were eligible, and all patients had ER-positive disease. Patients were randomly assigned to receive placebo or tamoxifen for 5 years, and those who received tamoxifen were reassigned at 5 years to stop therapy or to continue for 5 additional years.

Women who received tamoxifen had a significantly higher probability of being free of local and distant recurrences (78% vs. 65%, $p < .0001$) and survival (71% vs. 65%, $p = .0008$) than with placebo. Tamoxifen-treated patients also had fewer ipsilateral breast, local-regional, and distant recurrences than placebo-treated patients, and they had a substantial reduction (approximately 50%) in contralateral breast cancer. These benefits persist beyond 15 years of follow-up (19).

The most recent meta-analysis also suggests that the benefit of adjuvant tamoxifen is similar for node-negative and node-positive patients (12). The reductions in the odds of recurrence were 40%, 36%, and 44% for patients with negative nodes, one to three positive nodes, or four or more positive nodes, respectively. The estimated 10-year recurrence rate for node-negative patients was 19% with tamoxifen in the absence of chemotherapy and 35% without tamoxifen, while the recurrence rate for node-positive patients was 42% with and 57% without tamoxifen. Thus, the cumulative data confirm that tamoxifen improves recurrence and survival in both node-negative patients, who have a substantially lower baseline risk of recurrence and death, and in node-positive patients.

Tamoxifen in Different Hormone Receptor Expression Subgroups

Many of the early tamoxifen adjuvant trials included patients with ER-negative or ER-poor as well as ER-positive and ER-unknown tumors. These studies helped assess the potential benefits of tamoxifen in both subsets. The results are difficult to interpret, however, because of varying definitions of *ER-positive* and *ER-negative,* concerns about assay quality, and because only a fraction of the patients in some of these early studies had ER assays performed.

Earlier meta-analyses found a small but statistically significant survival benefit in women with ER-poor tumors treated with adjuvant tamoxifen, but the most recent meta-analyses with longer follow-up and a larger sample size do not (12). Patients with ER-poor tumors, a subset that includes tumors with undetectable or borderline-positive ER (4 to 9 fmol/mg protein by ligand-binding assay), showed no reduction in the annual odds of recurrence or death. For unclear reasons patients with ER-negative first tumors who are treated with adjuvant tamoxifen have no reduction in contralateral breast cancer either. Women with tumors known to be definitely positive for ER had a 39% reduction in the annual odds of recurrence and a 38% reduction in contralateral breast cancer when treated with tamoxifen for 5 years. Interestingly even patients with tumors expressing only low levels of ER (10 to 19 fmol/mg protein) had a significant reduction in recurrence from tamoxifen (Table 43-3). Why tumors with only a small fraction of cells expressing ER by either ligand binding or IHC benefit from adjuvant endocrine therapy remains a mystery. It is possible that other cells in the tumor have low ER levels undetectable by standard assay but still sufficient to affect gene transcription. Alternatively, cells not expressing ER at the time of the biopsy might express it later due to cell cycle variation in expression or other factors. Higher ER levels were associated with a greater risk reduction. The ligand binding assay is no longer used for clinical ER measurements but very low ER levels detected by IHC have also been associated with tamoxifen benefit (20).

TABLE 43-3

Results of Five Years of Tamoxifen by ER Level

	Ratios of the Annual Event Rates ± SE
ER Level (fmol/mg protein)	*Recurrence*
<10	NS
10–19	0.67 ± 0.08
20–29	0.70 ± 0.10
30–49	0.77 ± 0.08
50–99	0.62 ± 0.07
100–199	0.52 ± 0.07
≥200	0.52 ± 0.07

Older studies when ER was measured by ligand binding. The ratio for all ER-positive when ER was measured by other methods mostly IHC is 0.64 ± 0.06. (Adapted from Early Breast Cancer Trialists' Collaborative Group. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomized trials. *Lancet* 2011;378:771–784.)

The College of American Pathologists suggests that a cutoff of greater than 1% positively staining cells be used to define ER-positivity by IHC (21). This committee also provided technical guidelines in an attempt to standardize the entire procedure to reduce the high error rate observed in many studies. This procedure should be followed closely to obtain quality results for patient care. The role of PR in predicting benefit from tamoxifen adjuvant therapy or in predicting relative benefit of tamoxifen compared to aromatase inhibitors is more problematic. The assay itself has changed over time from ligand binding to IHC and has not been as well standardized as that for ER. Also PR, as an estrogen-regulated gene product, is affected by the level of estrogen circulating in blood and therefore would be expected to be higher in premenopausal women and postmenopausal women on hormone replacement therapy at the time of breast cancer diagnosis. PR might be negative in women who have been postmenopausal for some time and who are not taking estrogen replacement therapy even if the ER signaling pathway is intact. In the meta-analysis, among women with ER-positive tumors, the efficacy of tamoxifen was independent of the concentration of PR (18). Studies of patients with metastatic disease have shown consistently that patients with ER-negative, PR-positive tumors, although uncommon, benefit from tamoxifen and other endocrine therapies and that those with ER-positive, PR-negative tumors respond less well than those positive for both receptors. There is level-one evidence from a prospective clinical trial in patients with metastatic breast cancer treated with tamoxifen demonstrating the independent predictive role of PR expression (22). And, there are retrospective data from a very large patient cohort with receptor assays done in a single reference laboratory suggesting that PR does predict benefit from tamoxifen adjuvant therapy (23). But this has not been confirmed in the meta-analysis or in the ATAC or BIG 1-98 adjuvant trials (18,24,25). Nor has PR level correlated with selective benefit of either tamoxifen or an aromatase inhibitor in these comparative trials.

Therefore at the present time PR should not be used as a predictive marker for adjuvant endocrine therapy response, although its loss does correlate with a more aggressive luminal B subtype of breast cancer. This issue is discussed in detail in Chapter 26.

It is clear, however, that when the assays are done properly, patients with ER- and PR-negative tumors do not benefit from tamoxifen adjuvant therapy or any endocrine therapy that blocks the ER pathway. Nor do they benefit with a reduction in contralateral breast cancer (see above). On the other hand, patients even with a low but detectable level of ER in their tumors do benefit from tamoxifen and other forms of endocrine therapy, which should be an important component to their treatment.

Tamoxifen for Longer Than Five Years

Because tamoxifen has predominantly antiproliferative effects it was hypothesized early in its use that it might need to be given indefinitely in the adjuvant setting. However, early trials did not show an advantage for continuing tamoxifen beyond 5 years and in fact, two trials showed slightly worse outcome (19,26). This lack of benefit for more prolonged tamoxifen in these two trials persisted at 14 and 15 years of follow-up, respectively. These trials were small and not definitive leading to more recent trials with larger patient accrual. The aTTom trial in the United Kingdom randomized 7,000 patients, many of unknown ER status, to stop or continue tamoxifen to 10 years and recently reported long-term results. Its results a significant benefit for extending tamoxifen beyond 5 years (27). In late 2012 the ATLAS Trial (Adjuvant Tamoxifen: Longer Against Shorter) reported 15-year data (28). This trial randomized 12,894 women between 1996 and 2005 to stop tamoxifen at 5 years or to continue to 10 years; 6,846 of these patients had known ER-positive tumors. Among these patients, continuing tamoxifen to 10 years significantly reduced recurrence (p = .002), breast cancer deaths (p = .01), and overall mortality (p = .01). The relative risk (RR) for continuing tamoxifen was less impressive during years 5 to 9 than after 10 years (0.9 vs. 0.75, respectively) perhaps due to the known carryover effect of just 5 years of tamoxifen during years 5 to 9 (Table 43-4). A reduction in breast cancer mortality for extended tamoxifen was only seen after 10 years (RR = 0.97 vs. 0.71). The cumulative risk for recurrence during years 5 to 14 for extended tamoxifen was 21% compared to 25% for patients stopping at 5 years. The risk of breast cancer death during years 5 to 14 was 12% for continued tamoxifen compared to 15% for the control group.

TABLE 43-4

ATLAS Trial Results

RR (10 years vs. 5 years) of Annual Event Rates		
Years	*Recurrence*	*Mortality*
5–9	0.9 (0.79–1.02)	0.97 (0.79–1.18)
	p = .10	p = .74
10+	0.75 (0.62–0.90)	0.71 (0.58–0.88)
	p = .003	p = .001

Tamoxifen 10 years versus stopping at 5 years.
Adapted from Land LH, Dalton SO, Jensen MB, et al. Influence of comorbidity on the effect of adjuvant treatment and age in patients with early-stage breast cancer. *Br J Cancer* 2012;107(11):1901–1907.

Mortality without breast cancer recurrence overall was not affected by continuing tamoxifen for 10 years. Known tamoxifen side effects were higher in women assigned to 10 years of tamoxifen but these were counterbalanced by favorable effects. Relative risks for pulmonary embolus (1.87) and endometrial cancer (1.74) were higher but mortality was minimally affected. There was no increase in stroke and there was a significant reduction in ischemic heart disease (0.76, p = .02) for continuing tamoxifen. These data offer a new option for ER-positive patients being treated with adjuvant tamoxifen, and appropriately selected ER-positive patients should be considered for 10 rather than 5 years of treatment. Low-risk patients for whom the extra benefit of continuing tamoxifen beyond 5 years would be minimal might stop at 5 years while higher-risk patients should be considered for extended treatment. This strategy would have the greatest appeal for premenopausal patients who are still treated predominantly with tamoxifen. However, given that fewer than 10% of the ATLAS study population was premenopausal raises a small concern about young patients, although there is no legitimate reason why they would not also benefit from more prolonged therapy.

Tamoxifen in Elderly Patients

Adjuvant therapy is more problematic in elderly patients because of comorbidities more common in these patients that can cause death before breast cancer recurrence (29). The meta-analysis demonstrates a significant mortality reduction in patients older than 70 years treated with adjuvant tamoxifen (Table 43-2) (12,18). Furthermore, some individual trials have specifically targeted this population. The Eastern Cooperative Oncology Group (ECOG) study randomized 181 patients 65 years of age or older to tamoxifen or placebo for 2 years (30). The drug was well tolerated, and significant reductions in recurrence and borderline significant reductions in mortality were observed. Tamoxifen also reduced the incidence of contralateral breast cancers. Surprisingly, most of the older patients who died in this study (61%) succumbed to breast cancer, although, as anticipated, a significant number of them (22%) died of competing illnesses not related to cancer. Nonadherence to the prescribed dose and schedule of tamoxifen, which is relatively high overall, is even higher in elderly patients (31).

The ATAC and TEAM trials comparing tamoxifen with an AI evaluated comorbidities and age on death without recurrence (32,33). In the TEAM trial evaluation of disease-specific mortality, as a proportion of all-cause mortality, showed that 78% of deaths in patients less than 65 years of age were due to breast cancer, while in patients between 65 and 74 years or those 75 or greater, 56% and 36% of deaths, respectively, were due to breast cancer (32). Interestingly breast cancer recurrence and disease-specific mortality increased with age but other-cause mortality increased even more dramatically with age with a sevenfold increase in patients 75 years or greater. The increase in disease-specific mortality with age is not explained but could be due to inclusion in the trial of elderly patients with more aggressive disease. Similar findings were observed with longer follow-up in the ATAC trial (33).

Several small, randomized trials have also evaluated the use of tamoxifen as sole treatment without surgery for operable primary breast cancer in elderly patients (34,35). In one study with 20-year follow-up there was no difference in time to distant metastases or overall survival between tamoxifen alone and mastectomy alone as initial treatment despite the fact that the patients were not selected by ER (35). These findings were confirmed in a large Cochrane review of 7 trials

of 1,446 elderly women unselected by ER (36). This analysis found no difference in overall survival between surgery alone without or with tamoxifen, or tamoxifen alone as initial therapy. Hormonal therapy as a single modality with tamoxifen or an aromatase inhibitor might be reserved for elderly patients not suitable for surgery for temporary disease control. Because these patients have a relatively high risk of thromboembolic complications, an AI may be preferable in debilitated elderly patients in need of treatment, although AIs have not been tested in this setting.

Delayed Adjuvant Endocrine Therapy

Although a rare situation today, the question whether patients could still benefit from adjuvant hormonal therapy, even if initiated years after their primary treatment, remains important for a small subset of patients. One study addressed this question and found that patients who had ER- or PR-positive tumors, and whose adjuvant therapy with tamoxifen was started 2 years or more after initial diagnosis, had improved DFS and OS, even when the delay in starting *adjuvant* tamoxifen was more than 5 years (37). Thus, those patients whose tumors are receptor positive and who, for whatever reason, were not started on adjuvant hormonal therapy at the time of diagnosis may still benefit from delayed treatment. It is likely that a similar benefit would be also seen with AIs, although no studies have addressed this topic. However, the remaining risk of recurrence in such patients should be considered. Patients with a low risk at the time of diagnosis may have an extremely low risk of recurrence at the time of initiating endocrine therapy late, not justifying the side effects of therapy if several years have elapsed since diagnosis.

ANCILLARY BENEFITS OF TAMOXIFEN

Although we think of tamoxifen as an antiestrogen because of its antiproliferative properties in the breast, it is more appropriately classified as a SERM because it has estrogen agonist properties in many tissues and on certain genes, while it has estrogen antagonist properties on others. These unique dual activities of tamoxifen provide additional potential benefits for women taking the drug, although the agonist activity may cause other side effects and may also be a cause of resistance.

Serum Lipids and Mortality from Cardiovascular Causes

Side effects and deaths from other causes from tamoxifen have been addressed in meta-analyses of 5 years of tamoxifen treatment and in studies comparing tamoxifen and an aromatase inhibitor. The 2005 meta-analysis showed a reduction in all-cause and in breast cancer mortality with tamoxifen (18). Non–breast cancer mortality was similar for tamoxifen and no tamoxifen. There was a borderline statistically significant increased risk of stroke and a similar reduction in deaths from heart disease, primarily myocardial infarction, with tamoxifen. Long-term follow-up of the Cancer Research UK "Over 50s" trial comparing five with 2 years of tamoxifen showed a striking reduction in cardiovascular disease in women aged 50 to 59 that lessened as patients became older (38). Similar data were observed in a Swedish trial (39). Data from the placebo-controlled NSABP tamoxifen prevention trial (Breast Cancer Prevention Trial [BCPT]) provides additional information regarding cardiovascular mortality (40). At 4 years of follow-up, a shorter time frame compared to the other cancer trials, this study found no differences between tamoxifen and placebo in fatal myocardial infarction, nonfatal myocardial infarction, unstable angina, or severe angina. One possible explanation for differences in cardiovascular mortality might be the variable use of lipid lowering agents for hypercholesterolemia, a hypothesis that can be tested with available data.

Bone Mineral Density

Tamoxifen has estrogen agonist properties in bone. In postmenopausal women, long-term tamoxifen treatment increases the bone density of the axial skeleton and stabilizes the bone density of the peripheral skeleton (8). In premenopausal women, however, tamoxifen may decrease bone mineral density by antagonizing the more potent activity of endogenous estrogen (41). Although evaluating osteoporotic fracture rates in patients with a diagnosis of breast cancer is problematic, prevention trials of tamoxifen do show a significant reduction in fractures with 5 years of treatment (42). There is a marked reduction in fractures in trials comparing tamoxifen with an aromatase inhibitor (43).

Contralateral Breast Cancer

Individual clinical trials in patients with invasive breast cancer, as well as the updated meta-analysis, indicate a nearly 50% reduction in the risk of contralateral breast cancer after approximately 5 years of tamoxifen treatment (18). As described above, there is no reduction in contralateral breast cancer with tamoxifen if the original tumor is ER-negative. Continuing tamoxifen to 10 years compared to 5 years further reduces the risk of contralateral breast cancer, RR 0.88 (0.77–1.00, $p = .05$).

TOXICITY OF TAMOXIFEN

In general, tamoxifen is well tolerated by most patients with breast cancer. In one of the largest randomized, placebo-controlled trials, 7% of tamoxifen-treated patients and 5% of placebo-treated patients withdrew from the study early for reasons that were possibly related to toxicity (42).

Menopausal Symptoms

The most frequently reported side effects in patients taking tamoxifen are menopausal symptoms (44). At least 50% to 60% of these women report some hot flashes, but 40% to 50% of placebo-treated patients report similar episodes. Tamoxifen may cause hot flashes more commonly in premenopausal women than in older women. Approximately 20% of patients report severe hot flashes while taking tamoxifen compared with 3% of patients on placebo. Vaginal discharge and irregular menses are also slightly more common in patients taking tamoxifen than in those receiving placebo. In one study, however, general quality of life scores were similar for tamoxifen and placebo (44). Headaches were reported less frequently with tamoxifen. The incidence of nausea, arthralgias, insomnia, restlessness, depression, and fatigue was similar with tamoxifen and placebo in this study. In the BIG 1-98 trial hot flushes and night sweats were more common with tamoxifen than with letrozole but vaginal dryness was more common with the aromatase inhibitor (Table 43-5) (25,45).

Depression is not increased in randomized, placebo-controlled trials, but this may reflect underreporting of symptoms that may be brought out by more careful and detailed questioning. A nonrandomized, single-institution study suggests that symptoms of depression can be identified in up to 10% of patients taking tamoxifen (46). Symptoms

TABLE 43-5

Side Effects of Tamoxifen and Letrozole in the BIG 1-98 Trial

Side Effect	*Letrozole (%) (n = 3,975)*	*Tamoxifen (%) (n = 3,988)*	*p-Value*
Hot flashes	33.5	38.0	<.001
Musculoskeletal	20.3	12.3	<.001
Vaginal bleeding	3.3	6.6	<.001
Fractures	5.7	4.0	<.001
Hyperlipidemia	43.6	19.2	N/A[a]
Cardiac disease	4.1	3.8	NS
Cerebrovascular events	1.0	1.0	NS
Venous thromboembolic event	1.5	3.5	<.001

[a]*p*-value not reported. Adapted from Coates AS, Keshaviah A, Thürimann B, et al. Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1-98. *J Clin Oncol* 2007;25(5): 486–492.

are occasionally severe and may require antidepressant medication or even discontinuation of tamoxifen. Failure to identify depression as a side effect in placebo-controlled trials suggests, however, that discontinuation of estrogen replacement therapy or stress from the recent diagnosis of a potentially fatal disease may be causally more important than tamoxifen itself.

The detailed analysis of depression in women on the BCPT adds additional insight on this topic (47), although the women in a prevention trial may not accurately represent breast cancer patients who are diagnosed with a life-threatening disease and have more reason for depression. Nevertheless, no difference was seen in depression by treatment assignment (tamoxifen vs. placebo) in this study, suggesting that tamoxifen itself does not increase the risk of, or exacerbate, existing depression in women.

Although the diagnosis of depression may not be more common in women taking tamoxifen compared with other forms of treatment, depression is still a common and often overlooked condition in breast cancer patients, and the symptoms may be attributed to other causes.

Sexual Dysfunction

Sexual dysfunction is also common in breast cancer survivors, whether they are on endocrine therapy or not. Vaginal dryness, dyspareunia, and decreased sexual desire are common complaints. Vaginal discharge is a common symptom with tamoxifen. In addition to moisturizers, vaginal estrogen cream is often very helpful in women on tamoxifen in whom the systemic absorption of estrogen in these preparations is not of concern. Tamoxifen saturates ER systemically and is effective even in premenopausal patients with high estrogen levels. These problems tend to be much more severe and difficult to treat in women on aromatase inhibitors. Even small amounts of estrogen absorbed systemically could bind and activate ER and, then counteract the beneficial effects of the treatment on breast cancer recurrence. Clearly, more research is needed to evaluate the safety and efficacy of various treatments to improve these non-life-threatening but disabling side effects. Management of menopausal and gynecologic problems in breast cancer patients is also discussed in Chapter 51.

Thromboembolic and Hematologic Toxicities

An increased incidence of thromboembolic events has also been reported from studies of tamoxifen adjuvant therapy in patients with breast cancer as well as from tamoxifen prevention studies in high-risk women (42,48). This complication occurs more frequently when tamoxifen is combined with chemotherapy, and initiating tamoxifen after chemotherapy may decrease this problem. Most patients reported with this complication have superficial phlebitis and do not require hospitalization. Severe thromboembolic phenomena occur in less than 1% of patients given the drug. Deaths caused by thromboembolism have been reported, however, in patients with cancer and in healthy women in the prevention trials. In the ATLAS trial the risk of pulmonary embolism was increased with longer tamoxifen compared to 5 years, but mortality was infrequent and was similar in both groups (28). The risk of thromboembolic events in the BIG 1-98 trial was significantly greater on tamoxifen than letrozole but grades 3 to 5 were uncommon in both, 2.2% versus 1.3%, respectively (25). Nearly identical data were observed in a meta-analysis (43). The thromboembolic risk is especially high in women on tamoxifen having surgery, itself a risk for blood clotting, for an unrelated problem. Perhaps interrupting tamoxifen for a few weeks before surgery and during the surgical recovery period would be prudent. The 7-day half-life of the drug requires a relatively prolonged interruption before surgery. Thrombocytopenia and leucopenia have also been reported with tamoxifen, but are unusual and rarely require cessation of therapy.

Endometrial and Other Cancers

Tamoxifen use, much as with estrogen therapy, is clearly related to an increased incidence of endometrial cancer (18). Even just 1 year of adjuvant tamoxifen is associated with a slightly increased incidence, but the risk rises with more prolonged treatment. Eight-year follow-up of NSABP B-14 in which 2,843 patients were randomly assigned to receive at least 5 years of tamoxifen or placebo indicates that tamoxifen was associated with an annual hazard rate of 1.7 per 1,000, a relative risk of 2.2 compared with population-based rates of endometrial cancer from Surveillance

Epidemiology and End Results (SEER) program data (49). The type of endometrial cancer in patients taking tamoxifen is similar to that in patients not exposed to tamoxifen. Of the 23 cancers in NSABP B14, 18 were of low histologic grade, and most were stage I. Four patients died of uterine cancer, however, indicating the lethal potential of this complication and the need for early identification of symptoms, especially vaginal bleeding. The risk of endometrial cancer with tamoxifen is related to the duration of therapy and is higher in obese women and women who have received prior hormone replacement therapy (50). This was confirmed in the ATLAS trial. The cumulative risk of endometrial cancer was 3.1% with continued tamoxifen and 1.6% for patients treated with 5 years (28). Mortality, however, was very low in both arms, 0.4% versus 0.2%, respectively.

The role of endometrial cancer screening by vaginal ultrasound or endometrial biopsy and the role of progestins in reducing the risk of endometrial cancer have been reported (51,52). Routine transvaginal ultrasound did more harm than good in one study because of its false-positive rates, the requirement for additional tests, and increased iatrogenic morbidity. Neither transvaginal ultrasound nor regular screening endometrial biopsies at 6-month intervals was effective in diagnosing endometrial cancer. These procedures are not justified in asymptomatic patients, but should be considered in women presenting with abnormal bleeding. It is not yet clear whether systemic or intrauterine progestins are beneficial in this setting. An increased incidence of endometrial cancer has also been observed in the BCPT prevention trial in women without breast cancer, but all of the cases reported had a very favorable histology and the one death from endometrial cancer at the time of the report was in the placebo arm (48). Increased endometrial thickness and the incidence of hyperplasia, polyps, and ovarian cysts are increased by tamoxifen.

Tamoxifen is also a potent hepatocarcinogen in the rat, but not in the mouse. Although abnormal liver function tests, fatty liver, and massive liver steatohepatitis, rarely with cirrhosis, have been reported in patients receiving tamoxifen, only a few anecdotal cases of hepatoma have been reported thus far, and the incidence of hepatoma unrelated to hepatitis infection since the introduction of tamoxifen has not increased (53).

Data from individual trials, the meta-analysis and the ATLAS trial indicate that tamoxifen adjuvant therapy has not yet resulted in an increased incidence of other solid tumors (18,28). Specifically only three cases in each arm of liver cancer were seen in the ATLAS trial and there was no increase with prolonged tamoxifen of colorectal or other solid tumors. Long-term follow-up of the ATAC trial showed a higher incidence of death for endometrial cancer, melanoma, and ovarian cancer, but a lower incidence of death for colorectal and lung cancer on the tamoxifen arm (54). All of these events were uncommon. Raloxifene, another SERM with efficacy similar to tamoxifen in breast cancer prevention but less effective in breast cancer treatment, is not associated with an increased risk of endometrial cancer.

Cerebrovascular Disease

There was no increased risk of cerebrovascular disease with prolonged tamoxifen in the ATLAS trial (28). In the meta-analysis of the trials comparing tamoxifen with an aromatase inhibitor this side effect was uncommon, 1.4% on an aromatase inhibitor compared to 1.5% on tamoxifen (43). Finally, the BIG 1-98 and long-term follow-up of the ATAC studies also showed a low incidence of cerebrovascular disease that was not different between tamoxifen and the aromatase inhibitor (25,54).

ADJUVANT THERAPY WITH AROMATASE INHIBITORS

Aromatase inhibitors block the synthesis of estrogen in tissues containing the enzyme. The enzyme is present in breast tumor tissue, fat, muscle, and brain and it converts androgens of adrenal origin to estrogens. There are two classes of aromatase inhibitors that have slightly different mechanisms of action and different mechanisms of resistance leading to incomplete cross-resistance. The nonsteroidal aromatase inhibitors, including anastrozole and letrozole, bind aromatase in a reversible manner (55). Steroidal aromatase inhibitors such as exemestane form an irreversible complex (55,56). Patients with metastatic breast cancer progressing on a nonsteroidal aromatase inhibitor may respond occasionally to treatment with exemestane (56,57).

All of these drugs lower serum and tumor estrogen to very low levels. Although there are modest differences in the degree of aromatase inhibition among these agents, it is not clear whether they translate into differences in clinical benefit (58). Aromatase inhibitors are generally ineffective in premenopausal women. The reduced feedback of estrogen to the hypothalamus and pituitary increases gonadotropin secretion, which stimulates the ovary, leading to an increase in androgen substrate and aromatase (59). Therefore, it is imperative that women who receive aromatase inhibitors are verifiably postmenopausal.

It should probably be avoided in women with chemotherapy-induced amenorrhea as they may still have premenopausal estradiol levels and others may start menstruating again when therapy with an aromatase inhibitor is initiated due to rising gonadotropin levels (FSH and LH), which can stimulate the ovary (60). These women are better off receiving tamoxifen at least initially while they are observed for resumption of menses. Gonadotropins and estradiol levels should be followed as well in such women.

Several large randomized phase III clinical trials incorporating aromatase inhibitors in the adjuvant treatment of breast cancer have been completed (Table 43-6). These studies generally followed one or more of three different strategies: upfront treatment with an aromatase inhibitor compared to upfront tamoxifen; switching to an aromatase inhibitor after initial tamoxifen treatment for 2 to 3 years; or using aromatase inhibitors to extend adjuvant treatment after 5 years of tamoxifen.

Initial Therapy with Aromatase Inhibitors

The ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial was the first large randomized trial to report on the use of an aromatase inhibitor in the adjuvant treatment of breast cancer. In this trial, 9,366 patients were initially randomized after surgery to receive anastrozole, tamoxifen, or their combination. However, the combination arm was discontinued at 33 months of follow-up after this group was found to be equivalent to tamoxifen alone and inferior to anastrozole monotherapy (61). This trial first reported an advantage in DFS for the anastrozole treated group over the tamoxifen-treated group in 2002 and several updates have confirmed this benefit (61,62). At a median follow-up of 100 months, an updated analysis of the ATAC trial of the 6,241 patients randomized to anastrozole versus tamoxifen showed a continued DFS benefit for anastrozole (61). This advantage was observed in all randomized patients (intent-to-treat population) and in the hormone-receptor-positive subgroup, which comprised 84% of all patients on this study. In this subgroup the DFS (HR 0.85, $p = .003$), time-to recurrence (TTR) (HR 0.76, $p = .0001$), and time-to-distant-recurrence (TTDR)

TABLE 43-6

Adjuvant Trials with Aromatase Inhibitors

Study	*Experimental Arm*	*No. of Patients*	*Median Follow-Up (Months)*	*DFS*	*OS*
ATAC	Anastrozole for 5 years	9,366	100	HR = 0.85 p = .003	HR = 0.97 p = .70
BIG 1-98	Letrozole for 5 years Tamoxifen for 2 years → letrozole for 3 years Letrozole for 2 years → tamoxifen for 3 years	8,028	97	HR = 0.86[a] p = .007	HR = 0.87[a] p = .048
IES[b]	Tamoxifen for 2–3 years → exemestane for 2–3 years	4,724	56	HR = 0.76 p = .0001	HR = 0.85 p = .08
ITA[b]	Tamoxifen for 2–3 years → anastrozole for 2–3 years	448	64	HR = 0.57 p = .005	HR = 0.56 p = .10
ARNO95[b]/ ABCSG8	Tamoxifen for 2 years → anastrozole for 3 years	3,224	28	HR = 0.60 p = 0.0009	Not Reported
MA-17[c]	Tamoxifen for 5 years → letrozole for 5 years	5,187	30	HR = 0.58 p < .001	HR = 0.82 p = .30

[a]Upfront letrozole arm was compared to tamoxifen arm. Sequential arms were then compared to the letrozole arm and there was no significant difference in DFS or OS.
[b]Patients were randomized after receiving 2 years of tamoxifen.
[c]In MA-17 patients were randomized after 5 years of tamoxifen to letrozole versus placebo for 5 years.

(HR 0.84, p = .022) were superior for patients in the anastrozole-alone arm compared with tamoxifen alone. Anastrozole also showed a significantly lower ipsilateral and contralateral breast cancer recurrence rate (HR 0.60, p = .004) that was maintained after treatment was completed, especially for the hormone-receptor-positive population where the absolute benefit over tamoxifen was 2.8% (61).

The Breast International Group (BIG) 1-98 study is a large randomized, phase III, double-blind trial that enrolled over 8,000 women comparing the following four options: monotherapy with letrozole or tamoxifen for 5 years, sequential administration of tamoxifen for 2 years followed by letrozole for 3 years, or sequential administration of letrozole for 2 years followed by tamoxifen for 3 years. The trial was conducted in postmenopausal women with hormone-receptor-positive operable invasive breast cancer. This trial was designed to address whether an aromatase inhibitor is more effective as initial adjuvant therapy or as therapy following a few years of adjuvant tamoxifen.

The BIG 1-98 trial employed DFS as its primary end point, using a definition that included local recurrence after breast-conserving treatment, the appearance of metastatic disease, the development of a second primary tumor, or death from any cause. DFS in this trial included secondary non–breast cancers, while DFS in the ATAC study did not. On the other hand, it did not include DCIS in its DFS definition, while the ATAC study did (45,61). Over 8,000 patients were included in the trial, with a median follow-up of 8.1 years. Letrozole monotherapy was significantly better than tamoxifen (disease-free survival HR 0.86, overall survival HR 0.87) (25).

Additionally, the Tamoxifen Exemestane Adjuvant Multinational (TEAM) is another large trial that reported its results (63,64). This trial randomized close to ten thousand patients to 5 years of tamoxifen or exemestane. When results from the IES study were announced, the study protocol was amended and the tamoxifen arm was changed to a sequential arm with initial tamoxifen for 2 to 3 years followed by exemestane. Results from the TEAM trial were initially analyzed at the switching point and therefore the data represented a comparison between upfront exemestane and tamoxifen. The study showed a numerical trend for improved DFS (its primary end point) for upfront exemestane that was not significant (HR 0.85, p = .12) (63). Final results, which compared the upfront exemestane group to the sequential therapy group (after the change in design), showed similar DFS between the two groups (64).

Sequential Adjuvant Therapy with Aromatase Inhibitors following Tamoxifen

The Intergroup Exemestane Study (IES) enrolled 4,742 patients who were on tamoxifen for 2 to 3 years and randomized them to exemestane or continuing tamoxifen therapy for the remainder of the five years of treatment. The primary end point was DFS defined as the time from randomization to recurrence of breast cancer at any site, diagnosis of a second primary breast cancer, or death from any cause. Similar to the ATAC trial, non-breast primary cancers were not included in the definition of DFS.

The most recent update on this study at a median follow-up of 55.7 months reported a hazard ratio of 0.76 (p = .0001) favoring exemestane, with an absolute benefit of 3.3% (65). Fewer deaths occurred in the exemestane group compared to the tamoxifen group, which was statistically significant only after excluding 122 hormone receptor negative patients (HR 0.83, p = .05). In addition, switching from tamoxifen to exemestane demonstrated a significant reduction in contralateral breast cancer (HR 0.56, p = .04) (65).

A combined analysis of the ARNO 95, ABCSG 8, and ITA trials, which included over 4,000 patients, showed that patients who switched to anastrozole had fewer disease recurrences (92 vs. 159) and deaths (66 vs. 90) than did those who remained on tamoxifen, resulting in significant improvements in DFS (HR 0.59, p < .0001) and overall survival (HR 0.71, p = .04) (66).

Despite confirming results from each of the three studies (67–69), this report has the limitations of a meta-analysis. The three trials had different randomization schema; while patients were randomized upfront in ABCSG 8, they were randomized after 2 to 3 years of tamoxifen in the ARNO 95 and ITA trials. There were also differences in the definition of primary end points and in the entry criteria.

The BIG1-98 trial randomized more than three thousand patients to tamoxifen for 2 years followed by letrozole 3 years or letrozole for 2 years followed by tamoxifen for 3 years were compared to patients in the upfront letrozole arm. At a median follow-up of 8.0 years from randomization for the comparison of the sequential groups with letrozole monotherapy, there were no statistically significant differences in disease free or overall survival for either sequence (25). A detailed subset analysis is discussed below.

Extended Adjuvant Therapy with Aromatase Inhibitors

Several trials evaluated extending adjuvant therapy with an aromatase inhibitor after 5 years of tamoxifen. The largest of these is the NCIC-MA17 trial where over 5,000 women who had completed 5 years of tamoxifen were randomly assigned to placebo versus letrozole. The study was terminated early after the first interim analysis demonstrated a significant improvement in DFS in the letrozole group, which was confirmed on longer follow-up (HR 0.58; $p < .0001$) (70). Another analysis of MA.17 demonstrated that the hazard ratio in favor of letrozole continued to improve each year throughout the first 4 years of treatment, suggesting that longer treatment is better (71).

NSABP B-33, which had a similar design using exemestane, was closed to accrual when the results of MA.17 were made public, and patients assigned to placebo were given the option of crossing over to exemestane. At that time, only half of the planned 3,000 patients were enrolled, and more than 40% of patients initially assigned to placebo chose to cross over to receive exemestane. Despite these limitations, a similar trend for improved DFS was observed for the exemestane arm, although it did not reach statistical significance (HR 0.68, $p = .07$) (72). The ABCSG 6a study is a smaller study that showed a significant improvement in DFS (HR 0.64, $p = .048$) for extended adjuvant endocrine therapy. (73). None of these three trials have shown an impact on overall survival.

It should be noted that studies of extended adjuvant therapy using tamoxifen or an aromatase inhibitor were performed in patients who received 5 years of initial tamoxifen therapy, a situation that is less common today in postmenopausal women in the era of aromatase inhibitor therapy. However, just like the ATLAS trial, they support the concept of prolonging endocrine therapy beyond 5 years to prevent late recurrences. Other extended adjuvant studies will help elucidate the optimal duration and regimen of adjuvant endocrine therapy.

LONG-TERM EFFECTS AND TOXICITY OF AROMATASE INHIBITORS

By inhibiting the activity of the enzyme aromatase, aromatase inhibitors markedly suppress plasma estrogen levels in postmenopausal women. In contrast to tamoxifen, these compounds do not bind ER and therefore lack partial agonist activity and are not associated with the adverse effects of tamoxifen on the endometrium and thrombosis. However, they also lack the desirable effects of tamoxifen on bone and serum lipids.

In general and compared to tamoxifen, aromatase inhibitors have a lower incidence of ischemic cerebrovascular events, venous thromboembolic events, hot flashes, and vaginal bleeding. However, lipid disorders, bone fractures, and musculoskeletal pain are more frequent with aromatase inhibitors. Results from individual clinical trials showed no significant difference in the incidence of ischemic cardiovascular events (see Tables 43-5 and 43-7).

However, a meta-analysis of seven trials showed aromatase inhibitors to be associated with a 26% increase in risk of cardiovascular disease (43). Whether this excess in risk is due to a detrimental effect of aromatase inhibitors, a protective effect of tamoxifen, or a combination of the two, is not clear. But these findings are to be taken into consideration together with the patient's other comorbidity when making treatment recommendations for breast cancer patients. Tamoxifen might be preferable in a patient with known cardiovascular disease unless their breast cancer has adverse factors predicting a high risk of early recurrence.

TABLE 43-7

Side Effects of Tamoxifen and Anastrozole in the ATAC Trial

Side Effect	*Anastrozole (%) (n = 3,092)*	*Tamoxifen (%) (n = 3,094)*	*p-Value*
Hot flashes	35.7	40.9	<.0001
Musculoskeletal	35.6	29.4	<.0001
Vaginal bleeding	5.4	10.2	<.0001
Vaginal discharge	3.5	13.2	<.0001
Endometrial cancer	0.2	0.8	.02
Fractures	11.0	7.7	<.0001
Ischemic heart disease	4.1	3.4	NS
Cerebrovascular events	2.0	2.8	.03
Venous thromboembolic event	2.8	4.5	.0004

Adapted from Arimidex, Tamoxifen, Alone or in Combination Trialists' Group, Forbes JF, Cuzick J, et al. Effect of anastrozole and tamoxifen as adjuvant treatment for early-stage breast cancer: 100-month analysis of the ATAC trial. *Lancet Oncol* 2008;9(1):45–53; Baum M, Budzar AU, Cuzick J, et al. Anastrozole alone or in combination with tamoxifen versus tamoxifen alone for adjuvant treatment of postmenopausal women with early breast cancer: first results of the ATAC randomised trial. *Lancet* 2002;359(9324): 2131–2139.

Contralateral Breast Cancer and Second Primary Cancer

With 100-month follow-up, the ATAC trial provides the most mature comparison between the side effects and benefits of an aromatase inhibitor with those of tamoxifen (61). It reported a 40% proportional risk reduction of contralateral breast cancers. Since tamoxifen reduces the risk of contralateral breast cancer by about 50%, anastrozole might prevent more than 70% of ER-positive contralateral breast tumors compared to no adjuvant treatment. Additionally, anastrozole had a significantly lower incidence of endometrial carcinoma. There was no significant difference in the occurrence of any other cancer.

Musculoskeletal Symptoms and Effects on Bone

Musculoskeletal symptoms are significantly higher in patients on aromatase inhibitors compared to tamoxifen or no adjuvant therapy. Joint complaints have been reported to range from 20% to 50% in various trials of aromatase inhibitors depending on the definition of this side effect (45,61,65,70) (see Tables 43-5 and 43-7). The incidence of arthralgias, joint stiffness, and musculoskeletal disorders in patients on aromatase inhibitors may be higher than reported by some aromatase inhibitor trials. When patients are questioned carefully, many of them complain of joint stiffness and pain that they attribute to "getting older" and not to the drug.

In contrast to tamoxifen, which has protective effects on bone density of postmenopausal women by virtue of its agonist activity, all aromatase inhibitors are associated with bone loss by lowering endogenous estrogen levels (45,61,65,70,74). In a report of 167 women who received serial bone mineral density (BMD) measurements on the ATAC trial, significant bone loss occurred at the lumbar spine and hip in the anastrozole group (median BMD decrease of 6.1% and 7.2%, respectively) compared to the tamoxifen group (median BMD increase of 2.8% and 0.7%, respectively) (75). Fracture rates were significantly higher in the anastrozole compared to the tamoxifen group (22.6 vs. 15.6 per 1,000 woman-years). Likewise, in the BIG 1-98 trial, fractures were more frequent with letrozole (5.7% vs. 4%) (76). In the MA.17 trial, which compared letrozole to placebo after 5 years of tamoxifen, more modest reductions in bone mineral density were observed (hip = 3.6%, lumbar spine = 5.35%) (74). In the IES trial, loss of bone mineral density also was observed during the 2 to 3 years of treatment with exemestane after initial tamoxifen therapy. However, no patient with a normal bone mineral density at the start of therapy developed osteoporosis during treatment (77). Women receiving an aromatase inhibitor should be assessed for other risk factors for osteoporosis, and bone density should be measured at baseline, and periodically during therapy.

Serum Lipids

All major aromatase inhibitor trials reported a higher incidence of hyperlipidemia in patients receiving aromatase inhibitors. The BIG 1-98 trial showed a significantly higher incidence of hyperlipidemia in the letrozole arm compared to tamoxifen, although most cases were grade 1 (Table 43-5) (76). The ATAC trial reported a 6% incidence of hyperlipidemia in the anastrozole arm compared to 2.2% in the tamoxifen arm ($p < .001$) (61), and the ITA trial showed an 8% incidence of lipid disorders compared to 1.4% with tamoxifen ($p = .01$) at a median follow-up of 64 months.

This higher incidence can be attributed to a cholesterol-raising effect of aromatase inhibitors or to the cholesterol-lowering effects of tamoxifen. The MA.17L substudy reported the effects of letrozole on lipid profiles and showed no overall significant difference from placebo (78). However, treating physicians are generally aggressive in treating hyperlipidemia and the widespread use of lipid-lowering agents like statins may mask the effects of aromatase inhibitors on serum lipids. Women on aromatase inhibitors should be followed with serial serum lipid measurements and appropriate therapy should be initiated when necessary, especially in light of the increased risk of cardiovascular disease with aromatase inhibitors (43).

Cardiac and Cerebrovascular Events

Compared to tamoxifen, aromatase inhibitors were associated with a lower risk of venous thromboembolic and ischemic cerebrovascular events in all aromatase inhibitor trials. However, in some trials, aromatase inhibitors were associated with an increase in the risk of ischemic cardiac disease, although the added risk appears to be small (61,70,79,80).

A recent meta-analysis addressed these issues in seven trials that compared tamoxifen to an aromatase inhibitor (43). This analysis showed a 26% increased risk of cardiovascular disease with an aromatase inhibitor compared to tamoxifen alone. The absolute increase in the risk of cardiovascular disease was small (0.8%), but statistically significant, and the number needed to harm (NNH) was 132. On the other hand, thromboembolic events were significantly more frequent with tamoxifen (RR 0.55), with an absolute increase of 1.2% over aromatase inhibitor treatment, and the NNH was 79 patients.

DECIDING BETWEEN TAMOXIFEN AND AROMATASE INHIBITORS IN POSTMENOPAUSAL PATIENTS

There are two major treatment decisions to be made in patients with ER-positive breast cancer. First, should the patient receive chemotherapy in addition to endocrine therapy? Many patients with ER-positive tumors show little or no benefit from adjuvant chemotherapy. These tumors have high ER, high PR, negative HER2, low Ki-67, and are grades 1 or 2—in other words, well-differentiated or luminal A tumors. Multigene assays such as the 21-gene recurrence score also provide important information on the potential benefits of chemotherapy in such women. Those with low and perhaps many with intermediate scores do not benefit from chemotherapy. These assays and their implications are discussed in Chapters 26, 28, 29, and 44.

The second decision is whether patients should be treated initially with tamoxifen or an AI and, if so, for how long and should a switching strategy be employed? Several studies have addressed this question. First it should be emphasized that aromatase inhibitors overall may not provide a significant survival benefit compared to tamoxifen monotherapy or a switching strategy, and if they do, it must be very small (25,43). In some patient subgroups there might not even be a disease-free-survival benefit. The ATAC and BIG 1-98 trials examined several biomarkers and pathological variables and outcome (24,81). While individual factors like low ER or PR, amplification of *HER2*, high Ki-67, grade 3, positive lymph nodes, and lymphatic invasion predicted early relapse they did not predict a differential benefit for an AI over tamoxifen. In a prospectively planned substudy of the TEAM trial comparing exemestane with tamoxifen followed by exemestane using semiquantitative measurements, ER-rich tumors derived additional benefit

from initial treatment with exemestane while ER and PR low positive tumors did better with sequential therapy (32). In a study of Ki-67 in ABCSG Trial 8 comparing tamoxifen monotherapy with tamoxifen followed by anastrozole the switching arm was superior to tamoxifen in the patients with low Ki-67 (82). A retrospective small subset analysis of the ATAC trial of patients not confounded by the coadministration of chemotherapy showed that a score derived from immunohistochemical determination of ER, PR, *HER2*, and Ki-67 (IHC4 score) was similar to the 21-gene recurrence score in its prognostic utility, but neither these nor clinical variables provided predictive information on the choice of tamoxifen or anastrozole (83). Somewhat discrepant data were reported from the BIG 1-98 trial in a much larger patient subset at 5 years' follow-up (84). While the individual markers alone showed only a nonsignificant trend favoring letrozole monotherapy over the other three arms in patients with higher-risk tumors (lower ER and PR, high Ki-67, and *HER2* amplified), a composite STEPP analysis did discriminate between the arms. Letrozole monotherapy showed an advantage compared to the other arms in the highest risk group. Among patients with the lowest-risk score 5-year DFS was 96%, 94%, 93%, and 94% for the letrozole monotherapy, letrozole followed by tamoxifen, tamoxifen followed by letrozole, and tamoxifen monotherapy arms, respectively. Among patients with an intermediate risk score the DFS percentages were 90%, 91%, 93%, and 86%, and for those with the highest-risk score were 80%, 76%, 74%, and 69%, respectively. These interesting data suggest that patients with ER, PR, HER2, and Ki-67 all falling into the low risk stratum might be treated with any of the treatment arms including monotherapy with tamoxifen while those with high-risk features might be best treated with letrozole monotherapy. However, in view of the inconsistency of data of this type, the fact that the markers were all done in a central laboratory, and the retrospective nature of the studies, these factors should be considered with caution in treatment decisions. These data might, however, provide some comfort that patients given monotherapy with tamoxifen or patients switching to tamoxifen after 2 years because of side effects with an AI, will not have a major reduction in benefit, especially if they have low risk factors.

The role of obesity and breast cancer outcome in patients receiving adjuvant endocrine therapy has also been evaluated. Obesity, especially patients with a body mass index (BMI) greater than 30 kg/m^2, is an independent prognostic factor for recurrence and death (85). Obesity may also have an effect on the relative benefit of tamoxifen or an AI. Although obese patients have a higher risk of recurrence and death from breast cancer and other causes, tamoxifen's beneficial effects on these outcomes are not reduced in such women (86). However, obesity does negatively impact the suppression of plasma estrogens by AIs raising the possibility that they might be less effective in obese patients (87). Two studies, one in premenopausal patients and one in postmenopausal patients, suggest that the relative superiority of AIs compared to tamoxifen is greater in thin women (88,89). In the premenopausal study, ABCSG-12 Trial comparing ovarian suppression plus either anastrozole or tamoxifen, the negative effect of obesity on AI benefit was dramatic (88). Obese patients randomized to anastrozole had a 50% increase in recurrence and a threefold increase in deaths compared to patients treated with tamoxifen. In the BIG 1-98 trial in postmenopausal patients treated with tamoxifen or letrozole, there was no indication that the benefit of letrozole was less in overweight patients (90). The explanation for these differences among trials is not clear although it could be related to menopausal status, the AI used in the study, or other factors. These data do argue that premenopausal women should not be treated with ovarian suppression plus an aromatase inhibitor at this time.

Side effects of AIs versus tamoxifen and patient comorbidities might influence the decision about which drug to choose as initial therapy. Younger, sexually active women with low-risk disease might choose tamoxifen instead of an AI or a switching strategy because tamoxifen is associated with less atrophic vaginitis. This complication, which adversely affects quality of life, is also easy to treat with vaginal estrogens in patients on tamoxifen. Tamoxifen binds to and blocks estrogen receptors and would prevent absorbed estrogen from binding ER and stimulating the tumor. Vaginal estrogens cannot as easily be used in patients on AIs. Tamoxifen might also be preferred in patients with severe cardiac risk factors or those with osteoporosis. In contrast, in patients with high-risk breast cancer or those with a history of thromboembolic phenomenon an AI is an obvious choice. Thus, the characteristics of the tumor and the patient are helpful in making this treatment decision.

ADJUVANT OVARIAN ABLATION

There are three methods of inhibiting ovarian production of estrogen for breast cancer treatment in premenopausal women, ovariectomy, ovarian irradiation, and gonadotropin-releasing hormone (GnRH) agonists. GnRH is made in the hypothalamus and released in a pulsatile fashion. This, in turn, stimulates the pituitary release of follicle-stimulating hormone (FSH) and luteinizing hormone (LH), eventually resulting in the production of estrogen from the ovaries. The chronic administration of a GnRH agonist results in internalization of pituitary GnRH receptors, rendering them unresponsive to hypothalamic endogenous GnRH, and thus shutting off the downstream production of estrogen.

Among the first randomized trials of adjuvant therapy in breast cancer were studies of adjuvant ovarian ablation either by surgical oophorectomy or by irradiation (91,92). Some of these trials were not properly randomized by modern standards (93). Many were small, a few included both premenopausal and postmenopausal women, and none included ER analyses, which were not yet available. Most of these trials found a significant DFS advantage for ovarian ablation, and two reported a significant OS advantage (94,95).

The EBCTCG 2005 meta-analysis analyzed almost 8,000 women younger than 50 years of age with ER-positive or ER-unknown disease randomized into trials of ovarian ablation by surgery or irradiation (4,317 women, 63% ER-untested) or of ovarian suppression by treatment with a GnRH agonist (3,408 women, 26% ER-untested).

Overall, a definite effect of ovarian ablation or suppression was evident on both recurrence and breast cancer mortality (see Table 43-8). However, this effect is not as large as it was reported in earlier meta-analyses of these trials, when ovarian ablation was not generally being tested against a background of effective systemic chemotherapy (96).

The absolute effect on 15-year outcomes showed that for recurrence, most of the advantage for ovarian ablation occurs during the first few years and seems to be maintained in later years. This early difference in recurrence translates into a later difference in mortality. The meta-analysis found no indication that the benefits that accrue during the first decade of follow-up are lost during the second decade (96).

All of these women were younger than 50 years of age when randomized, and therefore there have been relatively few non-breast cancer related deaths. However, these

TABLE 43-8

Meta-Analysis of the Effects of Ovarian Ablation (OA), Ovarian Suppression (LHRH), ER Positive or Unknown—Overview 2005

	Reduction (± SE) in Annual Odds	
Group/Age	*Recurrence (%)*	*Breast Cancer Mortality (%)*
OA vs. nil		
<40	30 ± 17	29 ± 16
40–49	33 ± 8	32 ± 9
LHRH vs. nil		
<40	21 ± 16	27 ± 21
40–49	23 ± 9	21 ± 13
OA or LHRH vs. nil		
<40	25 ± 12	29 ± 13
40–49	29 ± 6	29 ± 7
OA or LHRH+ chemo vs. chemo		
<40	14 ± 9	4 ± 10
40–49	5 ± 7	–3 ± 8

Adapted from Early Breast Cancer Trialists' Collaborative Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365(9472):1687–1717.

deaths do not appear to be increased by treatment during either the first or the second decade (96).

Another meta-analysis of the role of medical ovarian suppression in early stage, hormone-receptor-positive breast cancer was reported in 2007 (97). The analysis included data from 11,906 premenopausal women with early breast cancer randomized in 16 trials. This report found that when used as the sole systemic adjuvant treatment, GnRH agonists did not significantly reduce recurrence or death after recurrence in hormone-receptor-positive cancers. However, the number of patients may have been too small to elicit the benefit. When added to other systemic therapy (tamoxifen, chemotherapy, or both), GnRH reduced recurrence in women younger than 40 by 12.7% (p = .02); and death after recurrence by 15.1% (p = .03). When individual therapies were evaluated, adding GnRH agonists to tamoxifen alone did not result in significant benefit (97).

The numbers of patients included in these ovarian ablation studies is still relatively small giving rise to large standard errors in some of the subgroups. These analyses may underestimate the true benefit since they include a large percentage of patients from the early ovarian ablation trials who were ER-unknown. Nevertheless, patients less than 40 years of age and those between 40 and 49 years of age (mostly premenopausal) benefit significantly from ovarian ablation. A benefit is not evident in patients receiving chemotherapy probably because many of those patients already achieve ovarian ablation as a "side effect" of the chemotherapy. There are no major differences between GnRH agonists and other forms of ovarian ablation, although this question has not been well studied directly. Data are insufficient, in any trial or either meta-analysis, to confirm whether like all other adjuvant endocrine therapies, ovarian ablation reduces the incidence of contralateral breast cancer.

The results with ovarian ablation or suppression are comparable to those achieved with chemotherapy or tamoxifen in women younger than 50 years of age. Based on available data, ovarian ablation appears equivalent to chemotherapy alone in premenopausal ER-positive patients (97,98).

Results of several other trials shed additional light on the relative effectiveness of chemotherapy and ovarian ablation. Nearly all of these trials, however, used CMF-based chemotherapy, which may be inferior to more contemporary regimens. The majority of these trials, showed equivalence between ovarian ablation and chemotherapy in ER-positive, premenopausal women (99).

Several other studies have compared ovarian ablation combined with tamoxifen versus chemotherapy. The largest trial, Trial 5 from the Austrian Breast Cancer Group, randomized 1,034 receptor positive patients to 3 years of goserelin plus 5 years of tamoxifen or to six cycles of CMF (100). At 5 years of follow-up there was a significant DFS advantage for the endocrine therapy and a trend for improved OS. Two smaller trials, comparing tamoxifen plus ovarian suppression with chemotherapy showed no difference in DFS and OS between the two groups (101,102).

Therefore, there is a suggestion that the addition of tamoxifen to ovarian ablation may provide superior results. For the moment, ovarian ablation with or without tamoxifen is a reasonable alternative to chemotherapy in patients with ER-positive tumors.

It is still difficult to know where ovarian ablation fits in our current adjuvant therapy options for premenopausal patients. It might be considered in those who refuse other therapies, as an alternative to chemotherapy in certain patients, as an adjunct to chemotherapy in women not achieving chemical ovarian ablation, or for prevention in patients with a hereditary breast cancer syndrome who have a high risk of developing breast and ovarian cancer. Tamoxifen is the better choice in patients needing endocrine adjuvant therapy.

The combination of tamoxifen plus ovarian ablation, and ovarian ablation combined with an aromatase inhibitor are currently being compared to tamoxifen in multiple studies. One of these studies, the ABCSG-12 randomized 1,801 patients according to a 2X2 design to the combination of the LHRH agonist goserelin with anastrozole, or to goserelin with tamoxifen, each with or without zoledronic acid every 6 months for 3 years (103). This study showed no significant difference in DFS between the two endocrine therapy combinations (HR 1.10, 95% CI 0.7–1.53; p = .59). However, overall survival was worse with anastrozole plus goserelin than with tamoxifen plus goserelin (46 vs. 27 deaths; HR 1.75, 95% CI 1.08–2.83; p = .02). The study also showed that the group that received zoledronic acid had a 36% reduction in the risk of recurrence. This benefit was observed in skeletal, visceral and local recurrence rates (103) (see Chapter 47 for further review of the role of bisphosphonates in adjuvant therapy). Results of other large trials, like the SOFT trial, will provide further insight about the role of aromatase inhibitors with ovarian suppression as adjuvant therapy for premenopausal women. Until then, ovarian ablation plus an aromatase inhibitor should not be routinely used as adjuvant endocrine therapy in premenopausal women unless a tamoxifen based regimen is contraindicated.

TOXICITY OF OVARIAN ABLATION

The side effects of ovarian ablation are due to lowering the level of estrogen. Menopausal symptoms and gynecological complaints are common and are similar to those observed with tamoxifen. Premature coronary artery disease and osteoporosis might be expected in some patients.

Even short-term treatment with goserelin in premenopausal women with endometriosis was associated with bone loss (104). The meta-analysis does not yet show increased vascular deaths in women with breast cancer treated by ovarian ablation, but the database is small (91,92,96). Bone loss and premature osteoporosis are likely to be significant in such patients who, therefore, demand close monitoring and the early institution of bisphosphonates when bone loss occurs. Zoledronic acid, administered every 6 months, has been shown to prevent treatment-related bone loss in premenopausal women receiving adjuvant endocrine therapy (105) and showed reduced risk for recurrence and distant metastasis in one study (106). This use of bisphosphonates as adjuvant therapy is discussed in Chapter 47.

COGNITIVE FUNCTION IN PATIENTS ON ENDOCRINE THERAPY

Estrogen regulates emotional responses and cortical activity during cognitive task performance in humans (107) and may have a protective effect on verbal memory (108). These data raise the question of the effects of SERMs or estrogen deprivation therapy such as anastrozole or ovarian ablation on cognitive function. Aromatase is expressed in the brain, although its importance in cognitive function is not known (109). Cognitive function was measured in the Multiple Outcomes of Raloxifene Evaluation (MORE) trial in women with osteoporosis (110). Overall, there was no difference between placebo and raloxifene in several different tests of cognitive function, suggesting that it does not have an adverse effect worse than that in women with postmenopausal estrogen levels. Whether tamoxifen would have a similar effect is not clear, although in a randomized study using magnetic resonance spectroscopy, both estrogen and tamoxifen had a favorable profile (111).

Cognitive assessments that measured a range of memory and attention functions were reported on 94 patients from the ATAC trial and 35 noncancer controls (112). The patient group did not differ from controls on measures of working memory, attention, and visual memory but was significantly impaired compared to the control group on measures of verbal memory ($p = .026$) and processing speed ($p = .032$). Cognitive performance in the patient group was not significantly related to length of time on trial or measures of psychological morbidity (112). Results from this small study suggest that anastrozole, like tamoxifen, may cause a specific deficit in verbal memory. However, a study done on patients from the BIG 1-98 study during their fifth year of therapy showed that patients on tamoxifen had significantly worse cognitive function than patients receiving letrozole (score difference of 28%, $p = .04$) (113). Cognitive function scores were improved for both groups after stopping endocrine therapy (114). Larger studies with longer follow-up are needed to assess the long-term consequences of treatment with endocrine therapy taking into consideration that patients with breast cancer score lower than healthy controls on their cognitive function tests, even before therapy is initiated. These findings indicate that factors other than systemic treatment can also affect cognitive function in women with breast cancer making it difficult to establish causality.

FUTURE DIRECTIONS

Since its introduction almost 40 years ago, significant progress has been made in the systemic adjuvant therapy for breast cancer. The population mortality reductions observed (25%) in most Western countries over the past 20 years have been attributed largely to the widespread use of adjuvant therapy, especially tamoxifen, and to a lesser extent chemotherapy (115). Thus, the hypothesis that many breast cancer patients already have subclinical distant metastases at the time of diagnosis, and that these microscopic foci can be more effectively treated than gross metastatic disease, has been confirmed.

However, several questions regarding adjuvant endocrine therapy remain unanswered, and many of these are now being addressed in ongoing clinical trials.

- Is ovarian ablation combined with tamoxifen or with an aromatase inhibitor, better than tamoxifen alone in premenopausal patients?
- What is the optimal duration of aromatase inhibition, and what are possible long-term sequelae of treatment?
- Are local slow-release vaginal estrogen preparations or other formulations safe to use with aromatase inhibitors and can we find a successful treatment for joint pain and stiffness?
- Do ER degraders like fulvestrant alone or in combination with aromatase inhibitors have a role in the adjuvant setting?
- Do combinations of endocrine therapy with targeted therapies that inhibit growth factor receptors, or downstream pathways like mammalian target of rapamycin (mTOR), the mitogen activated protein kinase pathway, the stress kinase pathway, or the phosphoinositide-3 kinase (PI3K)/Akt pathway improve outcome in the adjuvant treatment of breast cancer?

MANAGEMENT SUMMARY

- Adjuvant endocrine therapy is the most effective systemic treatment modality for hormone-receptor-positive breast cancer; it reduces the risk of recurrence by 50% or more across different tumor characteristics and clinical stages and this may be an underestimation given suboptimal compliance.
- Optimal duration is not yet established for all subgroups. However, all patients should receive at least 5 years of therapy and 10 years of therapy should be considered in certain patients.

Premenopausal Women

- All premenopausal women should be encouraged to enroll in clinical trials of adjuvant hormone therapy.
- For women who do not have access to clinical trials, are not eligible, or choose not to participate, 5 years of tamoxifen is still the most appropriate treatment. At the end of 5 years, in women with higher-risk breast cancer who remain premenopausal, extending treatment to 10 years should be considered.
- Ovarian suppression or ablation (medical or surgical) may be appropriate in selected patients who have a contraindication or do not tolerate tamoxifen. Optimal duration of ovarian suppression (if done medically) is not established, but treating for 3 to 5 years is reasonable.
- Combining tamoxifen and ovarian suppression may be utilized in patients at high risk of recurrence particularly if they are younger than 35 years.
- Aromatase inhibitors are indicated only for postmenopausal patients and should be avoided in women whose menopausal status is not established (60). The use of aromatase inhibitors with ovarian suppression should await results from completed large international trials. They might be useful in patients for whom tamoxifen is contraindicated.

Postmenopausal Women

- Aromatase inhibitors offer a small advantage over tamoxifen and should be at least a part of the adjuvant endocrine therapy of most postmenopausal women with ER-positive breast cancer.
- Upfront treatment with an aromatase inhibitor or sequencing with tamoxifen for 2 to 3 years followed by an aromatase inhibitor for 3 to 5 years or switching from an AI to tamoxifen after 2 to 3 years are considered acceptable options.
- The decision on whether to use upfront aromatase inhibitor therapy or sequential therapy should take into consideration many factors including patient age, years after menopause, risk of recurrence, bone health, history of thromboembolism, cardiac or cerebrovascular disease, menopausal symptoms, and sexual activity of the patient. Patients with more aggressive breast cancers on the basis of high grade, high proliferation, low ER, or *HER2* amplification should be considered for 5 years of an AI.
- Patients whose menopausal status is in question and those who develop amenorrhea after chemotherapy are best started on tamoxifen and hormone profiles followed. If they remain clinically amenorrheic and with postmenopausal hormone profiles for 2 years, they can be switched to an aromatase inhibitor.
- Postmenopausal women (or those who become postmenopausal) completing 5 years of tamoxifen should be considered for extended adjuvant therapy with an aromatase inhibitor. This group of patients is not large as many postmenopausal women now receive aromatase inhibitors initially or after 2 to 3 years of tamoxifen.
- Patients on tamoxifen should not have anything more than a routine annual gynecologic examination unless they present with vaginal spotting or bleeding.
- Patients on aromatase inhibitors should have serial monitoring of bone mineral density and serum lipids.

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CHAPTER 44

Adjuvant Systemic Chemotherapy in Early Breast Cancer

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CHAPTER CONTENTS

INTRODUCTION

In women, breast cancer is the most common life-threatening malignancy, but the second leading cause of cancer mortality with a falling mortality rate in the United States over the past few decades (1). This trend has been attributed to both large-scale screening leading to the identification of earlier stage disease with lower risk and to an improvement in systemic treatment strategies that reduce the likelihood of recurrence. Individual large-scale, randomized, controlled clinical trials have generally indicated modest improvements in disease-free survival (DFS) and overall survival (OS) but translated into a large population the public health impact can be substantial. Worldwide overviews conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) have confirmed the scale of these improvements. Based on these meta-analyses, the combination of chemotherapy and hormonal therapy would be expected to halve the rate of breast cancer mortality in patients with estrogen receptor (ER)-positive disease during the first 15 years after diagnosis (2). Similarly, polychemotherapy significantly improve outcomes in patients with ER-poor breast cancer (3). Recently, the EBCTCG reported long-term outcomes of various polychemotherapy regimens for early breast cancer, including trials that contained the taxanes (4). This chapter will focus on the evolution, and current status of adjuvant chemotherapy in the treatment of early breast cancer.

DEVELOPMENT OF COMBINATION CHEMOTHERAPY

First-Generation Trials with Alkylating Agents and Cyclophosphamide-, Methotrexate-, and Fluorouracil-Based Chemotherapy

The first trial of adjuvant chemotherapy for breast cancer was performed by the National Breast Cancer Bowel and Breast Project (NSABP) in 1958 (5). This study was based on the premise that cancer cells were sometimes dislodged at the time of surgery. Two days of perioperative thiotepa was compared to placebo in over 800 women undergoing radical mastectomy and showed a benefit in premenopausal patients. In an attempt to improve upon these results, the NSABP studied 2 years of postoperative adjuvant therapy with melphalan and again showed a more pronounced benefit in premenopausal, node-positive patients (6).

The observed activity of combination chemotherapy consisting of cyclophosphamide, methotrexate, and fluorouracil or 5-FU (CMF) for metastatic breast cancer led to its incorporation as adjuvant therapy. In 1975 Bonadonna et al. reported that 12 cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) resulted in a 19% advantage in 5-year DFS compared with no adjuvant chemotherapy ($p < .002$) and a 14% improvement in OS ($p < .04$) (7). This combination eventually became known as "oral" or classical CMF because the cyclophosphamide (100 mg/m^2) was administered orally for 14 days of the 28-day regimen.

Methotrexate (40 mg/m^2) and 5-fluorouracil (600 mg/m^2) were both administered intravenously (IV) on days 1 and 8. A follow-up study, comparing 6 months of therapy to 12 months, demonstrated an equivalent outcome (8). Bonadonna et al. reported the 30-year follow-up on randomized studies of adjuvant CMF and showed the enduring benefit of this regimen in the adjuvant setting (9). Similarly, the Cancer and Leukemia Group B (CALGB) conducted several trials of CMF-based therapies and demonstrated that the clinical benefit of chemotherapy was maintained with over 20 years of follow-up (10).

A joint analysis of two studies conducted by the International Breast Cancer Study Group and German Breast Cancer Study Group compared 6 months of CMF to 3 months (11). There was a trend toward a benefit for 6 months of therapy in women 40 years or younger (p = .22) and in those with hormone-receptor-negative breast cancer (p = .37). In the German Adjuvant Breast Cancer Group comparison of 6 months to 3 months of adjuvant treatment with CMF in 789 women there was no difference in outcome (12). The Southwest Oncology Group (SWOG) found that a 2-year duration of CMF with vincristine and prednisone (CMFVP) in patients with axillary-node-positive, hormone-receptor-negative breast cancer was no better than 1 year in terms of OS (p = .33) or DFS (p = .24) (13). The Ludwig Trial Group found that one peri-operative cycle of CMF chemotherapy was superior to surgery without any chemotherapy (p = .04) (14). However, a follow-up study was done by the Ludwig group compared one perioperative cycle of CMF to 6 cycles in node-positive breast cancer, and they concluded that CMF for 6 cycles was superior in terms of DFS (p < .0001) and OS (p = .011) (15). Based on the results of these earlier trials of CMF with 6 months of CMF adjuvant therapy being equivalent to longer durations of therapy, this has become the most popular duration of therapy for the three-drug combination. Furthermore, studies utilizing adjuvant CMF in combination with other agents (i.e., prednisone, vincristine) failed to demonstrate a consistent an impact on DFS or OS (10,16–18).

Most of the earlier trials were performed in the node-positive population. The trial NSABP B-13 evaluated no chemotherapy versus methotrexate/5-flourouracil (MF) in 760 patients with hormone-receptor-negative, node-negative disease and showed a benefit of MF through 16 years of follow-up in terms of relapse-free survival (RFS) (hazard ratio [HR] = 0.59, p < .001; OS: HR = 0.75, 95% CI = 0.58–0.98, p = .03) (19). In a subsequent trial (NSABP B-19), 1,095 patients with ER-negative, node-negative tumors were assigned to MF versus CMF, and through 13 years of follow-up, an overall benefit was seen in favor of CMF (RFS: HR = 0.59, p < .001; OS: HR = 0.71, p = .01), especially in patients 49 years or younger (19). The NSABP B-20 enrolled patients with hormone-receptor-positive, node-negative disease and with a median follow-up of 8 years, it demonstrated that the addition of chemotherapy (MF or CMF) to tamoxifen was superior to tamoxifen alone in both DFS (84% vs. 77%, p = .001) and OS (92% vs. 88%, p = .018) (20). Based on the results of these node-negative trials, the 2000 National Institutes of Health (NIH) Consensus Conference recommended that all patients with tumors of greater than 1 cm or positive lymph nodes should be offered adjuvant chemotherapy, regardless nodal status, menopausal status, and hormonal receptor status (21).

Adjuvant Anthracyclines

Doxorubicin

The anthracyclines were introduced in the adjuvant setting, mainly doxorubicin or epirubicin, in the 1980s. In 1981, NSABP B-11 added doxorubicin (A) to melphalan and fluorouracil (PAF) versus melphalan and fluorouracil (PF) in over 700 ER-poor patients (22). The study demonstrated that the addition of doxorubin conferred a DFS (p = .003) and OS (p = .05) benefit. The CALGB 8082 compared a prolonged regimen of cyclophosphamide, methotrexate, fluorouracil, vincristine, and prednisone (CMFVP) with CMFVP followed by anthracycline-based vinblastine, doxorubicin, thiotepa, and fluoxymesterone (VATH) in over 900 patients. At a median follow-up of 11.5 years, the incorporation of VATH led to significant improvements in DFS (p = .004) and OS (p = .043) (23). Bonadonna et al. conducted two trials involving doxorubicin given sequentially with CMF. The first trial compared CMF IV × 12 versus CMF IV × 8 followed by doxorubicin × 4 (CMF → A) in over 550 women with one to three positive nodes. The second study enrolled over 400 patients with four or more involved nodes and evaluated doxorubicin × 4 followed by CMF × 8 (A → CMF) versus alternating 2 courses of CMF with 1 cycle of doxorubicin (CMF/A) (24). There was a benefit in DFS and OS when sequential doxorubicin was given all before CMF in the second trial. This may be due to the importance of maintaining dose density which will be discussed later in this chapter. However, there was no benefit in DFS or OS with the addition of doxorubicin in the first trial, and perhaps this could be due to the inclusion of a lower-risk population in this study (one to three positive nodes).

The US Intergroup conducted a study (INT-0102) comparing CAF × 6 cycles (100 mg/m^2 orally days 1 to 14, 30 mg/m^2 IV days 1 and 8, 500 mg/m^2 IV days 1 and 8) against classical CMF in over 3,900 patients with high-risk (tumor size greater than 2 cm, ER-negative, or high S-phase fraction), node-negative disease, with or without tamoxifen. The study showed that CAF was associated with a marginal improvement in OS (85% vs. 83%, HR = 1.19 for CMF vs. CAF, p = .03) (25). The Grupo Espanol de Investigacion en Cancer de Mama (GEICAM) group enrolled over 980 patients with stages I to III breast cancer and compared FAC (500/50/500 mg/m^2) IV versus CMF (600/60/600 mg/m^2) IV, all given every 3 weeks × 6, and showed superiority in favor of FAC in DFS (RR 1.2, p = .03) and OS (RR 1.3, p = .05) (26).

The NSABP conducted study B-15 that enrolled over 2,100 patients with node-positive disease to a shorter course of an anthracycline-based treatment with the omission of fluorouracil. In this study patients were randomized to AC (60/600 mg/m^2) IV every 3 weeks × 4 versus classical CMF × 6 versus AC × 4 followed by 6 months of rest period followed by CMF IV every 28 days × 3 (750 mg/m^2 days 1 and 8, 40 mg/m^2 days 1 and 8, 600 mg/m^2 days 1 and 8) (AC → rest → CMF) and found no significant DFS or OS in all three arms (27). Next, the NSABP conducted trial B-16 and showed the benefit of the addition of AC therapy with tamoxifen over endocrine therapy alone in node-positive patients (28). Moving forward, the NSABP conducted study B-23 and randomized over 2,000 node-negative patients to classical CMF × 6 versus AC × 4, with or without tamoxifen. Similar to B-15, there was no difference in RFS or OS between the two regimens (18,29). Unlike other anthracycline-based regimens (CAF or FAC) and epirubicin-based therapies (discussed below), all given either as 6 cycles or over 6 months, AC was not better than classical CMF. There are several reasons to explain the lack of benefit of AC over classical CMF, and they include the short duration of this therapy, the omission of 5-fluorouracil, and the use of intravenous cyclophosphamide. However, the AC regimen was considered to be preferable to the classical CMF regimen due to ease of administration and its convenience, and it was incorporated into several subsequent sequential anthracycline-taxane combinations (Table 44-1).

TABLE 44-1

Trials of Doxorubicin- versus Non anthracycline-Containing Regimens

Study	*N*	*Treatment*	*DFS/RFS/EFSp-Value*	*OSp-Value*
NSABP B-11 (22)	707	PAF > PF	.003	.05
CALGB 8082 (23)	945	CMFVP-VATH > CMFVP	.004	.043
Bonadonna (24)	552	CMF = CMF → A	NS	NS
Bonadonna (24)	403	A → CMF > CMF/A	.0017	.018
INT-0102 (25)	2,690	CAF > CMF	NS	.03
GEICAM (26)	980	FAC > CMF	.03	.05
NSABP B-15 (27)	2,194	AC = CMF = A → CMF	NS	NS
NSABP B-23 (29)	2,008	AC +/− Tam = CMF +/− Tam	NS	NS

DFS, disease-free survival; RFS, relapse-free survival; EFS, event-free survival; OS, overall survival; NS, not statistically significant; NSABP, National Surgical Adjuvant Breast and Bowel Project; CALGB = Cancer and Leukemia Group B; INT-0102, US Intergroup Study 0102; GEICAM, Grupo Espanol de Investigacion en Cancer de Mama; P, melphalan; A, doxorubicin; F, fluorouracil; C, cyclophosphamide; M, methotrexate; V, vincristine; P, prednisone; VATH, vinblastine, doxorubicin, thiotepa, and fluoxymesterone; Tam, tamoxifen.

Epirubicin

The National Cancer Institute of Canada (NCIC) conducted trial MA.5 and enrolled over 700 node-positive patients to cyclophosphamide, epirubicin, and fluorouracil (CEF) (100 mg/m^2 orally days 1 to 14, 60 mg/m^2 IV days 1 and 8, 600 mg/m^2 IV days 1 and 8) versus classical CMF (30). Now at 10 years, results showed a statistically significant improvement in relapse-free survival (RFS) (52% vs. 45%; p = .007) and a trend in OS (62% vs. 58%, p = .085) in patients in the epirubicin-containing arm. Treatment with CEF was accompanied by more toxicities than CMF, including hospitalizations for febrile neutropenia (8.5% vs. 1.1%). Nevertheless, CEF became the standard chemotherapy in Canada for treating high-risk patients.

The French Adjuvant Study Group (FASG) conducted study FASG 05 and randomized 565 patients to FEC 100 (500/100/500 mg/m^2) versus FEC 50 (500/50/500 mg/m^2), all administered IV every 3 weeks × 6 cycles (31). At a median follow-up of 10 years, results were in favor of FEC 100 in DFS (50.7% vs. 45.3%, p = .036) and OS (54.8% vs. 50.0%, p = .05). Delayed cardiac toxicity after relapse occurred in 4.3% and 4.1% of patients in FEC 50 and FEC 100 arms, respectively. Thus, the survival advantage of FEC 100 was not offset by a higher incidence of cardiac toxicities. At that time FEC 100 then became a standard adjuvant treatment option in Europe.

Poole et al. reported on the combined results of two trials investigating the efficacy of epirubicin in the National Epirubicin Adjuvant Trial (NEAT) and the Scottish trial BR9601 in over 2,300 women (32). In the NEAT study, patients were randomized to E (100 mg/m^2) IV × 4 followed by classical CMF × 4 (E → CMF) versus classical CMF × 6. In BR9601, patients were randomized to E (100 m/m^2) × 4 followed by modified CMF (750/50/600 mg/m^2) IV every 3 weeks × 4 versus modified CMF × 8. Overall, results were in favor of the addition of epirubicin with 5-year RFS rates of 76% versus 69% and 5-year OS of 82% versus 75% (p < .001 for all comparisons). This study confirmed the benefit of an anthracycline-based regimen over CMF alone. Thus, E → CMF regimen, similar to the original Bonadonna regimen, became another standard option as adjuvant therapy in Europe (24) (Table 44-2).

The EBCTCG evaluated 14,000 patients in trials comparing CMF with an anthracycline-based regimen and demonstrated a modest, but statistically significant, benefit favoring the anthracyclines, with absolute benefits of 3.4% for recurrence and 3.3% for mortality at 15 years of follow-up, irrespective of age or hormone receptor status (2). Epirubicin-based regimens are commonly used in Europe and Canada. Epirubicin has almost half of the cardiotoxicity than seen doxorubicin, on a milligram by milligram basis (33). However, the cumulative doses of epirubicin in the adjuvant regimens are higher than those for doxorubicin, and thus, the cardiac toxicity of epirubicin-based regimens are quite similar to that with doxorubicin-containing therapies.

The anthracyclines have been a mainstay of breast cancer treatment for the past 30 years. The use of the anthracyclines has been declining due to various reasons, as specific treatments for different subgroups of women are being defined. However, the data are unclear on which subsets of patients may have the anthracyclines omitted. The literature on response to the anthracyclines, or not, based TOPO II gene aberrations or *HER2* overexpression or amplification is still unclear (34). Thus, given the established benefit of the anthracyclines, any decision to eliminate doxorubicin or epirubicin, especially in high-risk patient, should be based on the results of adequately powered, prospective randomized trials.

Despite the use of the anthracyclines, the risk of relapse remains significant, especially in those with poor risk features (35). Inherent or acquired drug resistance could result in disease relapse and variable drug sensitivity among subclones could also contribute to resistance (36). To overcome the limitations of chemotherapy, various strategies have been investigated, which include the manipulations of dose and schedule and the use of non-cross-resistant drugs, such as the taxanes.

Adjuvant Taxanes

Paclitaxel

The CALGB 9344 trial enrolled more than 3,100 node-positive women to receive AC versus AC → paclitaxel (P), and three different doses of doxorubicin were evaluated (60 mg/m^2, 75 mg/m^2, or 95 mg/m^2) (37). There was no benefit with the higher doses of A beyond the standard dose of 60 mg/m^2. At a follow-up at 5 years, the hazard reductions from adding paclitaxel to AC were 17% for recurrence (p = .0023) and 18% for death (p = .0064). The DFS was 65% for AC alone versus 70% for AC → P; OS was 77% for AC and 80% for AC→ P. The effects of adding paclitaxel were not significantly different in subsets defined by protocol. However, in an unplanned subset analysis, the hazard ratio (HR) of AC → P versus AC

TABLE 44-2

Trials of Epirubicin- versus Non Anthracycline-Containing Regimens

Study	*N*	*Treatment*	*DFS/RFS/EFS p-Value*	*OS p-Value*
NCIC MA.5 (30)	710	CEF > CMF	.007	NS
FASG 05 (31)	565	FEC > CMF	.036	.05
NEAT/BR9601 (32)	2,391	E → CMF > CMF	<.001	<.001

DFS, disease-free survival; RFS, relapse-free survival; EFS, event-free survival; OS, overall survival; NS, not statistically significant; NCIC, National Cancer Institute of Canada; FASG, French Adjuvant Study Group; NEAT, National Epirubicin Adjuvant Trial; C, cyclophosphamide; E, epirubicin; F, fluorouracil; M, methotrexate.

alone was 0.72 for those with ER-negative tumors and only 0.91 for those with ER-positive tumors. The additional toxicities of P were modest.

Similarly, the NSABP B-28 also randomized over 3,000 women with node-positive breast cancer to AC × 4 versus AC × 4 followed by P × 4 (38). The 5-year results were reported showing the benefit in the addition of P to AC in all node-positive breast cancer patients, regardless of ER status, use of tamoxifen, age, number of positive nodes, type of surgery, tumor grade, and histologic type. The 5-year DFS was 72% versus 76% (p = .008) in favor of addition of P. The 5-year OS was 85% in both groups. The lack of OS benefit with P in this study, unlike CALGB 9344, may be attributed to a better prognosis group (70% in NSABP B-28 vs. 46% of patients in CALGB 9344 with one to three positive nodes) and the concurrent use of tamoxifen with chemotherapy in NSABP B-28.

With the results of CALGB 9344 and NSABP B-28, every 3 weeks AC → P became the standard option for the treatment of high-risk breast cancer and became the standard arm in the next trial led by Eastern Cooperative Oncology Group (ECOG) in study E 1199 (39). This study randomized over 5,000 node-positive and high-risk node-negative patients to AC → P every 3 weeks versus AC → weekly P × 12 (80 mg/m^2) versus AC → docetaxel (D) (100 mg/m^2) every 3 weeks versus AC → weekly D × 12 (35 mg/m^2). Overall, when compared to control, AC → weekly P was superior in terms of DFS (81.5% vs. 76.9%, p = .006) and OS (89.7% vs. 86.5%, p = .01), and AC → D was better only in DFS (81.2%, p = .02). The result of this trial confirmed the benefit of the weekly paclitaxel over the every 3 weekly schedule as demonstrated in the metastatic setting (40). In an exploratory analysis, the addition of weekly paclitaxel was beneficial regardless of hormone receptor or *HER2* status. As AC → weekly P was better in both endpoints and there were higher rates of febrile neutropenia and infection with AC → D than in other groups, AC → weekly P emerged as the best option from this trial. A direct comparison of weekly versus dose-dense (every 2 weekly) adjuvant paclitaxel was performed by SWOG (0221) and results are anticipated in 2013.

Another trial demonstrating the benefit of weekly paclitaxel was conducted by the GEICAM group in study 9906 (41). In this study over 1,200 patients were randomized to standard 6 cycles of FEC (600/90/600 mg/m^2) IV every 3 weeks or FEC × 4 → P (100 mg/m^2) weekly × 8. The 5-year DFS was superior for the FEC → P arm (78.5% vs. 72.1%, p = .006). The FEC → P was associated with a 23% reduction in relapse (p = .022) and 22% decrease in death but this was not statistically significant (p = .110). This translated into a 37% risk reduction in recurrence (p = .0008) in all subsets. There was no significant interaction hormone receptor or *HER2* status and paclitaxel treatment. Toxicities were acceptable for both arms. Thus, this was another study strongly confirming the benefit of a taxane in the adjuvant treatment of breast cancer. Recently, the GEICAM group also showed the benefit with the addition of weekly paclitaxel to an anthracycline backbone in a node-negative population (42). In this trial patients were randomized to FAC (500/50/500 mg/m^2) every 3 weeks × 6 versus FAC × 4 → weekly P (100 mg/m^2) × 8. Overall, the 5-year DFS was in favor with the addition of P (93% vs. 90%, p = .043). Although the result of this study was consistent with most other anthracycline-taxane trials, 58% of the patients had T1 tumors and 73% had hormone-receptor-positive disease. In the era of precision medicine most of these patients should undergo genomic profiling (i.e., ONCOTYPE) to determine if they truly need chemotherapy. This will be discussed later in this chapter.

In terms of administering paclitaxel concurrently with an anthracycline, the European Cooperative Trial in Operable Breast Cancer (ECTO) randomized over 1,350 patients to control of sequential A (75 mg/m^2)→ CMF versus concurrent A/P (60/200 mg/m^2) → CMF preoperatively or postoperatively (43). The addition of paclitaxel significantly improved RFS over control (HR = 0.73, p = .03), and RFS outcomes were the same whether chemotherapy was given preoperatively or postoperatively. Another trial of concurrent P with A was conducted by the Loesch et al. comparing every 3 week AC → P against concurrent A/P (50/200 mg/m^2) → weekly P (80 mg/m^2) (44). This study did not show a benefit of concurrent A/P → weekly P. This may be attributed to the higher percentage of patients requiring dose reduction (14% vs. 3%) and delays (14% vs. 5%) in the A/P → weekly P arm. Thus, unlike the result in E1199 showing the benefit of AC → weekly P, the specific regimen (A/P → weekly P) cannot be considered a standard option (Table 44-3).

Docetaxel

Docetaxel is active in the adjuvant treatment of breast cancer. Docetaxel has no pharmacologic interaction with the anthracyclines, thus allowing its coadministration with an anthracycline in an effort to achieve a (theoretical) synergistic response, or to minimize treatment duration. However, toxicity generally means that such a combination will utilize lower doses of these active agents, especially when agents are combined concurrently. One such concurrent combination trial with docetaxel was conducted by the Breast Cancer International Research Group (BCIRG) 001 was a randomized phase III trial comparing FAC with docetaxel plus AC (DAC) in node-positive breast cancer patients (45–46). In this study almost 1,500 patients were randomly assigned to treatment with DAC (75/50/500 mg/m^2) or FAC (500/50/500 mg/m^2), all given every 3 weeks × 6 cycles. Now at a long-term follow-up of 10 years, the benefit of DAC was maintained for DFS (62% vs. 55%, p = .004) and OS (76% vs. 69%, p = .002) (46). In terms of toxicity, the febrile neutropenia rate was 10-fold

TABLE 44-3

Trials of Paclitaxel-Containing Regimens

Study	*N*	*Treatment*	*DFS/RFS/EFS p -Value*	*OSp -Value*
CALGB 9344 (37)	3,121	AC → P > AC	.0023	.0064
NSABP B-28 (38)	3,060	AC → P > AC	.008	NS
ECOG 1199 (39)	5,052	AC → wP > AC → P	.006	.01
		AC → D > AC → P	.02	NS
		AC → wD = AC → P	NS	NS
GEICAM 9906 (41)	1,246	FEC → wP > FEC	.006	NS
GEICAM 2003-02 (42)	1,925	FAC → wP > FAC	.0432	NS
ECTO (43)	1,355	AP → CMF > A → CMF	.03	NS
CALGB 9741 (68–69)	2,005	DD AC → P and DD A → P → C > AC → P and A → P → C	.010	.013
NCIC MA.21 (72)	2,104	CEF > AC → P	.005	NR
		DD EC → P > AC → P	.0006	NR
Loesch et al. (44)	1,830	AP → wP = AC → P	NS	NS

DFS, disease-free survival; RFS, relapse-free survival; EFS, event-free survival; OS, overall survival; NS, not statistically significant; NR, not reported; NSABP, National Surgical Adjuvant Breast and Bowel Project; CALGB, Cancer and Leukemia Group B; INT-0102, US Intergroup Study 0102; GEICAM, Grupo Espanol de Investigacion en Cancer de Mama; ECOG, Eastern Cooperative Oncology Group; ECTO, European Cooperative Trial in Operable Breast Cancer; NCIC, National Cancer Institute of Canada; A, doxorubicin; C, cyclophosphamide; P, paclitaxel; F, fluorouracil; D, docetaxel; M, methotrexate; E, epirubicin; w, weekly; DD, dose dense.

higher with DAC over FAC (25% vs. 2.5%) and thus, granulocyte colony stimulating factor (GCSF) should be used when administering DAC. The GEICAM group evaluated the efficacy of DAC against FAC in over 1,000 patients with node-negative disease in study 9805 (47). At a median follow-up of 77 months, DFS in favor of DAC (87.8% vs. 81.8%, $p = .01$), but and OS was not statistically different between the 2 arms. In this study about half of the patients had T1 tumors and two-thirds had hormone-receptor-positive breast cancer. Once again, in the modern era most of these patients should undergo genomic profiling to help determine if they are likely to benefit from chemotherapy.

Another trial of concurrent docetaxel and doxorubicin was conducted by the North American Breast Cancer Intergroup led by the Eastern Cooperative Oncology Group (Trial E 2197). In this study over 2,800 women with zero to three involved nodes were randomized to control of AC versus AD (60/60 mg/m^2) (48). Overall, there was no difference in DFS (85% in both arms) or OS (91% vs. 92%) at 5 years. Toxicities were higher with AD. Thus, there is no role for AD in the treatment of breast cancer.

A trial that evaluated the role concurrent versus sequential docetaxel with an anthracycline-based treatment was the BIG 02-98 in which over 2,800 patients with node-positive breast cancer were randomized to controls of A (75 mg/m^2) → CMF or AC (60/600 mg/m^2) → CMF versus the experimental arms of A (75 mg/m^2) → D (100 mg/m^2) → CMF or AD (50/75 mg/m^2) → CMF. The CMF was given in the classical schedule (49). At a median follow-up of 5 years, there was an improvement in DFS with the addition of docetaxel, regardless of its schedule (HR = 0.86, $p = .05$). Secondary comparisons showed that the sequential docetaxel was better than the concurrent taxane schedule (HR = 0.83). The superiority of sequential docetaxel arm was likely due to the ability to give higher doses of A and D. This trial confirmed the benefit of a taxane addition.

In terms of trials on sequential anthracyclines and taxanes, several studies were designed and NSABP B-27 was an add-on study of docetaxel preoperatively or postoperatively to 4 cycles of preoperative AC (50). In this study more than 2,400 patients were assigned to receive AC → surgery or AC → D → surgery or AC → surgery → D. There was a doubling of pathologic complete response (pCR) in those who received preoperative AC → docetaxel versus AC alone (26.1% vs. 13.7%, $p < .001$). However, in NSABP B-27, despite a doubling of pCR rates in patients who received AC → docetaxel over those given AC alone, there was no statistically significant difference in terms of DFS or OS. However, there was a trend in improvement in RFS in those who received docetaxel preoperatively (HR = 0.85, $p = .08$). This finding may be attributable to the maintenance of dose density leading to maximal cell kill. Pathologic complete response was a significant predictor of DFS and OS, regardless of treatment types. These results were updated and at a longer follow-up, the 5- and 8-year DFS and OS outcomes were the same across all 3 arms (51). Although the results of this trial were disappointing on the effect of docetaxel, there were many other trials in favor of the addition of the taxanes. Of note, NSABP B-27 is a preoperative trial and there are sufficient data demonstrating that DFS and OS outcomes are not affected when the same systemic therapy is given preoperatively or postoperatively. These data are discussed in detail in another chapter.

Yet another study that evaluated the sequential anthracycline and docetaxel schedule was the Programme Action Concerte Sein (PACS) 01 trial (52). Here, patients were randomized to receive standard FEC 100 × 6 versus FEC 100 × 3 → D (100 mg/m^2) × 3, all given IV every 3 weeks. Now at a median follow-up of 8 years, DFS rates were 70.2% versus 65.8% in favor of FEC → D (HR = 0.85, $p = .036$) and OS rates of 82.2% versus 78.0 % (HR = 0.75, $p = .007$). For many years FEC 100 was the standard option as treatment for high-risk patients in Europe. With the result of PACS 01, this was then supplanted by FEC → D as the new option. Similarly, the West German Study (WGS) group reported the result of sequential epirubicin-docetaxel regimen against the control regimens which consisted of FEC 100. In this study patients with 1–3 positive nodes were randomized to control, FEC 100 (500/100/500 mg/m^2) × 6 or CMF, and experimental EC

(90/600 mg/m^2) × 4 → D (100 mg/m^2) × 4 (47,53). Of note over 90% patients who were randomized to the control arm received FEC 100. At a median of 5 years, the event-free survival (EFS) (89.8% vs 87.3%, p = .03) and OS (94.5% vs. 92.8%, p = .035) were in favor of the docetaxel containing arm. Certainly, the result of this trial was consistent with the literature, and EC → D may be added to the list of anthracycline-taxane options as a standard adjuvant therapy.

Like the NSABP B-27 study, there was another sequential anthracycline-taxane that did not show benefit with the addition of docetaxel. The Taxotere as Adjuvant Chemotherapy Trial (TACT) randomized over 4100 patients to a control regimen [either FEC (600/60/600 mg/m^2) × 8 or E (100 mg/m^2) × 4 → CMF × 4] versus the experimental arm of FEC × 4 → D (100 mg/m^2) × 4 (54). At a median follow-up of 5 years, there was no benefit with the addition of docetaxel. An exploration of biomarker-defined subgroups may help to identify which group may still benefit from the addition of D in this study.

The NSABP reported the data on study B-30 which randomized over 5300 node-positive patients to standard AC → D (100 mg/m^2) versus DAC (60/60/600 mg/m^2 and amended to 75/50/500 mg/m^2) × 4 versus AD (60/60 mg/m^2 and then amended to 50/75 mg/m^2) × 4 (55). At a median follow-up of 6 years in terms of OS, AC → D was superior to AD (HR = 0.83, p = .034) and marginally better than DAC × 4 (HR = 0.86, p = .086). In terms of DFS, AC → D was better than DAC × 4 (HR = 0.83, p = .006) and AD (HR = 0.80, p = .001). Thus, AC → D remained the standard option in the treatment of high-risk breast cancer from this trial.

The BCIRG sought to determine whether sequential or concurrent use of anthracycline-taxane regimens differed in risks and benefits and conducted BCIRG 005, which compared two standard options of AC → D and DAC × 6 in almost 3300 node-positive women (56). At a median follow-up of 5 years, the DFS rates were 79% for both groups (p = .98) and OS rates were 88% and 89% (p = .37). Toxicities differed with more febrile neutropenia seen with DAC and more sensory neuropathy and nail changes reported with AC → D. The authors concluded that these two regimens were equivalent in efficacy. However, they could not address the issue of sequential versus concurrent therapy due to the various confounders (dose sizes and number of cycles).

In exploring the omission of an anthracycline, the US Oncology group conducted trial 9735, comparing DC (75/600 mg/m^2) × 4 against standard AC over 1,000 patients with stage I, II, or operable III breast cancer (57). Almost half of the patients in each arm had node-negative disease. At a median follow-up of 7 years, there was statistically significant improvement in DFS in those receiving DC over AC (81% vs. 75%, HR = 0.74, p = .033 and OS (87% vs. 82%, HR = 0.69, p = .032). However, it is still unclear when DC may be appropriate. First, half of the patients in this trial had node-positive disease, and the AC comparator was an obsolete regimen for the treatment of patients with high-risk disease in the modern era (37–38). Second, DAC × 4 was inferior to standard AC → D in NSABP B-30. The DC regimen was similar to DAC × 4 (without A), and thus it would be suboptimal as a treatment for high-risk patients. Third, since the other half of the patients in trial 9735 had node-negative breast cancer, with the majority having hormone-receptor-positive disease, genomic signatures would now be used to determine if they would even benefit from chemotherapy. Perhaps DC may be considered in those with hormone-receptor-positive, *HER2*-negative, node-negative disease with an intermediate recurrence score based on the 21-gene recurrence score (which will be discussed later in this chapter). However, this is also where another non-anthracycline-based therapy (i.e., CMF) may also be considered as a treatment option (Table 44-4).

Dose Intensity

Another way to improve the benefit of adjuvant chemotherapy is to increase the dose intensity formulated as body-size adjusted dose (mg/m^2) divided by time (per week) (58). One method of increasing dose intensity is dose-escalation, which is supported by preclinical models demonstrating that some forms of resistance to cytotoxic drugs can be overcome by increasing the dose size (59). Based on this hypothesis, a variety of clinical trials have tested dose-escalation to improve outcomes. CALGB 8541 evaluated three doses of CAF chemotherapy in 1,550 patients (low, moderate, and high dose intensity). At 9 years of follow-up, DFS and OS were superior for the moderate and higher dose arms when compared with the lower dose arm (60). Similarly as discussed previously FASG 05 demonstrated that FEC 100 was better than FEC 50 (31).

However, other trials have failed to demonstrate improved outcomes with supranormal levels of chemotherapy beyond the standard dose (61–62). NSABP B-22 and B-25 evaluated dose-escalation of the cyclophosphamide doses from the standard 600 mg/m^2 up to 2,400 mg/m^2. There was no improvement in outcomes in both trials, but there was a significant increase in cases of myeloproliferative disorders, including acute leukemia, observed in B-25. As mentioned previously CALGB 9344 did not demonstrate any benefit with the higher doses of doxorubicin over the standard dose (37). Thus, simple dose-escalation beyond standard dose levels at conventional dosing intervals may not be sufficient to improve outcome.

A number of trials have evaluated the role of myeloablative adjuvant regimens requiring autologous bone marrow or peripheral stem cell rescue. Despite promising phase II results, randomized trials have failed to demonstrate a clear benefit in disease-free or overall survival for the use of high-dose chemotherapy with stem cell transplant (HDC-SCT). An overview of 15 randomized trials of more than 6,200 patients demonstrated that HDC-SCT led to an improved RFS but not OS. Due to these findings, along with the much higher toxicities inherent with HDC-SCT, as well as lack of data on its comparison with modern taxane-based therapies or trastuzumab-based therapy (for *HER2*-positive patients), there is no role for this type of therapy in breast cancer treatment (63).

Dose Density

The Norton-Simon model predicts that the optimal treatment of a heterogeneous mix of cells (in terms of chemotherapy sensitivity) is to eradicate the numerically dominant, faster-growing cells first, followed by eradication of the more slowly growing, resistant cells (64). This is termed sequential therapy and was found to be superior to alternating therapy in a randomized clinical trial reported by Bonadonna et al. (24). Sequential therapy may be more effective because it increases the frequency ("density") of treatments as compared to alternating therapy, thereby minimizing the time during which sensitive cells can regrow before retreatment. When filgrastim (granulocyte colony-stimulating factor, G-CSF) became available, several pilot studies testing increased dose density at Memorial Sloan-Kettering Cancer Center (65–67). These studies led to a randomized trial led by the CALGB (C 9741) for the Intergroup in over 2,000 patients which compared every-2-week to every-3-week cycling of chemotherapy, given sequentially (A→ P→ C) or concurrently (AC → P) (68–69). This trial used a 2 × 2 factorial design to answer two questions: (1) Is dose dense (DD) superior to conventional chemotherapy? (2) Is sequential superior to concurrent combination chemotherapy? At a median follow-up of 36 months, outcomes were significantly

TABLE 44-4

Trials of Docetaxel-Containing Regimens

Study	*N*	*Treatment*	*DFS/RFS/EFS p -Value*	*OS p-Value*
BCIRG 001 (45–46)	1,491	**DAC** > FAC	.001	.008
GEICAM 9805 (47)	1,060	**DAC** > FAC	.01	NS
ECOG 2197 (48)	2,882	AC = AD	NS	NS
BIG 02-98 (49)	2,887	**A → D → CMF** and **AD → CMF >** A → CMF and AC → CMF	.05	NR
NSABP B-27 (50–51)	2,411	AC → surgery = AC → D → surgery = AC → surgery → D	NS	NS
PACS 01 (52)	1,900	**FEC →D >** FEC	.036	.007
WGS-AGO (53)	2,011	**EC → D** > FEC or CMF	.038	.035
TACT (54)	4,162	FEC or E → CMF = FEC → D	NS	NS
NSABP B-30 (55)	5,351	**AC → D >** AD and **AC → D >** DAC	.001 .006	.034 NS
BCIRG 005 (56)	3,298	AC →D = DAC	NS	NS
US Oncology 9735 (57)	1016	**DC** > AC	0.033	0.032

DFS, disease-free survival; RFS, relapse-free survival; EFS, event-free survival; OS, overall survival; NS, not significant; NR, not reported; BCIRG, Breast Cancer International Research Group; GEICAM, Grupo Espanol de Investigacion en Cancer de Mama; ECOG, Eastern Cooperative Oncology Group; BIG, Breast International Group; NSABP, National Surgical Adjuvant Breast and Bowel Project; PACS, Programme Action Concerte Sein; WGS, West German Study; TACT, Taxotere as Adjuvant Chemotherapy Trial; D, docetaxel; A, doxorubicin; C, cyclophosphamide; F, fluorouracil; M, methotrexate; E, epirubicin.

better in favor of the DD arms (risk ratio [RR] 0.74, p = .010) and OS (RR 0.69, p = .013) (Table 44-3). There was no difference in either DFS or OS between sequential and concurrent chemotherapy schedules. There was no interaction between dose density and sequence. These results were maintained with a longer follow-up of 6.5 years (69). This trial was a pure test of dose density with no confounders, as the dose size, the number of cycles per chemotherapy, and the number of agents were consistent across all arms. Thus, based on the results of C9741, DD AC → P became a popular and commonly used standard option in the United States.

SWOG is conducting a large phase III trial comparing two anthracycline schedules and two optimal schedules of paclitaxel (weekly vs. dose dense) as mentioned above. Trial S0221 has randomized over 2,700 patients in a 2 × 2 factorial design to experimental AC + granulocyte colony-stimulating factor (GCSF) versus DD AC and then to weekly P (80 mg/m^2) × 12 versus DD P (175 mg/m^2) × 6. In the AC + GCSF arm, A was given as 24 mg/m^2/week × 15 and C was administered as 60 mg/m^2/day orally, with GCSF daily (except on days of A administration). It has been reported that AC + GCSF is not superior to DD AC (70) and a comparison of the two paclitaxel schedules is expected in 2013. CALGB 40101, recently reported by Shulman et al., is a related trial in lower-risk disease. Here, over 3100 patients with zero to three positive nodes were randomized to AC × 4 or 6 or P × 4 or × 6 (71). After 2003 when CALGB 9741 showed the superiority of DD chemotherapy, all treatments were given in DD schedule. At a median follow-up of 5 years, the 4-year RFS (90.9% vs. 91.8%) and OS (95.3% vs. 96.3%) were the same with 6 versus 4 cycles of therapy. The result of C40101 on the comparison between A versus P is expected in 2013.

Another trial that tested dose density was led by the National Cancer Institute of Canada. Trial MA.21 randomized patients to DD EC (120/830 mg/m^2) × 6 →P (175 mg/m^2) × 4 every 3 weeks against two control arms (CEF and every 3 week AC → P). At a median follow-up of 30 months, the RFS was inferior with every 3 week AC → P when compared to both CEF (HR = 1.49, p = .005) and DD EC → P (HR = 1.68, p = .0006). Notably, in DD EC → P, the paclitaxel was given every 3 weeks so the additional gain of this regimen was attributable to the DD schedule of EC and possibly the higher number of cycles of this chemotherapy regimen as compared to what was given in AC → P. Although the study is not a pure test of the dose-dense hypothesis, the results support the concept that DD regimens have a role in adjuvant treatment (72) (Table 44-3).

Not all DD trials confirmed benefit. An Italian phase III study randomized over 1,200 patients to FEC (600/60/600 mg/m^2) × 6 every 3 weeks versus every 2 weeks (dose dense). At a median follow-up of 10 years, there was no improvement in EFS or OS with DD FEC (73). Cameron and colleagues recently reported the result of UK TACT 2 trial comparing standard versus DD epirubicin (74). This was a 2 × 2 factorial design in which patients were randomized to E (100) mg/m^2 × 4 every 3 weeks versus every 2 weeks and then to classical CMF versus capecitabine. In the first analysis of this study, there was no benefit with DD E. The reason for this is unclear and we await the final analysis. The comparison of CMF versus capecitabine will be reported later.

Moebus et al. tested the question of dose intensity and density in the AGO phase III study in which over 1,200 patients with four or more positive nodes were randomized to "intense dose dense" (IDD) E (150 mg/m^2) × 3 → P

(225 mg/m^2) × 3 → C (2,500 mg/m^2) × 3, all administered every 2 weeks with GCSF versus EC (90/600 mg/m^2) × 4 → P (175 mg/m^2) × 4 every 3 weeks (75). At a median follow-up of 5 years, the EFS (70% vs. 62%, $p < .001$) and OS (88% vs. 77%, $p = .0285$) were in favor of IDD chemotherapy. Not surprisingly, there were more nonhematologic and hematologic toxicities with the IDD regimen, including four cases of acute leukemia and myelodysplastic syndrome observed. With a longer follow-up of 10 years, these benefits were still maintained for both RFS and OS, regardless of subgroups (76) (Table 44-3). Unlike CALGB 9741, this trial was not a pure study of dose density as there were variations in dose size (dose intensity), cumulative dose, and number of cycles of each chemotherapy agent. Because NSABP B-25 (and B-22 before) showed the lack of benefit for dose-escalation of cyclophosphamide to 2,400 mg/m^2, the AGO study is relevant supporting for DD scheduling, but the high-dose regimen is not considered standard.

THE EARLY BREAST CANCER TRIALISTS' COLLABORATIVE GROUP PROCESS AND RESULTS

The Early Breast Cancer Trialists' Collaborative Group was formed in the mid-1980s to perform a meta-analysis of randomized trials in the adjuvant setting with updated reports published approximately every 5 years. The EBCTCG overview contains individual data from thousands of patients and has substantial power to detect relatively small differences in outcome with long-term follow-up. Data on hormone receptor status of the primary tumor were not available in many of the older trials, and most trials did not test for human epidermal growth factor receptor 2 (*HER2*). Both of these markers are now critically important for the decision making on adjuvant treatment. The EBCTCG meta-analyses demonstrated that single-agent chemotherapy was better than none and that polychemotherapy was superior to no therapy in improving recurrence, breast cancer mortality, and overall mortality. In 2005 the EBCTCG showed that 6 months of an anthracycline-based polychemotherapy reduced the annual breast cancer death by 38% for those younger than 50 years of age and 20% for those at 50 to 69 years at diagnosis. These regimens were superior to CMF chemotherapy ($2p = 0.0001$ for recurrence, $2p < 0.00001$ for breast cancer mortality) (2). The reduction in the risk of recurrence with chemotherapy was noted within the first 5 years after randomization and was maintained at the 10- and 15-year time points. Most notably, the improvement in survival continued to improve with the absolute decrease in the risk of death doubling between 5 years and 15 years of follow-up. The EBCTCG demonstrated that in women with ER-poor disease, polychemotherapy, compared to no chemotherapy, significantly reduced recurrence, breast cancer mortality, and death from any cause in those younger than 50 years and those at 50 to 69 years (3). In patients younger than 50 years, the 10-year risks of recurrence, breast cancer mortality, and death from any cause were 33% versus 45% (relative risk [RR] 0.73, $2p < 0.00001$), 24% versus 32% (RR 0.73, $2p = 0.0002$), and 25% versus 33% (RR 0.75, $2p = 0.003$), respectively. For the older group at 50 to 69 years of age, the 10-year risks of recurrence, breast cancer mortality, and death from any cause were 42% versus 52% (RR 0.82, $2p < 0.00001$), 36% versus 42% (RR 0.86, $2p = 0.0004$), and 39% versus 45% (RR 0.87, $2p = 0.0009$), respectively.

Recently, the EBCTCG updated the meta-analyses of long-term outcomes comparing different polychemotherapy regimens for early breast cancer among 100,000 women in 123 randomized trials (4). This overview included taxane-containing trials. The overview demonstrated that add a median follow-up of 8 years, adding four cycles of a taxane to a fixed dose of an anthracycline-based regimen led to an improvement to recurrence (30.2% vs. 34.8%, RR 0.84, $2p < 0.00001$), breast cancer mortality (21.1% vs. 23.9%, RR 0.86, $2p = 0.0005$), and overall mortality (16.3% vs. 18.2%, RR 0.86, $2p = 0.0002$). In the confounded taxane trials in which the effects of the taxanes were counterbalanced by the control arms with more (nonfixed) anthracycline treatment, at a short median follow-up of 5 years there were small, but significant, reductions in recurrence, breast cancer specific mortality, and overall mortality.

Clearly, the results from the EBCTCG meta-analyses confirm the essential role of adjuvant chemotherapy in breast cancer from single-agent chemotherapy and polychemotherapy versus none, to anthracycline-based treatments as superior therapy over CMF, and to the incremental gain with the addition of a taxane to an anthracycline. Yet, the absolute benefits vary with age, nodal status, and hormone receptor status of the tumor, meaning that clinicians still have to exercise judgment and investigators must develop and refine tools to enable more precise selection of patients for treatment.

NEWER AGENTS

New Chemotherapy Agents

With incremental benefits observed from the use of the anthracyclines and taxanes, new drugs were added to see if small additional gains could be attained. Gemcitabine (G) was tested in the tAnGo trial which randomized over 3,100 patients to EC (90/600 mg/m^2) × 4 → P (175mg/m^2) × 4 or EC → PG (1250 mg/m^2) while the doses of other agents were the same (77). Overall, the 3-year DFS and OS were the same in both arms. Likewise, the NSABP also tested the efficacy of gemcitabine in B-38 and found no benefit. This study compared two standard arms of DAC × 6 and DD AC → P against DD AC → PG (2,000 mg/m^2) in over 4,800 patients (78). Overall, there was no difference in the 5-year DFS and OS with the addition of gemcitabine when compared to each control arm. Additionally there was no difference in efficacy outcomes between DAC and DD AC → P, but febrile neutropenia and more deaths occurred on treatment with DAC. Based on these data, DD AC → P remains a preferred standard.

Two studies tested the efficacy of adding capecitabine (X) to the anthracycline–taxane combinations showing no benefit (79–80). FinXX compared standard D → CEF against DX → CEX in 1,500 patients and at a median follow-up of 59 months, there was no difference in RFS or OS (79). US Oncology conducted trial 01062 randomized over 2,600 patients to AC → D versus AC → DX. At a median follow-up of 5 years, again there was no difference in DFS or OS with the addition of capecitabine (80). Other agents that are being evaluated currently are the platinums, particularly in patients with triple-negative breast cancer. We have reached the end of an era of conducting large adjuvant chemotherapy trials and should move forward to designing trials of using less or no chemotherapy (based on genomic signatures) and incorporating more effective biologic or targeted agents.

Antiangiogenic Agents Added to Chemotherapy

One of the greatest advances in adjuvant therapy has been the addition of trastuzumab to chemotherapy in the treatment of patients with human epidermal growth factor

receptor 2 (*HER2*)-positive breast cancer. This is discussed in detail in another chapter. In the *HER2*-negative population there are several trials evaluating the efficacy of bevacizumab (B), a humanized monoclonal antibody against vascular endothelial growth factor. One such trial is ECOG 2104, a pilot study demonstrating the feasibility of bevacizumab combined with DD AC → P in the adjuvant setting (81). This has led to the design of ECOG 5103, a three-arm, phase III trial randomizing about 5,000 node-positive or high-risk, node-negative women to either AC → weekly P/placebo versus AC → weekly P/B versus AC → weekly P/B → B. This trial has completed accrual and results are forth coming. Recently the results of the BEATRICE trial were reported, demonstrating no benefit with the addition of bevacizumab added to standard adjuvant chemotherapy when compared to chemotherapy alone in the patients with triple-negative breast cancer (82). In light of the mixed and modest results in metastatic disease, the available data suggests a limited role for bevacizumab in early stage breast cancer.

THE ELDERLY POPULATION

Older women have been historically underrepresented in adjuvant clinical trials. A review of four CALGB studies demonstrated that older women derive clear benefits from the use of adjuvant chemotherapy, but the toxicity profiles differed by age, with more hematologic toxicity and greater risk of treatment-related death in the older population (83). Treatment decisions in older women should be individualized based on tumor characteristics as well as comorbid conditions and potential life expectancy. Muss et al. reported the result of CALGB 49907 trial, the largest prospective trial in the older population (84). In this study, 633 women at 65 years of age or older were randomized to receive standard chemotherapy with either AC × 4 or classical CMF × 6 (at the discretion of the physician and patient) versus experimental capecitabine therapy. Capecitabine was chosen as it was felt to be a less toxic chemotherapy than the control regimens. In contrast, this study demonstrated that capecitabine was relatively toxic in this setting. More importantly, patients on capecitabine were twice as likely to relapse (68% vs. 85%, $p < .001$) and die (86% vs. 91%, $p = .02$). The inferior outcome with capecitabine was particularly dramatic in patients with ER-negative disease (84). Thus, once the decision is made to treat older women with cytotoxic therapy, standard combination chemotherapy should be used.

THE TAXANE BENEFIT

In recent years, there had been considerable debate about the identification of the appropriate populations for taxane treatment. The CALGB analysis identified the ER-negative subset as deriving substantially more benefit from adjuvant paclitaxel than the ER-positive group (85). However, this relationship had not been consistent across various trials. De Laurentiis performed a meta-analysis of the 14 randomized taxane trials and demonstrated equivalent benefits regardless of ER status, number of involved nodes, age, or menopausal status (86). Although the subgroup analyses based on hormone receptor status were inconsistent, overall the taxanes appeared to provide benefit in patients with both ER-positive and -negative disease. The EBCTCG in 2012 also showed that in meta-analyses of anthracycline/taxane-based against anthracycline-based treatments, risk reductions were little affected by hormone receptor status as well as tamoxifen use, age, nodal status, size, or tumor differentiation (4). Thus, when the decision to treat high-risk patients with chemotherapy is made, the use or omission of the taxanes should not be based on hormone receptor status. The differential benefit from chemotherapy (in absolute terms), based on hormone-receptor-negative versus receptor-positive disease, underscores the need to develop more robust predictors of chemotherapy benefit, particularly in patients with hormone-receptor-positive breast cancer. The use of genomic signatures to aid in chemotherapy decision-making in patients with hormone-receptor-positive breast cancer is discussed below.

TOOLS TO AID IN DECISIONS ON ADJUVANT CHEMOTHERAPY

After surgical resection adjuvant chemotherapy should be considered for most patients with high-risk disease, based on histological parameters (i.e., nodal involvement, tumor size) and poor-risk biology (i.e., triple-negative or *HER2*-positive breast cancer). However, chemotherapy may not be suitable for all patients with hormone-receptor-positive/*HER2*-negative disease and is controversial for many with node-negative disease. There are guidelines set forth by the National Comprehensive Cancer Network and the St. Gallen International Breast Cancer Consensus that may be used in making decisions on when to recommend chemotherapy (87–88). There are also tools that can aid clinicians in objectively assessing the absolute benefits from systemic chemotherapy after local treatment. One such too is Adjuvant! Online, developed by Ravdin et al., which is a validated computer-based model that determines the risk of recurrence based on age, comorbidities, tumor size and grade, hormone receptor status, and nodal status to estimate the contribution of chemotherapy and hormonal therapy in risk reduction (89). However, several limitations of Adjuvant! Online exist, including the omission of *HER2* status and the incorporation of wide ranges of tumor sizes and numbers of involved nodes. Furthermore, it is based primarily on the anatomic spread, rather than molecular biology, and it uses average estimates of treatment effects.

The next step in assessing risk, and more importantly, response to chemotherapy is genomic analysis. These tools have made it possible to further characterize tumors based on the risk of recurrence after hormonal therapy in defined subsets based on expression profiles. In the NSABP B-14 trial, the OncotypeDX (Genomic Health, Redwood City, CA) assay provides individual, quantitative assessments of the likelihood of breast cancer recurrence after 5 years of treatment with tamoxifen in patients with node-negative disease. It is an RT-PCR assay that measures the expression of 21 genes, consisting of 16 cancer-related genes and 5 reference genes. The expression of these genes is used to calculate a recurrence score (RS) that predicts the likelihood of recurrence at 10 years (90). Patients are classified into three different categories based on the RS, namely low (RS <18), intermediate (RS 18–30) and high (RS ≥31) with associated 10-year distant recurrence rates of 6.8%, 14.3%, and 30.5%, respectively. More important than its accuracy as a prognostic tool is its role as a predictive one. Indeed, retrospectively applied to the NSABP B-20 study, the OncotypeDX was not only prognostic but also predicted the likelihood of chemotherapy benefit in patients with node-negative ER-positive cancer. Those with a low RS derived minimal benefit with adjuvant chemotherapy, whereas those with higher scores gained more significant improvements in disease free survival. Based on this, one would predict that those with low scores would be sufficiently treated with hormonal therapy

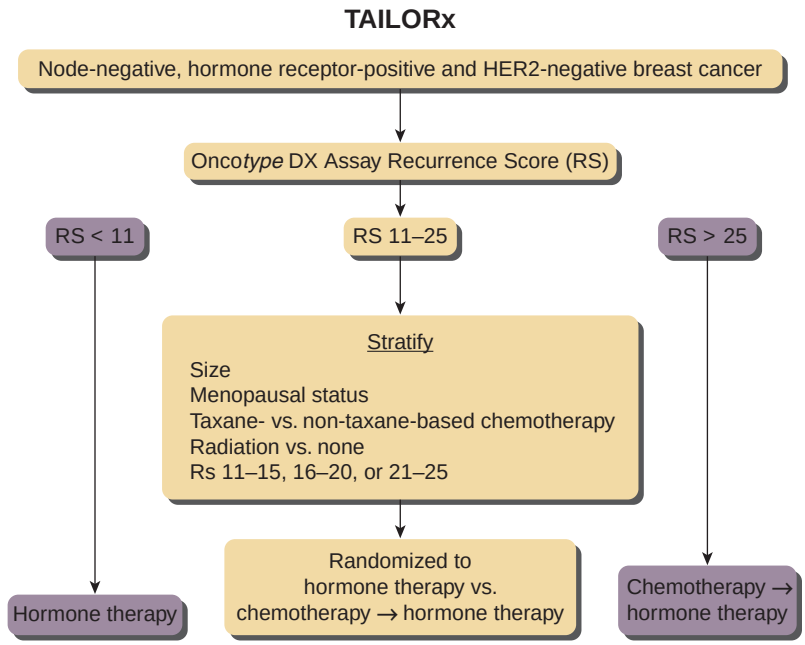

FIGURE 44-1 TAILORx (Trial Assigning Individualized Options for Treatment). RS, recurrence score.

alone (91). The Breast Cancer Intergroup of North America has concluded the Trial Assigning Individualized Options for Treatment (TAILORx) trial to evaluate the benefit, or not, of chemotherapy combined to hormonal therapy in patients with intermediate RS (Fig. 44-1). This study has reached its target accrual and the results are awaited (92).

The SWOG 8814 study demonstrated the efficacy of anthracycline-based chemotherapy plus tamoxifen when administered sequentially in patients with node-positive, ER-positive disease with a high RS. Here again a retrospective analysis from this study showed little benefit with the addition of anthracycline-based chemotherapy in women with node-positive disease with a low RS (93). Recently SWOG has activated a phase III trial, namely Rx for Positive Node, Endocrine Responsive Breast Cancer (RxPONDER) study focusing on patients with one to three involved nodes with low to intermediate RS (Fig. 44-2). These patients are randomized to chemotherapy followed by hormone therapy or hormone therapy alone (94). The result of this study will be critical as it may help us to identify the proper patient group with ER-positive, node-positive disease whom we may spare from chemotherapy exposure. Taken together, these results predict a future in which biology, in the form of a genomic assessment, is the dominant factor in determining the need for adjuvant chemotherapy.

The only Food and Drug Administration (FDA) approved microarray-based assay is the MammaPrint which uses a similar approach to explore a larger number of genes for prognostic purposes. MammaPrint is a 70-gene signature (also referred to as the Amsterdam signature) developed at the Netherlands Cancer Institute. It categorizes patients into two groups, good prognosis and poor prognosis,

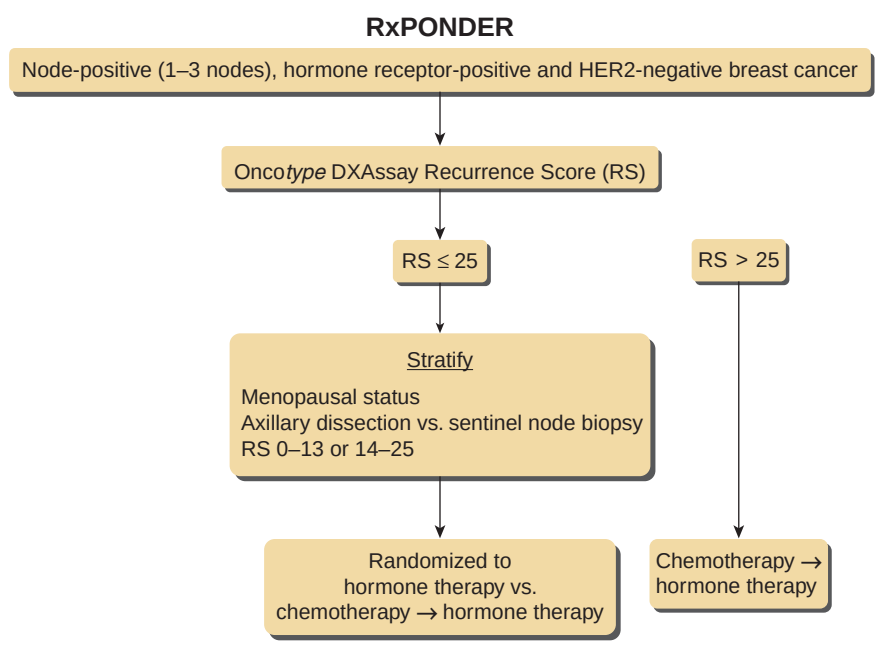

FIGURE 44-2 RxPONDER (Rx for Node-Positive, Endocrine Responsive Breast Cancer). RS, recurrence score.

irrespective of their ER status. The signature largely consists of genes regulating proliferation, plus those involved in invasion, metastasis, stromal integrity, and angiogenesis. Initial validation studies were done by the Translational Breast International Group (TRANSBIG) and this formed the basis of its use in the ongoing Microarray In Node-Negative Disease may Avoid ChemoTherapy (MINDACT) study that evaluates which patients can be spared chemotherapy (95). However, there are a few differences with this test from OncotypeDX, such as its clinical utility in ER-negative patients, where 0% to 4% are classified as good prognosis, and in *HER2*-positive patients, where up to 22% are classified as having good prognosis and not requiring therapy.

The use of these clinical tests of gene expression raises questions regarding the clinical utility of the five intrinsic molecular subtypes defined by gene profiling studies. The subtypes do not precisely reproduce the results of conventional immunohistochemistry testing. For example, there is discordance between tumors identified to have the *HER2*-positive molecular subtype and those identified by immunohistochemistry or fluorescence *in situ* hybridization. Other limitations of gene expression profiling for intrinsic subtypes include the requirement (at least until recently) for fresh frozen tissue for microarray-based signatures. To address this issue, an intrinsic 50-gene set has been used to develop an RT-PCR based predictor called PAM50 (96). The PAM50 gene assay identifies the five intrinsic subtypes (luminal A and B, *HER2*-enriched, basal-like, and normal-like) and provides a continuous risk score based on the similarity of an individual sample to prototypic subtypes. Recent data suggest that when the OncotyopeDX assay and PAM50 are compared, there is a large overlap in the ability of these tests to determine the recurrence risk in ER-positive breast cancer (97). In fact, 51% of the patients, classified to have an intermediate RS by OncotypeDX, have been recategorized as low-risk luminal A using PAM50. Although these results are encouraging, the prognostic utility of PAM50 is currently restricted to ER-positive, node-negative disease and its predictive utility has not been established (98). Please refer to Chapter 30 for more details on molecular prognostic and predictive factors.

SUMMARY

With an abundance of data over several decades, there are now several chemotherapy options to choose from when treating patients with high-risk disease (defined biologically or histologically). In terms of regimens containing paclitaxel, dose-dense AC → paclitaxel or dose-dense A → paclitaxel → C (CALGB 9741), AC-weekly paclitaxel (ECOG 1199), FEC-weekly paclitaxel (GEICAM 9906), dose-dense EC → paclitaxel (MA.21), and A/P → CMF (ECTO) (39,41,43,68–69,72) are acceptable. For regimens that contain docetaxel, they are DAC (BCIRG 001), AC → docetaxel (ECOG 1199, NSABP B-30, BCIRG 005), A → docetaxel → CMF (BIG 02-98), FEC → docetaxel (PACS 01), and EC → docetaxel (WGS) (39,45–46,49,52–53,55–56). Anthracycline-containing regimens without a taxane may also be considered such as CEF (MA.5 and MA.21) and E → CMF (NEAT/BR9601) for patients with contraindications to paclitaxel and docetaxel (30,32,72). When choosing a regimen, it is important to factor in the toxicity differences across these options as discussed earlier.

CONCLUSION AND FUTURE DIRECTIONS

Adjuvant chemotherapy for early breast cancer has been studied for nearly 50 years and has contributed to improved outcomes worldwide. This is an area where clinical trials have been highly successful and influential in establishing standards and benchmarks against which we can measure future progress. As a result of these studies and our communities' efforts, we have identified the value of specific agents, dosing, and scheduling, and have begun to apply advances in molecular biology to the problem of patient and tumor selection for treatment. At the moment, the best results in terms of OS and DFS are achieved in most patients through the use of sequential combination chemotherapy containing the anthracyclines, alkylating agents, and the taxanes. The absolute benefit from the addition of taxanes is most notable in patients with hormone-receptor-negative tumors but some patients with hormone sensitive disease also benefit. As we develop more sophisticated ways to characterize tumors using techniques such as gene array analysis, we are reminded that breast cancer is a heterogeneous disease. Rather than designing trials that segregate patients based on historically standard clinical criteria such as estrogen receptor status, we can now investigate the role of adjuvant therapy on patients stratified by risk based on specific genetic signatures of their tumors in both the node-negative (TAILORx) and node-positive (RxPONDER) groups. With the ongoing implementation of well-designed clinical trials incorporating new therapeutic agents in a rational way, we hope to continue to see a trend toward improved DFS and OS in patients presenting with early breast cancer.

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CHAPTER 45

Adjuvant Chemo Endocrine Therapy

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CHAPTER CONTENTS

INTRODUCTION

Adjuvant systemic therapy is associated with significant improvements in disease-free and overall survival benefits and is recommended to most women with stage I–III breast cancer. Adjuvant systemic therapy may include endocrine manipulation, cytotoxic therapy, anti-HER2 agents, or a combination of more than one of these approaches. The benefits and adverse effects associated with each of the individual treatments are discussed elsewhere in this textbook. As described in Chapter 43, endocrine therapies are recommended to most women with a tumor expressing the estrogen receptor α (ER) and/or progesterone receptor (PgR) proteins. The main challenge facing healthcare providers and women with newly diagnosed hormone receptor-positive tumors is to further determine who would benefit from the administration of chemotherapy in addition to endocrine manipulations, designated chemo endocrine therapy. Other questions pertain to the type, duration, and sequence of therapy that should be considered in this population. Notably, some women with hormone receptor–positive tumors are relatively resistant to endocrine manipulations, yet might not derive benefit from chemotherapy either. Identification of mechanisms and biomarkers of endocrine resistance will help in development of novel therapies that could be administered either with or instead of endocrine therapy. In this chapter, we review current considerations for administration of chemo endocrine therapy in properly selected women.

WHO IS A CANDIDATE FOR CHEMO ENDOCRINE THERAPY?

The presence of the hormone receptors ER and/or PgR is required for response to endocrine manipulations. However, not every woman whose tumor expresses the hormone receptors benefits from endocrine manipulations. Over the last two decades several analyses have helped provide guidance in the difficult task of separating women who would benefit from endocrine therapy alone from those for whom additional or alternative therapy is required.

Main Results from the Early Breast Cancer Trialists' Collaborative Group Overview

The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) Overview of patient-level data from prospective randomized trials continues to provide the largest data set estimating impact of single or multi-agent adjuvant endocrine and chemotherapy regimens on survival outcomes in women with early breast cancer. The 2005 publication of the 2000 Overview included 194 studies of combination chemotherapy including CMF (cyclophosphamide, methotrexate, fluorouracil), FAC or CAF (fluorouracil, doxorubicin, cyclophosphamide), or FEC (fluorouracil, epirubicin, cyclophosphamide), and the endocrine therapies tamoxifen or ovarian ablation/suppression. Treatment with approximately 6 months of anthracycline-based polychemotherapy was significantly more effective than CMF in reducing breast cancer recurrence ($2p = 0.0001$) and mortality ($2p = 0.00001$) (1). The benefit was more substantial in women younger than 50 years of age, with a 38% (Standard Error [SE] 5%) reduction in annual breast cancer death rate compared to about 20% (SE 4%) for those ages 50 to 69. The differences were irrespective of ER status, use of tamoxifen, nodal status, or other tumor characteristics. The number of women older than age 70 who were included in the prospective studies was too small to allow for meaningful conclusions for this subgroup. In women whose tumors were ER-positive, 5 years of tamoxifen was associated with a substantial reduction in annual breast cancer recurrence and death irrespective of the use of chemotherapy, age, PgR status, or other tumor characteristics.

The Overview suggested that allocation to ovarian ablation or suppression (n = 8,000) also significantly reduced breast cancer recurrence and mortality. However, the benefit was seen primarily in women who have not received other systemic treatments (1).

The most recent EBCTCG updates of relevant randomized trials shed further light on tamoxifen as well as newer chemotherapy regimens. In an overview of data from 20 trials (n = 21,457) in early breast cancer of about 5 years of tamoxifen versus no adjuvant tamoxifen, tamoxifen was associated with a substantial reduction of recurrence rates at 5 years (26.1% and 15.4% in control- and tamoxifen-treated women, respectively) and 10 years (37.7% and 24.8% in control- and tamoxifen-treated women, respectively) (2). Although women were allocated to tamoxifen for only 5 years, the benefits were observed up to 15 years from the initial assignment, well beyond the duration of administration and emphasizing the importance of this agent.

In the most recent analysis of 123 randomized trials addressing chemotherapy questions, the trialists compared results with polychemotherapy versus no chemotherapy (n = 32,000), different anthracycline-containing regimens (n = 7,000), CMF-containing regimens (n = 18,000), or any taxane plus anthracycline-based combinations to regimens of nontaxane chemotherapy (n = 44,000) (3). A comparison of CMF for six cycles with the standard combination of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC) for four cycles revealed equivalent breast cancer mortality rates (relative risk [RR] 0.98, SE 0.05; $2p$ = 0.67). However, the administration of anthracycline-based regimens that included a higher cumulative dose than standard AC, such as CAF or CEF, were superior to standard CMF (RR 0.78, SE 0.06; $2p$ = 0.0004). When comparing polychemotherapy to no chemotherapy, greater breast cancer mortality reductions were observed with CAF (RR 0.64, SE 0.09; $2p < 0.0001$) compared to standard AC (RR 0.78, SE 0.09; $2p = 0.01$) or CMF (RR 0.76, SE 0.05; $2p < 0.0001$). Finally, the administration of four cycles of a taxane following an anthracycline-based regimen was associated with significant reduction in breast cancer mortality (absolute gain 2.8%, SE 0.9; RR 0.86, SE 0.04; $2p$ = 0.0005) when compared with the anthracycline-based regimen alone. In contrast, when taxanes added to anthracycline-based therapy without changing the duration of treatment in the investigational arms were compared to roughly doubling nontaxane agents' dose in control arms, a significant difference in breast cancer mortality was not observed (RR 0.94, SE 0.06; $2p$ = 0.33). For all comparisons of taxane-based or anthracycline-based regimens, the EBCTCG noted that proportional risk reductions were independent of age, nodal status, tumor size, tumor differentiation, ER expression, or tamoxifen use. Subgroup analysis by ER status and subset analysis by expression, age, and differentiation in ER-positive tumors are presented in Table 45-1A–C.

While the EBCTCG provides substantial information regarding the value of specific therapies in reducing recurrence and mortality rates in women with early breast cancer, it is associated with several limitations. The Overview has not yet evaluated the role of newer agents such as third-generation aromatase inhibitors or trastuzumab or dose-dense anthracycline- and taxane-based regimens. Evidence regarding the benefit or harms of these newer agents or approaches is derived mostly from smaller meta-analyses or from large prospective randomized trials. Overview data regarding tumor or patient characteristics provide important information regarding odds of benefiting from endocrine strategies alone or whether additional agents should be considered. However, the Overview cannot provide data regarding benefits that an individual woman should expect from specific types of treatment or agents. Finally, there was no central review of ER, PgR, or other tumor characteristics in the Overview and results of new molecular analyses such as HER2 status or multigene assay results are not yet a part of the Overview. Nonetheless, the EBCTCG analyses have been pivotal in defining the benefits of adjuvant tamoxifen and chemotherapy for the population at large.

Meta-Analyses of Randomized Trials of Aromatase Inhibitors

A recent meta-analysis of randomized trials of aromatase inhibitors (AIs) compared with tamoxifen either as initial monotherapy (Cohort 1) or after 2 to 3 years of tamoxifen

TABLE 45-1A

Subgroup Analyses of Breast Cancer Mortality by Treatment, Results from the EBCTCG
Part A Any Anthracycline-Based Regimen versus Standard CMF (or Near-Standard CMF)

Category	*Deaths/Women*		*Anthracycline Deaths*		
	Allocated Anthracycline	*Allocated CMF*	*Log-rank O-E*	*Variance of O-E*	*Ratio of Annual Death Rates (Anthracycline:CMF)*
ER Status					
ER poor	120/4488 (26.8%)	1287/4518 (28.5%)	–43.7	564.6	0.93 (SE 0.04)
ER positive	569/3279 (17.4%)	610/3257 (18.7%)	–26.5	267.0	0.91 (SE 0.06)
ER unknown	239/1176 (20.3%)	293/1151 (25.5%)	–3.2	115.2	0.74 (SE 0.08)
Subsets of ER-Positive Tumors					
ER 10–99 fmol/mg	247/1072 (23.0%)	279/1094 (25.5%)	–21.2	108.3	0.82 (SE 0.09)
ER ≥100 fmol/mg	86/450 (19.1%)	116/450 (25.8%)	–15.4	42.0	0.69 (SE 0.13)
ER+, age <55 years	426/2359 (18.1%)	461/2345 (19.7%)	–22.9	202.3	0.89 (SE 0.07)
ER+, 55–69 years	134/846 (15.8%)	140/847 (16.5%)	–3.6	61.1	0.94 (SE 0.12)
ER+, poorly differentiated	131/868 (15.1%)	130/793 (16.4%)	–4.1	52.7	NS
ER+, moderately/well differentiated	125/952 (13.1%)	136/1047 (13.0%)	–1.8	58.3	NS

TABLE 45-1B

Subgroup Analyses of Breast Cancer Mortality by Treatment, Results from the EBCTCG
Part B Subgroup Analyses of Breast Cancer Mortality (Mortality with Recurrence, by Log-Rank Subtraction) for Taxane-plus-Anthracycline-Based Regimens versus the Same, or More (less than doubled or roughly doubled), Non-Taxane Cytotoxic Chemotherapy

Category	*Deaths/Women*		*Taxane Deaths*		
	Allocated Taxane	*Allocated Nontaxane*	*Log-Rank O-E*	*Variance of O-E*	*Ratio of Annual Death Rates (Taxane:Nontaxane)*
ER Status					
ER poor	1087/5883 (18.5%)	1271/6027 (21.1%)	–78.0	505.0	0.86 (SE 0.04)
ER positive	1044/12848 (8.1%)	1164/12790 (9.1%)	–67.1	502.3	0.87 (SE 0.04)
ER unknown	510/3397 (15.0%)	533/3306 (16.1%)	–15.9	169.1	0.91 (SE 0.07)
Subsets of ER-Positive Tumors					
ER 10–99 fmol/mg	273/4613 (5.9%)	296/4656 (6.4%)	–11.3	136.2	0.92 (SE 0.08)
ER ≥100 fmol/mg	98/978 (10.0%)	114/1022 (11.2%)	–6.2	47.5	0.88 (SE 0.14)
ER+, age <55 years	666/8316 (8.0%)	725/8223 (8.8%)	–37.7	317.9	0.89 (SE 0.05)
ER+, 55–69 years	355/4338 (8.2%)	413/4368 (9.5%)	–25.8	174.5	0.86 (SE 0.07)
ER+, poorly differentiated	440/3362 (13.1%)	398/3330 (12.0%)	14.8	189.8	1.08 (SE 0.08)
ER+, moderately differentiated	273/5552 (4.9%)	354/5595 (6.3%)	–38.0	143.0	0.77 (SE 0.07)
ER+, well differentiated	48/1501 (3.2%)	74/1430 (5.2%)	–11.1	28.7	0.68 (SE 0.16)

(Cohort 2) was also reported. Data submitted to the EBCTCG were used in separate meta-analyses of the two cohorts, which included postmenopausal women with ER-positive tumors (4).

Cohort 1 included data from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) and Breast International Group (BIG) 01-98 trials and was comprised of 9,856 patients with a mean of 5.8 years of follow-up. At 5 years, AI therapy was associated with an absolute decrease in recurrence of 2.9% (SE 0.7%, 9.6% for AI vs. 12.6% for tamoxifen; $2p < 0.00001$) and in breast cancer mortality of 1.1% (SE 0.5%, 4.8% for AI vs. 5.9% for tamoxifen; $2p = 0.1$).

TABLE 45-1C

Subgroup Analyses of Breast Cancer Mortality by Treatment, Results from the EBCTCG
Part C Any Anthracycline-Based Regimen versus No Chemotherapy

Category	*Deaths/Women*		*Anthracycline Deaths*		
	Allocated Anthracycline	*Allocated Control*	*Log-Rank O–E*	*Variance of O–E*	*Ratio of Annual Death Rates (Anthracycline:Control)*
ER Status					
ER poor	403/1095 (36.8%)	464/1043 (44.5%)	–40.5	180.4	0.80 (SE 0.07)
ER positive	831/3100 (26.8%)	1063/3177 (33.5%)	–84.6	328.5	0.77 (SE 0.05)
ER unknown	182/559 (32.6%)	174/513 (33.9%)	–14.9	72.3	0.81 (SE 0.11)
Subsets of ER-Positive Tumors					
ER+, chemotherapy + endocrine vs endocrine	659/2622 (25.1%)	853/2675 (31.9%)	–56.2	247.0	0.80 (SE 0.06)
ER 10–99 fmol/mg	416/1371 (30.3%)	544/1442 (37.7%)	–35.3	162.5	0.80 (SE 0.07)
ER ≥100 fmol/mg	274/1146 (23.9%)	337/1160 (29.1%)	–20.6	95.6	0.81 (SE 0.09)
ER+, age <55 years	250/845 (29.6%)	316/943 (33.5%)	–19.4	102.4	0.83 (SE 0.09)
ER+, 55–69 years	542/2071 (26.2%)	677/2055 (32.9%)	–53.9	215.3	0.78 (SE 0.06)
ER+, poorly differentiated	100/461 (21.7%)	120/477 (25.2%)	–12.2	45.8	0.77 (SE 0.13)
ER+, moderately/well differentiated	228/985 (23.1%)	286/1026 (27.9%)	–27.8	112.8	0.78 (SE 0.08)

EBCTCG, Early Breast Cancer Trialists' Cooperative Group; NS, not significant; ER, estrogen receptor; O–E, observed minus expected.
Data from Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. *Lancet* 2012;379(9814):432–444.

Cohort 2 consisted of four trials including German Adjuvant Breast Cancer Group/Arimidex-Nolvadex, Intergroup Exemestane Study/BIG 02-97, Italian Tamoxifen Anastrozole Trial (ITA), and Austrian Breast & Colorectal Cancer Study Group (ABCSG) 8, with a total of 9,015 women and a mean of 3.9 years of follow-up. At 3 years from treatment separation, AI therapy was associated with an absolute decrease in recurrence of 3.1% (SE 0.6%, 5.0% for AI vs. 8.1% for tamoxifen; $2p < 0.00001$) and in breast cancer mortality of 0.7% (SE 0.3%, 1.7% for AI vs. 2.4% for tamoxifen; $2p = 0.02$). The use of chemotherapy was not described in this analysis; however, review of the individual studies reveals that approximately 20% to 30% of participants received chemo endocrine therapy and these results are reviewed below. This meta-analysis confirms that use of an AI, administered instead of or in sequence with tamoxifen, is superior to use of tamoxifen alone in most postmenopausal women. This analysis helps to evaluate the role of AI instead of or in addition to tamoxifen, but unfortunately it does not provide specific guidance regarding the use of chemo endocrine therapy.

Prognostic and Predictive Markers

Clinicians use important tools, such as Adjuvant! Online, derived from and based on results from the Overview and other data sets, to provide estimates of recurrence and death and to predict response to specific treatments for their patients (5). However, increasing understanding of the molecular characteristics of individual tumors is expected to aid further in personalized treatment recommendations. The EBCTCG and AI meta-analyses have examined the role of prognostic and predictive markers that can be used to determine who would benefit from endocrine therapy alone, and who should be recommended chemo endocrine therapy. Prognostic factors reflect the natural biology of the tumor in the absence of systemic therapy and are used to estimate risk of recurrence (6–8). In contrast, predictive factors reflect likelihood of benefit from specific treatments or agents. Most factors are both prognostic and predictive as reviewed in Chapter 28. Although initial investigations concentrated on single biomarkers such as ER, PgR, or markers of proliferation or differentiation, newer analyses are assessing the role of multiple markers simultaneously.

ER and PgR Status

The EBCTCG assessed benefit from tamoxifen versus not based on level of ER expression and PgR status. In 7,378 women with ER- and PgR-positive tumors, tamoxifen use led to a relative risk of recurrence at 10 years of 0.63 (95% Confidence Interval [CI], 0.58–0.68; Log-rank $2p < 0.00001$) (1). A similar substantial benefit was observed in 2,310 women with ER-positive and PgR-poor tumors (RR 0.60, 95% CI, 0.52–0.69; Log-rank $2p < 0.00001$) (Table 45-2A), and in women whose tumors were marginally ER-positive. No benefit was seen in those women whose tumors were ER-poor.

In Cohort 1 of the AI meta-analysis, a difference in outcome was observed with respect to PgR status in the 8,745 patients (89%) with a known PgR status. The proportional reduction in recurrence in AI compared to tamoxifen was 40% (SE 9%) in the 22% of women with ER-positive, PgR-poor tumors and 17% (SE 6%) in those with ER-positive, PgR-positive tumors (Table 45-2B). The authors noted, however, that the results could be attributed to chance alone given that the global test of heterogeneity was nonsignificant, the total number of subgroups was large, and the PgR-associated effect was seen only in one of the two trials (ATAC) (4). In Cohort 2, PgR status was known in 8,184 patients (91%), and was associated with a similar proportional reduction in recurrence in women with ER-positive, PgR-poor disease (37%, SE 12%) and those with ER-positive, PgR-positive disease (21%, SE 8%) (Table 45-2B). No significant difference was seen between the groups, regardless of PgR status, age, nodal status, and tumor grade, and the global test of heterogeneity for the subgroup analyses was negative.

The role of PgR in determining response to endocrine therapy alone was also examined in several studies that have consistently demonstrated superior benefit for women whose tumors contain both ER and PgR compared to those with ER-positive, PgR-poor tumors (9–11). One of the largest cohorts included two databases, the first consisting of 3,739 patients who did not receive adjuvant systemic therapy and 1,688 patients who received adjuvant endocrine therapy alone, and the second consisting of 10,444 patients who received adjuvant endocrine therapy alone and whose tumors were subjected to central biochemical ER and PgR testing. The majority of women (>95%) received tamoxifen. PgR status was associated with disease-free and overall

TABLE 45-2A

Relevance of Quantitative Progesterone Receptor Measurement in Women with ER-Positive Tumors to Outcome by Allocated Treatment in Trials of about 5 Years of Adjuvant Tamoxifen or AI
Part A Recurrence Rate Ratio for Tamoxifen versus Control in the EBCTCG

	Events/Woman-Years (rate [% per year])		*Tamoxifen Events*		
PgR Status (fmol/mg cytosol protein)	*Allocated Tamoxifen*	*Allocated Control*	*Log-rank O–E*	*Variance of O–E*	*Ratio of Annual Event Rates (Tamoxifen:Control)*
PgR = 0	167/7076 (2.4)	273/6055 (4.5)	–68.1	96.6	0.49 (SE 0.07)
PgR 1–9	141/4241 (3.3)	171/3620 (4.7)	–23.5	60.7	0.68 (SE 0.11)
PgR 10–49	347/11413 (3.0)	442/10001 (4.4)	–74.3	163.6	0.63 (SE 0.06)
PgR 50–99	184/6422 (2.9)	258/5801 (4.4)	–43.2	95.5	0.64 (SE 0.08)
PgR ≥100	446/18490 (2.4)	611/15639 (3.9)	–122.0	238.1	0.60 (SE 0.05)
Other PgR	180/3992 (4.5)	244/3575 (6.8)	–39.3	92.1	0.65 (SE 0.08)
PgR unknown	188/4907 (3.8)	219/3981 (5.5)	–36.2	83.9	0.65 (SE 0.09)
Subtotal			–406.6	830.5	0.61 (SE 0.03)

TABLE 45-2B

Relevance of Quantitative Progesterone Receptor Measurement in Women with ER-Positive Tumors to Outcome by Allocated Treatment in Trials of about 5 Years of Adjuvant Tamoxifen or AI
Part B Recurrence Rate Ratio for Aromatase Inhibitor versus Tamoxifen in the AI Meta-Analysis

	Events/Woman (%)		*AI Events*		
PgR Status	*Allocated AI*	*Allocated Tamoxifen*	*Log-Rank O–E*	*Variance of O–E*	*Ratio of Annual Event Rates (AI:Tamoxifen)*
PgR poor	118/958 (12.3)	182/937 (19.4)	–36.9	72.5	0.60 (SE 0.09)
PgR positive	381/3452 (11.0)	443/3398 (13.0)	–37.3	201.8	0.83 (SE 0.06)
PgR unknown	85/544 (15.6)	96/567 (16.9)	–4.4	43.6	0.90 (SE 0.14)

EBCTCG, Early Breast Cancer Trialists' Cooperative Group; NS, not significant; ER, estrogen receptor; PgR, progesterone receptor; AI, aromatase inhibitor; O–E, observed minus expected.
Data from Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005;365(9472):1687–1717; Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol* 2010;28(3):509–518.

survival in endocrine therapy–treated patients, and was independent of nodal status, tumor size, and age. Compared to women with ER- and PgR-negative tumors as a baseline, the relative risk of recurrence and death was reduced more substantially in women with ER-positive, PgR-positive tumors than in those with ER-positive, PgR-negative tumors ($p < .0001$), suggesting that women whose tumors express both hormone receptors derive more benefit from endocrine therapy, primarily tamoxifen (9). Since these data sets excluded women who received chemotherapy, this study cannot answer whether women whose tumors are PgR-negative derive preferential benefit from chemo endocrine therapy compared to those whose tumors are PgR-positive. However, given a reduced benefit from endocrine therapy alone compared to women whose tumors contain both hormone receptors, women with ER-positive, PgR-negative tumors may be candidates for chemo endocrine therapy.

A comprehensive review of the role of ER and PgR in breast cancer is provided in Chapter 27. In aggregate, available data provide a strong rationale for the consideration of endocrine therapy in every woman with an invasive cancer that contains ER or PgR expression at any level. Indeed, the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) International Expert Panel recommended that ER and PgR immunohistochemistry (IHC) assays should be considered positive if there are at least 1% positive tumor nuclei in the sample on testing in the presence of proper internal and external controls (12). This would then trigger a discussion about the value of adjuvant endocrine therapy.

ER and PgR assessment by IHC alone, however, may not be useful in determining who should also be advised to receive chemotherapy. Overall the data suggest that women with tumors lacking PgR may suffer inferior benefit with endocrine therapy alone compared to women whose tumors express both hormone receptors, and for those women additional evaluation of the tumor may be considered prior to making recommendations regarding chemotherapy use. Newer methods may enable better determination of quantitative ER and PgR expression. Assessment of the functional status of the ER, optimal balance of coactivators and corepressors, and crosstalk between ER and growth factor signaling may be available in the future and could perhaps allow prediction of response to endocrine therapy or requirement for alternative or additional therapies. It is likely, however, that the presence and strength of hormone receptor expression correlates with intrinsic tumor subtypes, as described below, and that newer, more comprehensive assays may be more informative in selecting women who should consider chemo endocrine therapy.

Tumor Differentiation and Markers of Proliferation

Historically, poor differentiation or a high tumor grade or proliferative index has been associated with inferior prognosis in the absence of treatment, an improved response to cytotoxic therapy, and a poor response to endocrine therapy. In the Overview, information regarding tumor differentiation and outcome was available from approximately 47% of all tumors. The proportional risk reductions produced by chemotherapy in each of the differentiation categories were statistically similar (Table 45-3A) (3). In the AI meta-analysis, subgroup analyses of the recurrence results based on grade showed no significant difference (Table 45-3B) (4). However, as is the case with hormone receptor status, central review of grade was not conducted in either the EBCTCG or the AI meta-analyses.

Most other evaluations assessing grade, differentiation, or other proliferation factors are also retrospective in nature, but collectively they suggest that highly proliferative tumors are associated with a relative endocrine resistance and enhanced sensitivity to cytotoxic therapy, thus supporting chemo endocrine approaches. As is the case with other individual biomarkers, the use of assays that allow for multi-gene assessment may be more informative than tumor grade in determining relative responsiveness or resistance to endocrine therapy.

Growth Factors and Other Tyrosine Kinase Receptors

As we noted previously, chemo endocrine therapy has been recommended to women with ER-positive tumors that are associated with biomarkers predictive of endocrine resistance. Suggested mechanisms of endocrine resistance include activation of downstream regulatory molecules in other growth factor signaling pathways such as epidermal growth factor (EGFR, HER1) and human epidermal growth factor receptor 2 (HER2), expression of other tyrosine kinase receptors, and alterations in the balance of coregulators (13).

Cross-talk between the ER and HER1 and HER2 has been implicated as a predictor of relative resistance to endocrine manipulations in several preclinical and clinical

TABLE 45-3A

Relevance of Tumor Differentiation for ER-Positive Patients to Outcome by Allocated Treatment in Trials of about 5 Years of Adjuvant Tamoxifen or AI
Part A Tamoxifen Versus Control Recurrence Rate Ratio in the EBCTCG

	Events/Woman-Years (rate [% per year])		*Tamoxifen Events*		
Tumor Grade	*Allocated Tamoxifen*	*Allocated Control*	*Log-rank O–E*	*Variance of O–E*	*Ratio of Annual Event Rates (Tamoxifen:Control)*
Poor	101/2022 (5.0)	170/1730 (9.8)	–38.5	58.1	0.52 (SE 0.10)
Moderately/well	201/4285 (4.7)	251/3513 (7.1)	–48.8	99.3	0.61 (SE 0.08)
Unknown	1351/50461 (2.7)	1797/43645 (4.1)	–333.2	734.9	0.64 (SE 0.03)

investigations (14). In addition, ER-positive, PgR-negative tumors are often associated with overexpression of HER1 or HER2 compared to tumors expressing both ER and PgR. The expression of HER1 and overexpression of HER2 in ER-positive, PgR-negative but not in ER-positive, PgR-positive tumors predicted tamoxifen resistance and a high risk of recurrence (15). Recent results from studies in advanced breast cancer clearly demonstrate that the addition of an anti-HER2 agent to an AI is associated with improved progression-free survival (PFS) and provide rationale for studies in the adjuvant setting. In TAnDEM, postmenopausal women with hormone receptor–positive, HER2-positive metastatic breast cancer were randomly assigned to first-line anastrozole with or without trastuzumab. The combination was associated with improved PFS compared to anastrozole alone (Hazard Ratio [HR] 0.63; 95% CI, 0.47–0.84; median PFS 4.8 vs. 2.4 months; Log-rank p = .0016) (16). In a second study in a similar population, women were randomly assigned to letrozole with or without lapatinib. The combination was associated with superior PFS (HR 0.71; 95% CI, 0.53–0.96; p = .019; median PFS 8.2 vs. 3.0 months) (17). Small underpowered studies have provided conflicting results regarding the role of AI and EGFR tyrosine kinase inhibitors. PFS was longer in patients receiving the combination of anastrozole and the EGFR inhibitor gefitinib compared to those receiving anastrozole plus placebo (HR 0.55; 95% CI, 0.32–0.94; median PFS 14.7 vs. 8.4 months) (18), but other studies suggested that the likely benefit from EGFR inhibition added to AI or fulvestrant is small and not likely to outweigh increased toxicity (19).

Activation of other tyrosine kinase receptors may also predict for a more aggressive tumor phenotype and relative resistance to endocrine therapy. In these situations, although the estrogen-dependent growth is inhibited via endocrine manipulations, other growth signals stimulate proliferation and lead to relative endocrine resistance. Activation of other growth signals is usually associated with higher grade tumors and those women have traditionally been offered chemo endocrine therapy (20,21). Emerging results in the advanced, acquired endocrine-resistance disease setting provide strong support for prospective studies of novel targeted agents in the adjuvant setting in tumors with de novo endocrine resistance and are summarized in the "Future Directions" section of this chapter.

Molecularly Defined Tumor Subtypes

In the last decade emphasis has been given to designating tumors not only by their ER and PgR status but also by using a more careful determination of their intrinsic subtype. Initial gene expression analysis led to the recognition that several tumor subtypes exist and these carry differential prognostic and predictive implications (22). Tumors that

TABLE 45-3B

Relevance of Tumor Differentiation for ER-Positive Patients to Outcome by Allocated Treatment in Trials of about 5 Years of Adjuvant Tamoxifen or AI
Part B Aromatase Inhibitor versus Tamoxifen Recurrence Rate Ratio in the AI Meta-Analysis

	Events/Woman (%)		*AI Events*		
Category	*Allocated AI*	*Allocated Tamoxifen*	*Log-rank O–E*	*Variance of O–E*	*Ratio of Annual Event Rates (AI:Tamoxifen)*
Poor	181/854 (21.2)	209/823 (25.4)	–23.8	92.1	0.77 (SE 0.09)
Moderate	265/2417 (11.0)	331/2388 (13.9)	–40.4	145.2	0.76 (SE 0.07)
Well	63/1186 (5.3)	93/1217 (7.6)	–14.6	38.4	0.68 (SE 0.13)
Unknown	75/497 (15.1)	88/474 (18.6)	–9.8	39.3	0.78 (SE 0.14)

AI, aromatase inhibitors; EBCTCG, Early Breast Cancer Trialists' Cooperative Group; O–E, observed minus expected.
Data from Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011;378(9793):771–784. PMCID: 3163848; Dowsett M, Cuzick J, Ingle J, et al. Meta-analysis of breast cancer outcomes in adjuvant trials of aromatase inhibitors versus tamoxifen. *J Clin Oncol* 2010;28(3): 509–518.

express ER or PgR may be Luminal A or B, or fall into the HER2 subtype. Luminal A tumors are generally associated with a high expression of ER, expression of PgR, and a low proliferation profile. Women with this tumor subtype are expected to derive benefit from endocrine manipulations. In contrast, Luminal B tumors, although ER-positive, are more likely to lack PgR and are associated with high proliferation indices. Luminal B tumors are more likely to be resistant to endocrine manipulations alone and women with this tumor subtype may benefit from chemo endocrine therapy.

In the clinic, several assays can aid in classification of individual tumors to intrinsic subtypes and thus in treatment recommendations. A more comprehensive overview of the role of molecular prognostic and predictive markers is provided in Chapter 30. The most commonly used commercial assay is Onco*type* DX. The assay includes 21 prospectively selected genes (16 cancer-related genes and 5 housekeeping genes) that are performed via reverse-transcriptase-polymerase-chain-reaction (RT-PCR) on paraffin-embedded tumor tissue in a central laboratory. The expression of each of the genes is evaluated and tabulated using a proprietary formula and reduced to a single Recurrence Score. The assay was initially developed and validated in trials that included women with T1-2, node-negative, hormone receptor–positive tumors and is commercially available for women meeting these general criteria (23,24). Although the Recurrence Score is continuous, it is further categorized as low, intermediate, or high. Tumors with low Recurrence Score are likely hormone-sensitive and chemotherapy does not appear to offer significant benefit. In contrast, tumors with high Recurrence Scores are relatively hormone-resistant and chemotherapy should be strongly considered. The initial studies suggest that women with tumors scoring in the intermediate range are also not likely to benefit from chemotherapy but were constrained by small sample size. It is anticipated that the prospective study, **T**rial **A**ssigning **I**ndividua**L**ized **O**ptions for Treatment (**Rx**), or TAILORx, which has recently completed accrual, will help provide true estimates of risk with endocrine therapy alone or in combination with chemotherapy.

The predictive role of the Recurrence Score was also evaluated in node-negative or -positive postmenopausal women receiving anastrozole or tamoxifen in ATAC. Reportable Recurrence Scores were available from 1,231 evaluable patients. Recurrence Score was significantly associated with time-to-recurrence in both node-negative and -positive patients (25). Importantly, the prognostic value of the Recurrence Score was similar in both anastrozole- and tamoxifen-treated patients.

Additional studies suggest that Onco*type* DX is also a prognostic and predictive factor in women with node-positive disease. Southwest Oncology Group (SWOG) investigators analyzed samples from node-positive, hormone receptor–positive, postmenopausal women who enrolled in Trial S8814 (Intergroup 0100). The women were randomly assigned to tamoxifen alone or CAF with either concurrent or sequential tamoxifen (CAF-T). Compared to tamoxifen alone, CAF-T was associated with superior disease-free and overall survival (26). Specimens from approximately 40% of the participants were evaluable for the biomarker study (tamoxifen: n = 148, CAF-T: n = 219). The investigators reported that the Recurrence Score provided prognostic information in the tamoxifen arm (p = .006). CAF did not provide significant additional benefit in women with low Recurrence Score tumors (HR 1.02, 95% CI, 0.54–1.93; Log-rank p = .97), but was associated with a significant improvement in disease-free survival in women with a high Recurrence Score (HR 0.59, 95% CI, 0.35–1.01; Log-rank p = .03) (27). Similarly, Eastern Cooperative Oncology Group (ECOG) investigators evaluated the role of Onco*type* DX in women with 0-3 positive nodes who received the combination of AC or doxorubicin and docetaxel (AT) in Trial E2197. Disease-free and overall survival rates were identical in the two arms in the parent trial (28). The investigators compared Recurrence Score in a subset of the participants with hormone receptor–positive disease who received chemo endocrine therapy and suffered a recurrence (n = 99) versus a similar subset who did not suffer a recurrence (n = 366). Recurrence Score was a significant predictor of recurrence both in node-negative (p = .0007) and node-positive (p = .0004) patients, all of whom received adjuvant chemotherapy (29).

More recently, National Surgical Adjuvant Breast and Bowel Project (NSABP) investigators evaluated the role of Onco*type* DX as a prognostic and predictive factor in 3,060 node-positive women who received AC with or without paclitaxel in Trial B-28. In the entire trial population, the addition of paclitaxel to AC was associated with a significantly reduced annual hazard for disease-free survival event by 17% (HR 0.83, 95% CI, 0.72–0.95; p = .006). In the 2,007 women with ER-positive disease, the annual hazard for a disease-free survival event was reduced by 24% (HR 0.76, 95% CI, 0.63–0.91, p = .003). Tissue blocks were available and evaluable from 1,065 participants (AC: n = 519, AC followed by paclitaxel: n = 546). The group included in the biomarker analysis had slightly inferior breast cancer–related outcomes compared to the entire study population. Approximately 36%, 34%, and 30% of the specimens were associated with low, intermediate, and high Recurrence Scores, respectively. Women who were older and those with smaller tumors were more likely to have low Recurrence Score tumors. Preliminary data suggest that Recurrence Score was predictive of outcomes of women with node-positive, ER-positive tumors treated with adjuvant chemo endocrine therapy, including disease-free survival, distant recurrence-free survival, breast cancer–specific free survival and overall survival (30). In addition, in the subset available for analysis, Recurrence Score did not significantly predict benefit from the addition of paclitaxel to AC. Overall, however, the number of subjects available for each analysis was small and the power to detect differences among the groups was low (31).

Together, these retrospective analyses in women with node-positive disease suggest that, as with women with node-negative tumors, the Recurrence Score, consisting of multiple estrogen responsiveness, proliferation-associated, and other genes, may predict the sensitivity to endocrine interventions and may be a useful tool to separate women who can be prescribed endocrine therapy alone from those requiring chemo endocrine therapy. In the ongoing SWOG RxPONDER (**Rx** for **Po**sitive **Nod**e, **E**ndocrine **R**esponsive Breast Cancer, S1007) trial, 4,000 women with hormone receptor–positive, HER2-negative tumors involving 1-3 positive nodes are being recruited to evaluate the benefit of chemotherapy in those with low or intermediate Recurrence Score. Those with a Recurrence Score of ≤25 are randomized to endocrine therapy with or without chemotherapy, while those with Recurrence Score >25 will be recommended to receive chemo endocrine therapy.

Other assays that combine assessment of more than one factor have been proposed. For example, a combination of standard IHC measurements of four factors, including ER, PgR, HER2, and Ki-67, designated IHC4 Score is a prognostic model that uses classical variables. It was developed in a study that included 1,125 ER-positive specimens from ATAC participants who did not receive adjuvant chemotherapy and who had a Recurrence Score analysis and then assessed in a separate cohort of 786 patients. The investigators demonstrated that all four IHC markers provided independent

prognostic information and that the IHC4 Score provided prognostic value similar to that provided by the Recurrence Score; this was further validated in the second separate cohort (32). One noteworthy aspect of the IHC4 score is that it is not assessed in a central laboratory. This decentralized approach enhances its potential utilization but also mandates that individual laboratories will need to validate the assay prior to implementation in practice. Another multigene assay is PAM50, a quantitative RT-PCR assay for 50 genes identifying intrinsic breast cancer subtypes. Its value has been assessed in 786 specimens with IHC analysis of ER, PgR, and Ki-67 and linkage to clinical data. PAM50 signatures for proliferation genes were more prognostic than clinical assays for hormone receptors or Ki-67 (33). The assay is validated in formalin-fixed, paraffin-embedded blocks and is commercially available in the United States. This assay may allow for accurate subtyping without the need to obtain fresh tissue for analysis and for estimates of recurrence.

Other multiparameter assays are also in development. For example, the MammaPrint® assay, which includes a panel of 70 genes that predicts prognosis of primary breast cancer, may help select patients who should receive adjuvant therapy (34). The assay is currently under investigation in the large international MINDACT (**M**icroarray **I**n **N**ode negative and 1–3 positive lymph node **D**isease may **A**void **C**hemo**T**herapy) Breast Cancer Clinical Trial. In this study, the use of MammaPrint® is compared to Adjuvant! Online in selecting patients with 0–3 positive nodes for adjuvant chemotherapy in breast cancer. Another assay is the RT-PCR-based assay that includes a ratio of 2-genes (HOXB13 and IL17BR), and is designated H/I (35). The H/I ratio may also predict outcomes in tamoxifen-treated women (36). Another commercially available assay is Mammostrat®, a panel that provides an assessment of risk of recurrence that is independent of proliferation and grade (37). It is anticipated that samples obtained through TAILORx, RxPONDER, MINDACT, and other studies will be available for analysis using emerging assays and technologies.

A key question is how these assays will assist in adjuvant treatment decisions, especially in decisions about chemo endocrine therapy. The 2013 St. Gallen Expert Panel recommended that clinical-pathological features continue to be used to classify intrinsic biological breast tumor subtypes to assist in treatment recommendations. Members of the panel recognized that several multi-gene molecular assays provide accurate and reproducible prognostic information or prediction of response to chemotherapy. However, it was also recognized that the assays cannot be applied globally due to cost constraints. Therefore, when access to molecular assays is not possible, biomarkers obtained through IHC for ER, PgR, Ki-67, and IHC or *in situ* hybridization for HER2 continue to provide strong support for approximate stratification to tumor subtypes. "Luminal A" tumors are generally ER-positive and HER2-negative, with high PgR expression, and with a low Ki-67. In contrast, "Luminal B" tumors are ER-positive and HER2-negative, with either low PgR expression or a high Ki-67. "HER2-positive" subtypes are associated with overexpression or amplification of HER2, whereas "basal-like" tumors do not express ER, PgR, and are HER2 negative. Women with tumors consistent with the "Luminal A" subtype should be offered endocrine therapy alone, whereas those with the "Luminal B" tumor subtype should be recommended chemo endocrine therapy. Trastuzumab-based therapy should be added to women with the "HER2-positive" subtype, regardless of hormone receptor status (38,39). Ongoing clinical trials will also help assess whether treatment strategies should be considered based on tumor characteristics, disease stage, or both.

Other Tumor and Host Factors

Additional factors that are potentially predictive of relative endocrine resistance include factors in the microenvironment such as angiogenesis, modifications in epigenetic regulation, and other tumor and host genetics (13). A comprehensive discussion regarding the role of these markers is beyond the scope of this chapter except to state that emerging data suggest that combinations of endocrine agents with anti-angiogenic agents or epigenetic modulators are under study.

Whether host factors modulate benefit from endocrine therapy is under debate. While there is strong rationale to hypothesize that genetic variants in genes encoding for drug target or metabolizing enzymes may influence drug efficacy and safety, clinical data have been mostly retrospective and results are mixed. For example, the presence of variant alleles in the cytochrome P450 2D6 gene (*CYP2D6*) leads to an inactive or low-activity enzyme and thus to a reduced conversion of tamoxifen to its active metabolite, endoxifen (40–42). Several small studies suggested that women with *CYP2D6* variants may have reduced benefit from tamoxifen (43), but more recent data from ATAC and BIG 1-98 fail to show a correlation (44,45). Similarly single-nucleotide polymorphisms (SNPs) in the gene-encoding aromatase (CYP19A1) have been shown to influence AI-associated benefits (46,47). If indeed genetic variants influence response to endocrine strategies, these data can be used to inform treatment decisions and are discussed in more detail in Chapter 48.

In summary, chemo endocrine therapy is generally recommended to women with ER-positive tumors that are associated with individual biomarkers predictive of endocrine resistance such as lack of PgR expression, high histological grade, or HER2 overepression or amplification. Assays that provide information regarding multiple gene products performed in dedicated laboratories, such as Onco*type* Dx, can be utilized to determine with more accuracy endocrine sensitivity or resistance as well as the utility of chemotherapy in addition to endocrine therapy. Until other data are available regarding use of multiple endocrine agents, the addition of novel therapies, or elimination of endocrine agents, women with tumors that are classified as endocrine resistant should be considered for chemo endocrine therapy. Other known and emerging tumor and host characteristics may also influence endocrine responsiveness but are not sufficiently validated for use in routine clinical decision making. It is expected that a better understanding of the molecular heterogeneity of breast tumors will ultimately yield an individualized risk stratification and treatment approach.

CHEMO ENDOCRINE THERAPY: SELECTION OF ENDOCRINE TREATMENT

Once a decision is made to recommend chemo endocrine therapy, the selection of endocrine agents must be considered. General factors regarding the choice and duration of adjuvant endocrine therapies for women whose tumors express hormone receptors are described in detail in Chapter 43. Until validated evidence is available to inform clinicians which specific tumors are endocrine resistant, every woman whose invasive tumor expresses ER or PgR should be considered for endocrine therapy. Below we review the evidence that may guide the selection of endocrine therapy when a decision is made to also administer chemotherapy.

Tamoxifen

At least 5 years of tamoxifen continues to be the endocrine treatment of choice in premenopausal women.

In postmenopausal women, tamoxifen may be used in sequence with AIs for a total of 5 to 10 years, or administered as single agent to those with a contraindication or intolerance to AIs. Whether tamoxifen should be administered for 10 years in women who have received chemotherapy has not been specifically reported (48).

The EBCTCG results suggested that chemo endocrine therapy is superior to either modality alone, regardless of factors such as age, nodal status, or tumor grade. The most recent EBCTCG specifically evaluated the use of tamoxifen with or without chemotherapy. The addition of chemotherapy to tamoxifen provided substantial additional reduction in 10-year recurrence risk compared to the use of tamoxifen alone in both node-negative and node-positive women. Specifically, in the absence of chemotherapy, relative risk of recurrence was superior in women taking tamoxifen versus no therapy (Node negative: RR 0.57, 95% CI, 0.51–0.63; Log-rank 2p < 0.00001. Node positive: RR 0.63, 95% CI, 0.52–0.76; Log-rank 2p <0.00001), and, in the presence of chemotherapy, relative risk of recurrence was superior in women receiving chemotherapy and tamoxifen versus chemotherapy alone (Node negative: RR 0.74, 95% CI, 0.60–0.92; Log-rank 2p = 0.005. Node positive: RR 0.66, 95% CI, 0.60–0.74; Log-rank 2p < 0.00001) (2). The recurrence reductions were significant both in trials with no chemotherapy (6 trials) or those with chemotherapy plus tamoxifen versus the same chemotherapy alone (14 trials) (Table 45-4). In both instances, the effect of tamoxifen was greater in women with tumors expressing higher degrees of ER. Women who received chemotherapy benefited equally whether it was administered in a concurrent or sequential manner (Table 45-4).

A review of key pivotal trials that contributed to the EBCTCG is illustrative. NSABP investigators analyzed outcomes of node-negative hormone receptor–positive women who were randomized in B-14 to placebo (n = 1,453) or tamoxifen (n = 1,439), and in B-20 to tamoxifen alone (n = 788) or in combination with six cycles of CMF (CMFT, n = 789) or MF. In B-14, recurrence-free survival was significantly improved in tamoxifen-treated women compared to placebo irrespective of age, menopausal status, or tumor ER concentration (49,50). In B-20, CMFT was associated with improved 5-year disease-free and overall survival compared to tamoxifen alone (50,51). In the combined analysis, the investigators reevaluated outcomes by age (<50 years, 50 to 59 years, >60 years) and menopausal status. In B-14, tamoxifen provided a substantial benefit compared to placebo, regardless of age, menopausal status, or tumor ER concentration. In B-20, CMFT was associated with greater benefit compared to tamoxifen alone. By indirect comparison, compared to placebo, CMFT was associated with a 65% reduction in treatment failure, regardless of age. These results suggest that neither age nor menopausal status is sufficient to dictate recommendations for the addition of chemotherapy to tamoxifen. Rather, recommendations for tamoxifen versus chemo endocrine therapy should rely more strongly on tumor characteristics for patients whose general health is such that they would have qualified for these trials.

Additional studies of chemotherapy and tamoxifen have specifically enrolled women who were only postmenopausal or premenopausal. Postmenopausal node-negative women were randomized to three cycles of CMFT or tamoxifen alone in International Breast Cancer Study Group (IBCSG) Trial IX. Whereas disease-free and overall survival were superior in CMFT-treated ER-negative participants, those with ER-positive tumors benefited equally from tamoxifen or CMFT (52). Given the brevity of the chemotherapy, which is likely suboptimal by today's standards, it cannot be assumed that women with similar characteristics would not benefit from more established regimens such as six cycles of CMF chemotherapy or an anthracycline or taxane-based regimen added to tamoxifen.

In Intergroup Trial 0100 (SWOG 8814), postmenopausal women with node-positive, hormone receptor–positive breast cancer were randomly assigned to tamoxifen alone or six cycles of CAF followed by T (CAF-T) or concurrent CAF and tamoxifen (CAFT-T). CAF-T was associated with superior disease-free and overall survival compared with tamoxifen alone (26).

The use of tamoxifen in premenopausal women became prevalent only after the 1995 EBCTCG analysis showing that hormone receptor–positive women <50 years, who were presumably mostly premenopausal, gained substantial benefit from the use of tamoxifen, regardless of chemotherapy administration. More recent analyses of the Overview

TABLE 45-4

Subgroup Analyses of the Tamoxifen versus Control Recurrence Rate Ratio for ER-positive Disease. Outcome by Allocated Treatment in Trials of about 5 Years of Adjuvant Tamoxifen

	Events/Woman-Years (rate [% per year])		*Tamoxifen Events*		
Category	*Allocated Tamoxifen*	*Allocated Control*	*Log-rank O–E*	*Variance of O–E*	*Ratio of Annual Event Rates (Tamoxifen:Control)*
Background Chemotherapy					
Present	837/22900 (3.7)	1057/20528 (5.1)	–170.5	430.1	0.67 (SE 0.04)
Absent	816/33847 (2.4)	1161/28348 (4.1)	–263.1	451.3	0.56 (SE 0.04)
Background Chemotherapy					
Concurrent	352/7096 (5.0)	433/5817 (7.4)	–81.8	169.2	0.62 (SE 0.06)
Sequential	485/15804 (3.1)	624/14711 (4.2)	–88.7	260.9	0.71 (SE 0.05)
Absent	816/33847 (2.4)	1161/28348 (4.1)	–263.1	451.3	0.56 (SE 0.04)

ER, estrogen receptor; O–E, observed minus expected, with variance.
Data from Davies C, Godwin J, Gray R, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet* 2011;378(9793):771–784. PMCID: 3163848.

indeed confirmed that women age 45 or younger and those ages 45 to 54 years enjoy similar benefits from tamoxifen compared to older women (2).

Only a few individual studies provide data regarding the role of chemotherapy and tamoxifen in premenopausal women. In IBCSG Trial 13-93, node-positive premenopausal women received three cycles of anthracycline-based chemotherapy followed by three cycles of CMF with or without 5 years of tamoxifen (53). Disease-free survival, but not overall survival, was superior in women receiving chemo endocrine therapy, and this result was observed in women younger than age 40 as well as those age 40 or older.

Together, the Overview data and older prospective trials demonstrate that the addition of chemotherapy to tamoxifen is overall associated with superior survival outcomes in premenopausal and postmenopausal women with hormone receptor–positive disease. With the recent improvement in understanding of the importance of biological tumor characteristics as predictors of benefit from chemotherapy versus endocrine therapy, it is not possible to use a specific age cutoff or menopausal status to recommend chemo endocrine therapy. Rather, it appears prudent to evaluate a woman's tumor carefully using assays such as Onco*type* DX or IHC4 to identify those patients whose tumors suggest they are likely to benefit from chemotherapy in addition to endocrine therapy.

Aromatase Inhibitors

Following the recognition that AIs were superior to tamoxifen in the setting of metastatic postmenopausal breast cancer, the AIs were evaluated in adjuvant clinical trials using several different approaches—AI compared with tamoxifen for a total of 5 years of each (upfront), administered in sequence with tamoxifen for a total of 5 years of endocrine therapy (sequential), or administered for 5 additional years following 5 years of tamoxifen versus placebo (extended). Several of these pivotal studies allowed adjuvant chemotherapy prior to initiating endocrine therapy and reported outcomes by chemotherapy use or not, although the AI meta-analysis investigators have not reported outcomes based on chemotherapy use versus not.

In ATAC, approximately 20% of women received adjuvant chemotherapy. No difference between assignment to tamoxifen or anastrozole was observed in this subgroup (HR 0.89, 95% CI, 0.70–1.13); however, the number of observed events was small (54,55). Similarly, only 25% of participants in BIG 1-98 received chemotherapy. Disease-free survival was superior in the letrozole- compared to tamoxifen-treated women, regardless of chemotherapy use (Women who received chemotherapy: HR 0.74, 95% CI, 0.56–0.97; $p = .03$. No chemotherapy: HR 0.86, 95% CI, 0.73–1.01; $p = .07$) (56). Although these two large studies comparing AI monotherapy to tamoxifen provide conflicting results, the subgroups are small and cannot be regarded as conclusive. Therefore, the assignment to specific endocrine therapy should be made based on other factors such as menopausal status and bone health and irrespective of the decision whether to administer chemotherapy or not.

Likewise, small proportions of women included in the studies comparing sequential AI administration after tamoxifen to tamoxifen monotherapy received adjuvant chemotherapy. Approximately 32% of IES participants received adjuvant chemotherapy, and similar disease-free survival benefits were observed in AI-treated women, regardless of chemotherapy use (57). Neither ABCSG 8 nor ARNO 95 allowed adjuvant chemotherapy, and only a small proportion of ITA participants received adjuvant chemotherapy. In a combined analysis of the three studies, 8% of the patients received adjuvant chemotherapy, and anastrozole was superior to tamoxifen irrespective of adjuvant chemotherapy use (Women who received chemotherapy: HR 0.33, 95% CI, 0.18–0.61. No chemotherapy: HR 0.67, 95% CI, 0.53–0.85) (58).

Finally, in National Cancer Institute of Canada (NCIC) Trial MA.17, outcomes were compared among women receiving 5 years of tamoxifen followed by 5 years of letrozole or placebo. In this study, 45% of participants received adjuvant chemotherapy. Disease-free survival was identical, regardless of chemotherapy use (Women who received chemotherapy: HR 0.58, 95% CI, 0.40–0.83. No chemotherapy: HR 0.58, 95% CI, 0.40–0.84) (59).

With the exception of ATAC, studies of AIs in the upfront, sequential, and extended setting demonstrated that women benefit from assignment to AI or tamoxifen, regardless of adjuvant chemotherapy administration. More recent studies compared outcomes in women receiving different AIs. For example, in NCIC MA.27, in which women were randomly assigned 5 years of anastrozole or exemestane, 31% of participants received adjuvant chemotherapy. Event-free survival was identical among the groups, and regardless of chemotherapy use (Women who received chemotherapy: HR 1.02, 95% CI, 0.80–1.29; $p = .89$. No chemotherapy: HR 1.01, 95% CI, 0.84–1.23; $p = .89$) (60). Future analyses may provide additional guidance regarding the use of AI versus other endocrine interventions in chemotherapy-treated women. Importantly, the women enrolled in the AI studies were relatively older and the majority died without a breast cancer recurrence, suggesting that chemotherapy played a minor role. Overall, tumor characteristics predictive of endocrine sensitivity appear to apply equally to tamoxifen and to AIs. At this time there is no reason to recommend AI over tamoxifen or vice versa based on specific tumor or host characteristics. AIs should be administered as monotherapy or in sequence with tamoxifen to women without regard for the use of chemotherapy (61,62).

Given the substantial benefit observed in postmenopausal women, the role of AI is under investigation with ovarian suppression or ablation in hormone receptor–positive premenopausal women. AIs should not be used as monotherapy in premenopausal women because suppression of peripheral aromatase may cause a reduced feedback to the hypothalamus and a resulting surge in ovarian stimulation (63). A confounding factor is that many pre- and perimenopausal women will experience chemotherapy-induced amenorrhea or ovarian failure. Due to lack of good predictors of chemotherapy-induced ovarian failure, whose likelihood varies greatly based on patient age and type and duration of chemotherapy, and the knowledge that hormone levels immediately following chemotherapy may not accurately predict ovarian function, tamoxifen should be the initial agent of choice in those women (64). AI use is associated with an increase in circulating estrogens in younger women and may stimulate ovarian function; indeed, pregnancies have been reported in this group (65,66). In premenopausal women for whom tamoxifen is contraindicated or for those participating in clinical trials, AIs may be used with ovarian ablation or suppression. In those women with chemotherapy-induced ovarian failure who have received tamoxifen for 2 to 3 years, a transition to an AI should be considered with extreme caution and with serial determinations of high-sensitivity estradiol concentrations (65,67,68).

The use of AI with ovarian suppression in premenopausal women is still under investigation. Results of pivotal clinical trials such as **S**uppression of **O**varian **F**unction **T**rial (SOFT) and **T**amoxifen and **E**xemestane **T**rial (TEXT) are expected in the next few years and will clarify the role of routine use of ovarian ablation in addition to tamoxifen or AI.

Ovarian Ablation

The role of ovarian suppression or ablation for premenopausal women with hormone receptor–positive breast cancer has been recognized for many more decades than tamoxifen's. Ovarian ablation can be achieved directly either by surgery or radiotherapy (ovarian ablation), medically by suppression with luteinizing hormone-releasing hormone (LHRH) agonists (ovarian suppression), or indirectly by chemotherapy.

The 2000 EBCTCG Overview included studies in which approximately 8,000 women younger than age 50 with tumors that were ER-positive or unknown were allocated to chemotherapy plus ovarian ablation (15 studies) or suppression (six studies) versus chemotherapy alone. Ovarian ablation/suppression was associated with a substantial reduction in both risk of breast cancer recurrence ($2p < 0.00001$) and mortality ($2p = 0.004$) in the absence of other therapy (1). There was no apparent difference between ovarian ablation and suppression approaches and the risk reductions among women younger than 40 years were similar to those seen in women ages 40 to 49. When both groups received chemotherapy, the absolute benefit from ovarian treatment was smaller compared to trials that did not employ chemotherapy. It is not clear whether the reduced benefit from the use of ovarian ablation/suppression and chemotherapy is due to the concurrent use of the endocrine and cytotoxic interventions or due to chemotherapy-induced ovarian suppression that led to an indirect endocrine intervention in women who received chemotherapy alone.

The LHRH agonists in the Early Breast Cancer Overview group reported a separate meta-analysis that included individual patients from 11,906 premenopausal breast cancer patients in 16 trials who were randomized to LHRH agonists versus other treatments. Administration of LHRH agonists, as the only systemic adjuvant treatment to women with hormone receptor–positive cancer, was not associated with significant improvements in relative reduction in risk of recurrence ($p = .08$) or death after recurrence ($p = .49$), although the numbers were small. When LHRH agonists were added to tamoxifen, chemotherapy, or both, recurrence and death were substantially reduced ($p = .02$ and $p = .03$, respectively) (69). When compared to chemotherapy, LHRH agonists provided similar risk-reduction benefits. Unfortunately, there were no comparisons of LHRH agonists and tamoxifen to chemotherapy and tamoxifen because these trials predated the recognition of tamoxifen's benefit in premenopausal women.

A Cochrane Analysis reported in 2009 included 14 randomized trials assessing LHRH agonists as adjuvant treatment in 13,000 premenopausal women with early-stage, mostly ER-positive, breast cancer. The investigators noted that, for most comparisons, there were too few trials, too few randomized patients, and/or too little follow-up to draw meaningful conclusions regarding the relative effects of different treatments. In addition, most of the chemotherapy regimens included in the comparison were older and may be viewed as suboptimal by today's standards. Four main comparisons were conducted (70). (i) LHRH agonists versus another treatment: In ER-positive patients LHRH monotherapy provided similar recurrence-free and overall survival benefits compared with first-generation chemotherapy regimens such as CMF. There were insufficient data to compare LHRH agonist monotherapy to tamoxifen alone, but these treatments appeared comparable in terms of recurrence-free survival. (ii) LHRH agonists plus anti-estrogen versus another treatment: Data were insufficient to compare LHRH agonists plus tamoxifen to tamoxifen alone, but results suggested that the combination of LHRH agonists plus tamoxifen may be superior to an LHRH agonist alone or to chemotherapy alone. The data comparing LHRH agonists plus AI to LHRH agonists plus tamoxifen were inconclusive. (iii) LHRH agonists plus chemotherapy versus another treatment: There were insufficient data to compare the LHRH agonists plus chemotherapy combination to LHRH agonists alone, but one study suggested the two provided identical outcomes in ER-positive patients. In comparison to chemotherapy alone, LHRH agonists plus chemotherapy combination was associated with a trend toward improved recurrence-free and overall survival. (iv) LHRH agonists plus anti-estrogen plus chemotherapy versus another treatment: compared to chemotherapy alone, LHRH agonists plus tamoxifen plus chemotherapy provided a trend toward improved recurrence-free and overall survival.

Together, results of several meta-analyses suggest that ovarian ablation or suppression provided an effective endocrine intervention to premenopausal women with hormone receptor-positive breast cancer. Individual studies may help further define who may be appropriate for treatment with ovarian ablation/suppression.

In E5188/Intergroup 0101, 1,503 premenopausal women with hormone receptor–positive, node-positive tumors were randomly assigned to CAF chemotherapy alone or CAF followed by goserelin or CAF followed by goserelin and tamoxifen. Although 5 years of goserelin added to CAF did not provide significant additional benefits compared to chemotherapy alone for the entire study population, women younger than age 40 derived substantial benefit from the combination (71). In IBCSG Trial 13-93, node-positive premenopausal women received three cycles of anthracycline-based chemotherapy followed by three cycles of CMF with or without 5 years of tamoxifen (53). The combined therapy was associated with a significant improvement in disease-free but not in overall survival, and was observed both in women age 40 or older (HR 0.60, 95% CI, 0.44–0.81; $p = .0009$), and in those younger than 40 (HR 0.57, 95% CI, 0.38–0.86; $p = .008$). Importantly, the investigators observed that the women with ER-positive tumors who achieved chemotherapy-induced amenorrhea had a significantly improved outcome (amenorrhea vs. no amenorrhea HR 0.61, 95% CI, 0.44–0.86; $p = .004$) (53). These studies suggest that chemotherapy-induced amenorrhea predicts improved outcomes in premenopausal women with hormone receptor–positive tumors. Therefore, the addition of ovarian suppression may provide survival benefit to young women who resume menstruation following chemotherapy.

In NSABP B-30, 5,351 women with node-positive breast cancer were randomly assigned to four cycles of doxorubicin and cyclophosphamide followed by four cycles of docetaxel (sequential ACT); four cycles of doxorubicin and docetaxel; or four cycles of doxorubicin, cyclophosphamide, and docetaxel (concurrent ACT). Disease-free and overall survival were superior in the sequential-ACT group compared with the doxorubicin and docetaxel and concurrent-ACT groups. Overall survival was improved in patients with amenorrhea for 6 months or more across all treatment groups; a landmark analysis showed that this was seen for women with hormone receptor–positive but not –negative disease (72,73).

Two other relevant studies were not included in the meta-analyses: Adjuvant Breast Cancer Trials Collaborative Group Ovarian Ablation Or Suppression Trial and IBCSG Trial 11-93. The collaborative study included 2,144 pre- or perimenopausal women with ER-positive or unknown tumors who received tamoxifen for 5 years with or without ovarian suppression. Chemotherapy was administered to those at high risk. No difference was observed between women who

received ovarian suppression and tamoxifen and those who received tamoxifen alone (74). In 11-93, 174 premenopausal women with node-positive, hormone receptor–positive tumors were randomly assigned to 5 years of ovarian suppression and tamoxifen with or without four cycles of adjuvant anthracycline-based chemotherapy. Although disease-free and overall survival were identical in the two arms, this study closed early due to low accrual rate and underpowered analysis.

In aggregate, neither the individual studies reported to date nor the completed meta-analyses provide us with the knowledge required to select with certainty premenopausal women who should receive ovarian suppression in addition to optimal chemotherapy, when appropriate, or to tamoxifen. It seems unlikely that women who receive modern chemotherapy and tamoxifen will obtain more than a modest benefit, if any, from the addition of ovarian ablation/suppression. One exception may be a group of women younger than age 40 whose menstrual cycles resume following adjuvant chemotherapy. Women older than age 40 are more likely to undergo chemotherapy-induced ovarian failure and may not obtain additional benefits from ovarian ablation/suppression. Given that few studies evaluated the role of ovarian ablation/suppression with modern chemotherapy and 5 years of tamoxifen, and fewer still have evaluated the role of AIs in premenopausal women, results from the SOFT trial will be instrumental in defining the role of ovarian suppression plus tamoxifen compared to tamoxifen alone with or without prior chemotherapy. The study will also identify the role of ovarian suppression and AIs compared to tamoxifen. For individuals where ovarian suppression is considered, initial results from the ABCSG 12 study comparing ovarian suppression with goserelin plus tamoxifen or anastrozole demonstrated that the disease-free and overall survival rates were equivalent between the two endocrine treatment–assigned groups (75). More recently, a 62-month follow-up revealed that there was no significant difference in disease-free survival between patients receiving tamoxifen alone or anastrozole alone (HR 1.08, 95% CI, 0.81–1.44; $p = .591$), but overall survival was worse in anastrozole-treated women compared to those receiving tamoxifen (HR 1.75, 95% CI, 1.08–2.83; $p = .02$) (76). Other studies such as TEXT will further assist in assessing the role of ovarian suppression and tamoxifen versus ovarian suppression and AI. Other studies evaluating the role of chemotherapy in premenopausal women receiving endocrine therapy were unfortunately closed prematurely due to poor accrual; these include Premenopausal Endocrine Responsive Chemotherapy Trial (PERCHE) and Premenopausal Optimal Management IS Endocrine therapy (PROMISE), meaning that this critical question is not likely to be addressed in a prospective randomized fashion.

At present single-agent tamoxifen is the standard approach for premenopausal women with hormone receptor–positive breast cancer. Ovarian suppression can be discussed with individual women with high-risk hormone receptor–positive breast cancer who retain or regain ovarian function after chemotherapy, especially those younger than age 40.

CHEMO ENDOCRINE THERAPY: CHEMOTHERAPY CONSIDERATIONS

Once a decision has been made that a woman with hormone receptor–positive breast cancer will receive chemotherapy, another question is whether a preferred chemotherapy agent or regimen should be considered. The EBCTCG demonstrated that polychemotherapy consistently continues to outperform single-agent therapy and that anthracycline-based therapy is superior to CMF-based regimens (1). In the 14 trials of chemotherapy plus tamoxifen versus the same chemotherapy alone, the EBCTCG reported a substantial reduction in risk of recurrence and death in those receiving chemo endocrine therapy, suggesting a benefit for the addition of tamoxifen to first- or second-generation chemotherapy regimens in women with hormone receptor–positive tumors (2). Furthermore, regimens that contain a higher cumulative anthracycline dose than in standard AC are superior to CMF, and sequential taxane following anthracycline-based therapy is superior to anthracycline-based therapy alone (3). As reviewed in Table 45-1, the superiority of each generation of treatment regimens is independent of hormone receptor status.

We have previously discussed the role of ER and HER2 as predictors of response to endocrine therapy. Others have evaluated the role of these markers as predictors of benefit from specific chemotherapy agents in women with ER-positive tumors. Cancer and Leukemia Group B (CALGB) investigators evaluated ER and HER2 status and benefit from adjuvant chemotherapy in 6,644 women included in three studies. In C8541, women received one of three CAF regimens, in C9344 participants received four doses of combination AC, with or without sequential paclitaxel, and in C9741 women received sequential doxorubicin, paclitaxel, and cyclophosphamide or AC followed by paclitaxel, administered every 2 or 3 weeks. Endocrine therapy was recommended but not mandated for hormone receptor–positive women enrolled in these trials. Overall, women with ER-negative tumors enjoyed greater benefits from chemotherapy compared with ER-positive tumors. The investigators then compared outcomes of women who received the most intense regimen in C9741 (chemotherapy administered every 2 weeks) to the low-dose CAF in C8541. They reported that 22.8% more ER-negative patients were disease-free at 5 years compared to 7.0% for ER-positive patients (77). ER-negative women also had an enhanced overall survival benefit at 5 years compared to ER-positive patients (improvement by 16.7% and 4.0%, respectively). Every 2 weeks AC followed by paclitaxel in C9741 lowered the rate of recurrence and death in ER-negative breast cancer by more than 50% compared to low-dose CAF used in C8541. The magnitude of benefit in ER-positive patients was more modest, with a 26% and 23% reduction in recurrence and death, respectively, compared to the benefits observed for patients with ER-negative disease.

The CALGB investigators have also evaluated whether hormone receptor and HER2 status predicted benefit from adjuvant doxorubicin doses higher than standard levels, or from the addition of paclitaxel to AC, or from both using tumor blocks from 1,322 of 1,500 women that were randomly selected from those previously enrolled in C9344. HER2 status was not predictive of response to doxorubicin in doses above 60 mg/m^2, but women with HER2-positive tumors were more likely to benefit from paclitaxel compared to those with HER2-negative disease (HR for recurrence of 0.59; $p = .01$), regardless of ER status (78). In contrast, women with HER2-negative, ER-positive tumors did not gain benefit from the addition of paclitaxel. These results suggest that patients with HER2-negative, ER-positive, node-positive breast cancer gained little value from the administration of paclitaxel following combination AC; however, since all women received AC, it is not clear whether the tumor phenotype is predictive of little benefit from chemotherapy in general. In addition, women with HER2-positive tumors are currently expected to receive anti-HER2 agents in addition to chemo endocrine therapy.

Several studies conducted in the 1990s evaluated the role of taxane administered either in combination with or following anthracycline-based regimens in the adjuvant setting. In E2197, 2,882 women with high-risk node-negative or 1-3 node-positive disease were randomized to AC or to AT. Disease-free and overall survival were identical. In an exploratory analysis of prespecified stratification factors by hormone receptor expression, the investigators observed a trend toward improved disease-free survival in women with hormone receptor–negative disease receiving AT (28). Other studies have not confirmed differences in outcomes by hormone report status. In Breast Cancer International Research Group (BCIRG) 001, the docetaxel, doxorubicin, and cyclophosphamide (TAC) combination was superior to FAC both in hormone receptor–negative and –positive women (79,80). In Spanish Breast Cancer Research Group GEICAM Study 9805, high-risk node-negative women were randomly assigned to six cycles of TAC or FAC. TAC was associated with improved disease-free (HR 0.68, 95% CI, 0.49–0.93; $p = .01$), regardless of hormone receptor status (81).

Other studies evaluated the role of taxane following anthracycline-based therapy. In B-28, NSABP investigators randomly assigned node-positive women to AC with or without sequential paclitaxel. AC followed by paclitaxel was associated with superior disease-free survival (RR 0.83, 95% CI, 0.72–0.95; $p = .006$), and a non-significant overall survival benefit (RR 0.93, 95% CI, 0.78–1.12; $p = .46$) (82). The benefit of paclitaxel was observed, regardless of hormone receptor status or tamoxifen administration. In GEICAM 9906, women with node-positive disease were randomly assigned to FEC or FEC followed by weekly paclitaxel; disease-free and overall survival were superior in the FEC followed by paclitaxel arm (83). Tumor samples from approximately 75% of participants were assessed for hormone receptor expression and HER2 amplification testing at a central laboratory; no statistically significant interaction between hormone receptor status or HER2 status and/or paclitaxel administration was observed.

Newer studies comparing anthracycline- and taxane-based regimens tested different combination or sequences. In NSABP B-30, disease-free and overall survival were superior in women receiving sequential-ACT compared with the doxorubicin and docetaxel and/or concurrent-ACT groups. The benefits were observed both in ER-negative and in ER-positive patients, regardless of hormone therapy use (72). BCIRG 005 investigators compared TAC versus AC followed sequentially by docetaxel in women with node-positive breast cancer. The two regimens provided similar disease-free and overall survival benefits, regardless of hormone receptor status (84). In a preliminary report of B-38, no differences in survival outcomes were observed among women receiving TAC versus dose-dense AC followed by dose-dense paclitaxel or dose-dense doxorubicin and cyclophosphamide followed by dose-dense paclitaxel and gemcitabine (85). Whether outcomes differ by hormone receptor status is not yet known.

In E1199, ECOG investigators evaluated optimal taxane use following four cycles of AC in women with node-positive or high-risk node-negative breast cancer. The women were randomly assigned to either paclitaxel or docetaxel administered either every 3 weeks for four cycles or weekly for 12 cycles. Disease-free survival and overall survival were improved with weekly paclitaxel compared to paclitaxel every 3 weeks. Docetaxel administered every 3 weeks was also associated with improved disease-free survival compared to every 3-week paclitaxel, but not overall survival. In an exploratory analysis of the influence of hormone receptor status and HER2 expression, improvements in disease-free and overall survival were observed with weekly paclitaxel in women with HER2-negative disease, regardless of the hormone receptor status (86). In C9741, an exploratory analysis suggested that women with hormone receptor–positive disease were not likely to gain additional benefit from a dose-dense schedule compared to women who received the same regimen on an every 3-week schedule (87).

Finally, newer studies compared outcomes of women treated with taxane-based therapy with or without an anthracycline. In a study of node-negative women who received four cycles of AC or docetaxel and cyclophosphamide (TC), TC was slightly superior to AC both in women with hormone receptor–positive and –negative tumors (88). Ongoing studies in women with node-positive or high-risk node-negative invasive breast cancer such as NSABP B-49 compare the TC combination to anthracycline-based chemotherapy regimens in HER2-negative disease.

Although not completely consistent, the data presented to date support the use of the same chemotherapy regimens for women at high risk of recurrence based on tumor characteristics or nodal status, regardless of hormone receptor status. Thus decisions about type of chemotherapy should continue to be made based on estimates of risk of recurrence and death without consideration of hormone receptor status.

Importantly, current and future studies will be likely enriched for women who are expected to benefit from chemo endocrine therapy compared to those included in older studies because of a more careful determination of tumor characteristics in addition to anatomical features. Therefore new studies may provide additional answers regarding optimal cytotoxic agents, regimens, and duration in women with hormone receptor–positive disease.

The role of hormone receptor status was also investigated in pivotal trials comparing outcomes following the administration of chemotherapy with or without trastuzumab. In the combined analysis of NSABP Trial B-31 and North Central Cancer Treatment Group (NCCTG) Trial N9831, women with HER2-positive tumors were randomly assigned AC followed by paclitaxel with or without trastuzumab. Trastuzumab was administered for a total of 52 weeks. Women randomized to trastuzumab had a significant improvement in disease-free and overall survival. The benefits were independent of hormone receptor status (89). In the Herceptin Adjuvant (HERA) (BIG 01-01) Trial, women with HER2-positive tumors were randomized to a minimum of four courses of (neo)adjuvant chemotherapy with or without 1 or 2 years of sequential trastuzumab. Adjuvant endocrine therapy was given after chemotherapy to the 52% of women with hormone receptor–positive disease. The magnitude of benefit was most significant in the hormone receptor–negative cohort; however, the investigators cautioned that survival benefits may emerge with further follow-up (90,91). Finally, in the BCIRG 006 study, women with HER2-positive early-stage breast cancer were randomly assigned to AC followed by docetaxel every 3 weeks with or without trastuzumab, or docetaxel and carboplatin with 52 weeks of trastuzumab. Disease-free survival and overall survival were improved in the trastuzumab-containing arms compared to the non-trastuzumab-containing arm. The two trastuzumab-containing regimens provided similar benefits. The improvement seen with trastuzumab was independent of the hormone-receptor status (92).

Together, these studies provide strong evidence that women with HER2-positive tumors benefit from trastuzumab-based regimens, regardless of hormone receptor status. As is the case with HER2-negative tumors, clinicians should consider the use of the same chemotherapy regimens for women at high risk of recurrence based on

tumor characteristics or nodal status without consideration of hormone receptor status.

DOSE, DURATION, AND SCHEDULE OF CHEMO ENDOCRINE THERAPY

Since data available to date have not specifically addressed dose and duration of either endocrine agents or chemotherapy regimens specifically in women prescribed chemo endocrine therapy, the optimal dose and duration of specific endocrine and chemotherapy regimens should be made based on the principles presented in Chapters 43 and 44, respectively. In brief, 5 years of tamoxifen is recommended to pre- or postmenopausal women who cannot take or tolerate AIs. Five additional years of tamoxifen may also be considered in select women (48). AIs should be administered as monotherapy for a total of 5 years or in sequence with tamoxifen for a total of 5 to 10 years of endocrine therapy for most postmenopausal women (61,62). Ovarian ablation/suppression may be considered in select young women with high-risk tumors or in premenopausal women who cannot take tamoxifen. The value of a first-, second-, or third-generation chemotherapy regimen should be discussed with an individual woman based on her tumor characteristics, estimates of recurrence, value added, and potential side effect profile with each type of regimen. There are no conclusive data suggesting that specific regimens or agents should or should not be recommended preferentially to women with hormone receptor–positive tumors.

Several studies investigated the question of sequential versus concurrent administration of chemo endocrine therapy, mainly using tamoxifen. The EBCTCG reported that the administration of chemotherapy and tamoxifen was superior to tamoxifen alone, whether administered concurrently (RR 0.62, SE 0.06) or sequentially (RR 0.71, SE 0.05, Table 45-4) (2). While concurrent use of chemotherapy and tamoxifen appears to be slightly better than sequential administration, the comparisons are indirect and do not represent results from prospective data trials.

The largest single study that has assessed the concurrent versus sequential use of tamoxifen and chemotherapy is Intergroup Trial 0100 in which concurrent CAF and tamoxifen (CAFT-T) was associated with inferior outcomes compared to CAF followed by tamoxifen (CAF-T). Disease-free survival at 8 years was 67% for CAF-T, 62% for CAFT-T, and 55% for tamoxifen alone (26). This direct comparison generated sufficient concern about concurrent chemo endocrine therapy that most modern studies have required that tamoxifen, and by extrapolation other endocrine therapies, would be administered after completion of adjuvant chemotherapy. Whether other endocrine therapies such as AIs or ovarian ablation/suppression should also be administered sequentially has not been investigated prospectively and it is unlikely that large randomized prospective data will become available. While it is possible that smaller studies in the neoadjuvant setting will address sequence questions prospectively, sequential administration appears to be the most cautious strategy in the absence of other randomized data. As we move toward a better identification of women with hormone receptor–positive disease who require chemotherapy, it is likely that women with truly hormone-sensitive disease will receive hormonal therapy earlier in the course of adjuvant therapy.

In summary, the selection of dose and duration of endocrine agents and chemotherapy regimens should be made independent of the decision to prescribe chemo endocrine therapy. Until other prospective data are available, chemotherapy should generally precede endocrine treatment.

TOXICITY OF ADJUVANT CHEMO ENDOCRINE THERAPY

Each endocrine agent and chemotherapy regimen is associated with specific toxicities that are reviewed in detail in other chapters. Women receiving both treatments will likely receive chemotherapy followed by the endocrine agent and will be subjected to the possible side effects of each. Whether the sequential administration of the treatments will lead to a different or greater side effect profile has not been evaluated in detail. It is noteworthy that the concomitant administration of endocrine therapies and chemotherapy, in particular tamoxifen, can be associated with increased risk of thromboembolic events compared to each modality given alone—another argument against concurrent chemo endocrine therapy.

Premenopausal women who receive chemotherapy who suffer treatment-related amenorrhea or ovarian failure may be more likely to report high prevalence and severity of menopausal symptoms compared to postmenopausal women or to their counterparts who have not received chemotherapy. Early menopause may also result in greater bone loss. Ovarian suppression following CAF (CAF-Z) was associated with a slightly higher risk for weight gain, hypertension, diabetes, anemia, and hot flashes. The addition of tamoxifen to CAF-Z slightly increases the incidence of diabetes, hot flashes, and anemia (71). Whether chemo endocrine therapy will have a detrimental effect on cognitive function compared to either approach alone is not known.

One concern is that women treated with chemotherapy agents that are associated with specific toxicities will have a prolonged or worsening symptomatology once the endocrine treatment is initiated. For example, anthracycline or trastuzumab-based therapy is associated with increased risk for cardiac toxicity and AIs may lead to a slight increase in cardiac events (89,90,92,93). Whether the administration of AIs following anthracycline or trastuzumab-based therapy will lead to a higher risk of cardiac events is not known. Likewise, women who receive chemotherapy, in particular taxane-based, may be more likely to report AI-associated musculoskeletal complaints (94–96). It is not known whether women who have suffered taxane-associated neurotoxicity are more likely to develop AI-associated neurotoxicity or musculoskeletal complaints.

SUMMARY AND FUTURE DIRECTIONS

Results from dozens of randomized clinical trials conducted over four decades have shaped the adjuvant treatment approaches used in our clinics every day. A greater understanding of tumor biology coupled with sophisticated assays allows us to make increasingly better informed recommendations to individual women. We now recognize that the decision to prescribe each individual type of treatment, including endocrine, chemotherapy, and anti-HER2 agents, or a combination, continues to be highly dependent on tumor size, nodal status, age, and menopausal status, but relies ever more heavily on intrinsic tumor subtype and other characteristics. Results from ongoing studies in women with hormone receptor–expressing tumors such as TAILORx, MINDACT, and RxPONDER will provide us with an even greater ability to prescribe a more individualized treatment. Likewise, a better understanding of host factors such as pharmacogenetics, and environmental factors such as diet or activity level, will lead to even better understanding of endocrine resistance and new methods to overcome it. Prospective studies should help generate a better

understanding whether specific regimens are more suitable to women with hormone receptor–positive disease who will also be receiving endocrine therapy.

Questions include not only whether specific chemotherapy regimens, dose, duration, or sequence are important, but also whether there is a group of women with tumors that are endocrine-resistant despite the expression of hormone receptors and who may not benefit from endocrine therapy either. Activation of tyrosine kinase receptors, for example, may predict for a more aggressive tumor phenotype and relative resistance to endocrine therapy. In these situations, although the estrogen-dependent growth is inhibited via endocrine manipulations, other growth signals stimulate proliferation and lead to relative endocrine resistance. Activation of other growth signals is usually associated with higher-grade tumors and those women have traditionally been offered cytotoxic-based therapy in addition to the endocrine manipulation. Data regarding combination approaches to target the estrogen-signaling pathways using multiple agents such as AIs and antiestrogens have been mixed and it is unlikely that other signaling pathways will be successfully blocked by this approach alone (20,21). Emerging results in the advanced, acquired endocrine-resistance setting provide strong support for prospective studies of novel targeted agents in the adjuvant setting in tumors with de novo endocrine resistance.

While studies in the metastatic setting support an improved benefit with the combination of agents that target ER and HER2, studies in the adjuvant setting using such combinations have not been conducted. Therefore, we cannot recommend the use of combinations of endocrine and anti-HER2 agents to women with early disease outside of clinical trials. However, given the strong evidence that the coexpression of hormone receptors and HER2 is associated with relative endocrine resistance, women in good health with hormone receptor–positive and HER2-positive tumors should be offered trastuzumab-based chemotherapy, as recommended in Chapter 47, followed by endocrine therapy.

Activation of the mammalian target of rapamycin (mTOR) intracellular signaling pathway contributes to endocrine resistance. A study of letrozole with or without temsirolimus in AI-naive patients with metastatic disease demonstrated no improvement in PFS (97). The recent BOLERO-2 study, however, revealed that women with hormone receptor–positive advanced breast cancer who have received a prior nonsteroidal AI had superior PFS with the combination of everolimus and exemestane compared to exemestane and placebo (10.6 and 4.1 months, respectively, by central assessment, HR = 0.36, 95% CI, 0.27–0.47; $p < .001$) (98). Everolimus is currently under study in the adjuvant setting. Activated protein kinases may also contribute to endocrine resistance. The CDK 4/6 inhibitor (PD0332991) was recently reported to provide a substantial improvement in PFS in combination with letrozole, over letrozole alone, in a randomized phase 2 clinical trial (99). Agents that reverse epigenetic modification may also overcome endocrine resistance (100). Preliminary data suggests that the addition of the histone deacetylase inhibitor entinostat to an AI may provide superior survival benefits and definitive studies are planned (101). Finally, studies evaluating the role of genetic variants in predicting differential response to endocrine therapies may also lead to identification of a subgroup of women that may benefit from modification of endocrine therapy (102).

In closing, given the substantial benefits observed from both chemotherapy and endocrine therapy, it is likely that in the next decade almost every woman with hormone receptor–positive tumors will receive endocrine agents, and those with predictors of endocrine resistance will receive chemo endocrine therapy. However, enhanced understanding of tumor biology and mechanisms of endocrine resistance has already led the way into new trial designs in which targeted treatments are investigated. Studies in the adjuvant or neoadjuvant settings will not only investigate early predictors of response and resistance, but will also attempt to integrate new targeted therapies or agents that enhance sensitivity or reverse resistance. Indeed, new generations of clinical trials will incorporate tumor-intrinsic subtype and host factors more commonly than ever before.

MANAGEMENT SUMMARY

- Every woman with an invasive primary tumor that expresses estrogen or progesterone receptor protein should be considered for endocrine therapy.
  - Selection of the type of endocrine manipulation varies by menopausal status and is discussed in detail in Chapter 43.
- The recommendation for endocrine therapy should be made, regardless of the decision whether or not to administer chemotherapy. Use of chemotherapy should be based on the guidelines discussed in detail in Chapter 44.
  - At present, data suggest that the addition of chemotherapy should be considered for women with high risk of recurrence based on anatomic stage and specific tumor characteristics. For example, the absence of the progesterone receptor and/or the overexpression of the HER2 receptor or a high Recurrence Score may indicate a relative endocrine resistance and drive a decision to use chemotherapy.
  - The decision regarding type and duration of chemotherapy should be independent of the hormone receptor status. Data today suggest that polychemotherapy with anthracycline and/or taxane-based regimen is superior to other therapies. The available data support the use of the same regimen for women at high risk for a systemic recurrence, regardless of hormone receptor status.
- When chemo endocrine therapy is recommended, sequential rather than concurrent administration appears to be the most prudent strategy.

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CHAPTER 46

Adjuvant and Preoperative Systemic Therapy for HER2-Positive Breast Cancer

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CHAPTER CONTENTS

INTRODUCTION

HER2/neu is a member of the ErbB family of transmembrane tyrosine kinases. The family includes the epidermal growth factor receptor (EGFR), HER2, HER3, and HER4. HER2 is activated through dimerization, either with other HER2 proteins (homodimerization) or with other HER family members (heterodimerization). Once activated, HER2 potently initiates downstream signaling, including signaling through the PI3-kinase and MAP kinase pathways. As a result, HER2 activation produces an array of cellular changes leading to increased proliferation, invasiveness, angiogenesis, and enhanced survival.

Amplification of the HER2 gene occurs in approximately 20% of breast cancers (1,2). This amplification causes marked overexpression of HER2 protein on the cell surface—typically over a million HER2 proteins per cell (3)—and leads to constitutive activation of HER2 signaling. HER2 amplified breast cancers are typically highly proliferative and are associated with adverse clinical behavior. In the absence of systemic adjuvant therapy, HER2 amplification is independently associated with a greater risk of disease recurrence in both node negative and node positive cancers (4–7). Several studies have also demonstrated that HER2 amplification is a negative prognostic feature for cancers ≤1 cm (8,9).

Despite its negative prognostic effects, HER2 amplification and/or overexpression predicts sensitivity to several classes of chemotherapy. In Cancer and Leukemia Group B 9344, a phase III adjuvant study in patients with node positive disease in which patients were randomized to four cycles of AC (doxorubicin/cyclophosphamide) alone or AC followed by four cycles of paclitaxel, HER2 overexpression was associated with a significant benefit from the addition of the paclitaxel (10). Similar findings were observed in a phase III metastatic trial comparing epirubicin/paclitaxel (ET) with epirubicin/cyclophosphamide (EC). In that study, patients with HER2-positive cancers who received ET had improved progression-free survival and overall survival relative to the patients with HER2-positive cancers who received EC (11).

HER2-positive cancers also demonstrate specific sensitivity to anthracyclines. In MA.5, a randomized phase III adjuvant study in patients with node positive disease in which patients received either cyclophosphamide/methotrexate/fluorouracil (CMF) or cyclophosphamide/epirubicin/fluorouracil (CEF), patients with HER2-positive cancers had improved relapse-free survival (hazard ratio [HR] = 0.52, 95% CI, 0.34–0.80; p = .003) and overall survival (HR = 0.65, 95% CI, 0.42–1.02; p = .06) with the anthracycline regimen (12). Patients with HER2 negative cancers did not have an improvement in outcome with the anthracycline (interaction p value p = .01) (12). A meta-analysis of eight randomized studies comparing anthracycline-based regimens to non-anthracycline regimens (total n = 6564) also demonstrated that anthracyclines were superior to non-anthracycline regimens in HER2-positive cancers (HR of death from any cause = 0.73, 95% CI, 0.62–0.85; p < .001), while no benefit was observed in HER2-negative cancers (HR of death from any cause = 1.03, 95% CI, 0.92–1.16; p = .6) (13). The interaction

between HER2 status and anthracycline benefit was significant (chi-square statistic for overall survival = 12.6; $p < .001$) (13).

The preclinical data pointing to the importance of HER2 signaling together with the clinical data demonstrating the poor prognostic effect of HER2 amplification sparked interest in utilizing HER2 as a therapeutic target. This idea led to the development of trastuzumab, a humanized monoclonal antibody specific for the extracellular domain of HER2. In preclinical studies, trastuzumab demonstrated multiple potential mechanisms of action, including inhibition of HER2 signal transduction, induction of antibody-dependent cell-mediated cytotoxicity (ADCC), and inhibition of shedding of the HER2 extracellular domain (reviewed in [14]). The clinical effectiveness of trastuzumab was evaluated in a pivotal phase III study in patients with HER2-positive metastatic breast cancer who were randomized to chemotherapy with or without trastuzumab. The chemotherapy backbone was either paclitaxel or AC, depending on whether patients had previously been exposed to anthracycline treatment. The addition of trastuzumab to chemotherapy markedly improved outcomes, with a longer time to disease progression (median, 7.4 months vs. 4.6 months; $p < .001$) and overall survival (25.1 months vs. 20.3 months; $p = .01$) compared to chemotherapy alone. (15) The benefits of trastuzumab were associated with minimal increases in toxicity, with one notable exception—the addition of trastuzumab to the anthracycline regimen caused a high incidence of symptomatic cardiomyopathy (16% had New York Heart Association class III or IV cardiac dysfunction) (15). Patients who received trastuzumab with paclitaxel (all of whom had previously received an anthracycline) had a much lower rate of severe cardiac toxicity (2%). The unequivocal benefits of trastuzumab in combination with a taxane led to the widespread use of taxane–trastuzumab combinations for patients with HER2-positive metastatic breast cancer. The synergistic benefits of trastuzumab with chemotherapy were subsequently shown to extend across a wide range of regimens. In addition, two randomized clinical trials demonstrated that continuation of trastuzumab after disease progression on a prior trastuzumab regimen is beneficial (16,17). These studies have far reaching clinical and biologic significance, and as a result, trastuzumab based combinations are widely used in multiple lines of therapy for HER2-positive metastatic breast cancer.

The clinical benefits of trastuzumab observed in these trials provided definitive proof that targeting HER2 was an effective approach in HER2-positive breast cancer. This demonstration led to the successful development of other HER2-targeted agents, such as the EGFR/HER2 tyrosine kinase inhibitor lapatinib, the HER2 specific monoclonal antibody pertuzumab, and the antibody drug conjugate trastuzumab emtansine. All three of these agents have significant activity in patients with HER2-positive metastatic breast cancer, either combined with chemotherapy or hormonal therapy (in the case of lapatinib), combined with trastuzumab and chemotherapy (in the case of pertuzumab), or as monotherapy with trastuzumab emtansine.

The benefits of trastuzumab seen in patients with metastatic disease also provided the rationale to evaluate this agent in the adjuvant and neoadjuvant settings. In 2005, initial results from the first three phase III adjuvant trials of trastuzumab were reported, demonstrating significant improvements in disease-free survival, and ultimately overall survival, with the addition of trastuzumab to chemotherapy in the adjuvant setting. The improvements in outcome were so impressive that adjuvant trastuzumab became the standard of care within weeks after the trial results were presented. This chapter will review these adjuvant studies and subsequent randomized adjuvant trials of HER2 directed therapy. In addition, the chapter will discuss the results of smaller neoadjuvant trials as well as future directions in the treatment of early stage HER2-positive breast cancer.

BENEFIT OF TRASTUZUMAB IN THE ADJUVANT TREATMENT OF HER2-POSITIVE BREAST CANCER

Six randomized phase III studies have evaluated the addition of trastuzumab to chemotherapy in the adjuvant setting. The details of these studies are summarized in Tables 46-1 and 46-2. All of the studies were restricted to patients with HER2-positive cancers, although the definition of HER2 positivity and the requirement for central testing differed across the trials. All the studies focused on a relatively high-risk population (node positive or high-risk node negative) and all except FinHer included at least one year of trastuzumab.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-31 and North Central Cancer Treatment Group (NCCTG) N9831 were both conducted in North America and shared similar designs. The chemotherapy backbone consisted of four cycles of AC followed by paclitaxel. In B-31, the paclitaxel was given as 175 mg/m^2 every 3 weeks × 4 cycles, and in N9831 it was administered weekly for 12 weeks. Trastuzumab was administered concurrently with paclitaxel and was continued for a total of one year. In N9831, a third arm was included in which the year of trastuzumab was delayed until the completion of all chemotherapy. Because of the similarities of the trial designs, the investigators performed a pooled analysis of the two trials, combining the two control arms and the two investigational arms that involved concurrent administration of trastuzumab and paclitaxel. Patients from N9831 who received sequential paclitaxel followed by trastuzumab were excluded from this analysis. A total of 3,351 patients (1,679 in combined control group and 1,672 in combined trastuzumab group) were included. Both studies initially excluded node negative patients, but ultimately the N9831 trial was amended to include high-risk node negative patients (defined as a tumor >2 cm for hormone receptor positive cancers and tumor >1 cm for hormone receptor negative cancers), but less than 6% of the patients in the combined analysis had node negative disease.

The results from this analysis were initially presented after 2.0 years median follow-up because the results had crossed an early-stopping boundary. At that time, there were 261 DFS events in the control group and 133 in the trastuzumab group. This difference translated to a hazard ratio of 0.48 (95% CI, 0.39 to 0.59; $p < .0001$) (18). The addition of trastuzumab was also associated with a 33% reduction in the risk of death ($p = .015$) (18). The improvement in outcome seen with the addition of trastuzumab led to the approval of trastuzumab by the United States Food and Drug Administration (FDA) in 2006.

More recently, the final results from the pooled analysis of N9831/B31 were presented with 8.4 years median follow-up. With this additional follow-up, the relative benefits of trastuzumab remain robust with a 40% reduction in DFS events (HR = 0.60, 95% CI, 0.53–0.68; $p < .0001$) (19). The absolute improvement in DFS is 11.5%, and the majority of the events (8.2%) were distant recurrences. Overall survival was also meaningfully improved with the addition of trastuzumab with a HR = 0.63, 95% CI, 0.54–0.73; $p < .0001$, corresponding to an increase from 74.2% in the control arm to 82.0% in the trastuzumab arm (19). Because of the clear benefit of trastuzumab observed in the first pooled analysis in 2005, patients on the control arm of the study were offered treatment with one year of trastuzumab. A total of 413 women (20.4%) in the combined control arm elected to receive trastuzumab. These patients are included in this final analysis according to intention to treat, and if anything, this crossover would lead to an underestimation of the true benefit of trastuzumab.

TABLE 46-1

Efficacy Results of Adjuvant Studies of Trastuzumab in HER2-Positive Early Breast Cancer

Study	*Patients (N)*	*Patient Characteristics*	*Treatment Regimens*	*Primary End Point*	*Median Follow-Up (yr)*	*DFS HR (CI; p value)*	*OS HR (CI; p value)*
NSABP B-31/ Intergroup N9831 Joint Analysis (19)	4,046	Node-positive[a]	AC × 4 →P × 4 AC × 4 →P × 4 + T[b] (T started concurrently with P)	DFS	8.4	0.60 (CI, 0.53–0.68, $p < .0001$)	0.63 (CI, 0.54–0.73, $p < .0001$)
HERA (38)	5,102	All except small (<1 cm) node-negative	Chemotherapy (CT) alone T for 1 yr after completion of CT T for 2 yr after completion of CT	DFS	8	0.76 ($p < .0001$)	0.76 ($p < .0005$)
BCIRG 006 (22)	3,222	Node-positive or high risk node-negative	AC × 4 →D × 4 (I) AC × 4 →D × 4 + T (II) D + Cb × 6 + T (III)	DFS	5.4	0.64 (II vs. I) ($p < .0001$) 0.75 (III vs. I) ($p = .04$)	0.63 (II vs. I) ($p < .001$) 0.77 (III vs. I) ($p = .04$)
FinHer (37)	232	Node-positive or high risk node-negative	V or D × 3 with or without T 9 wk followed by FEC × 3	DDFS	5.2	0.65 (CI, 0.38–1.12, $p = .12$)	0.55 (CI, 0.27–1.11) ($p = .09$)
PACS-04 (24)	528	Node-positive	FEC × 6 or ED × 6 with or without T	DFS	3.9	0.86 (CI, 0.61–1.22, $p = .41$)	1.27 (CI, 0.68–2.38, $p = NS$)

AC, doxorubicin; BCIRG, Breast Cancer International Research Group; Cb, carboplatin; CI, confidence interval; D, docetaxel; DFS, disease-free survival; ED, epirubicin, docetaxel; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; HERA, HERceptin Adjuvant; HR, hazard ratio; NSABP, National Surgical Adjuvant Breast and Bowel Project; PACS, Protocole Adjuvant dans le cancer du sein; OS, overall survival; P, paclitaxel; RFS, relapse-free survival; T, trastuzumab; V, Vinorelbine. NS, not significant.
[a]N9831 included a small percentage of node negative patients (5.7% overall).
[b]In B31 the paclitaxel was given every 3 weeks for four cycles. In N9831, paclitaxel was weekly × 12.
Adapted from de Azambuja E, Piccart M. Adjuvant treatment of ERBB2 positive breast cancer. In: Morrow M, Harris JR, Lippman ME, Osborne CK, eds. *Diseases of the Breast*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2011. (Ref. 90.)

The largest adjuvant trastuzumab trial was HERA (Herceptin Adjuvant), a global, but non-U.S. trial that included a total of 5,081 evaluable patients. Like the joint analysis of N9831/B31, initial results from HERA were also reported in 2005.The study population of HERA was more heterogeneous than N9831/B31. The eligibility criteria were relatively broad, allowing both node positive and node negative patients as long as tumor size was at least 1 cm. Overall, approximately 32% of patients on the trial had negative nodes. The chemotherapy backbone in HERA was not specified apart from requiring that patients receive at least four cycles of treatment. Ninety-four percent received an anthracycline-based regimen and 26% also received a taxane. The HERA study design differed from the pooled analysis of N9831/B31 in that trastuzumab therapy was initiated after completion of all chemotherapy. The trastuzumab, which was given every 3 weeks, was mandated to begin no more than 7 weeks from day 1 of the conclusion of chemotherapy or 6 weeks from the completion of radiation or definitive surgery, whichever was last. Unlike the North American trials, HERA asked a duration question, with participants randomized to 1 or 2 years of trastuzumab, or observation.

The initial publication of HERA in 2005 reported the results of 1 year of trastuzumab versus the observation group. This first interim analysis crossed the prespecified early stopping boundary with a median follow-up of only 1 year. In that analysis, there were 127 DFS events in the 1 year of trastuzumab arm compared to 220 events in the observation arm (20). The hazard ratio for DFS events was 0.54 (95% CI, 0.43–0.67; $p < .0001$) (20). There was no significant effect on survival with the short follow-up time. A subsequent analysis with 8 years median follow-up continued to demonstrate improved DFS associated with 1 year of trastuzumab therapy (HR = 0.76; $p < .0001$) as well as a significant survival benefit (HR = 0.76; $p = .0005$) (21). As was the case with the North American trials, patients on the observation group were offered 1 year of trastuzumab; fully 52% crossed over, which presumably had an effect on the observed benefit of trastuzumab.

The Breast Cancer International Research Group (BCIRG) conducted the fourth large randomized trial evaluating trastuzumab in the adjuvant setting. This global study was unique in that it included an arm with a non-anthracycline regimen. Participants were randomized to a control arm of four cycles of AC followed by four cycles of docetaxel (100 mg/m^2) every 3 weeks, or the same regimen with 1 year of trastuzumab starting with the first dose of docetaxel. There was also a third arm on which patients received docetaxel (100 mg/m^2) and carboplatin (area under the curve of 6 mg/mL/min) given every 3 weeks for six cycles

TABLE 46-2

Study Design and Demographic Characteristics of the Trastuzumab Adjuvant Trials

	HERA	*NSABP B-31/N9831 Joint Analysis*	*BCIRG 006*	*FinHer*	*PACS-04*
Trastuzumab schedule	Every 3 weeks	Weekly/weekly	Weekly with CT, then every 3 weeks	Weekly	Every 3 weeks
Sequential or concurrent T	Sequential	Concurrent[a]	Concurrent	Concurrent	Sequential
HER2 testing	Centralized IHC ± FISH	Centralized IHC and FISH[f]	Centralized FISH	Centralized CISH	Centralized IHC ± FISH
Age <50 years (%)	51	50	52	NR	NR
Node-negative (%)	32[b]	6	29[c]	16[d]	0
Grade 3 tumors	60	69	NA	64	66
Taxane-based CT	26	100	100	50	50
ER + and/or PR +	47	58	54	46[e]	58
Baseline LVEF assessment	At completion of CT and RT	At completion of 4 AC	After surgery	After surgery	At completion of CT and RT
Cross-over to trastuzumab after first analysis (%)	50	20.9	1.6	NA	NA

AC, doxorubicin, cyclophosphamide; CISH, chromogenic in situ hybridization; CT, chemotherapy; ER estrogen receptor; FISH, fluorescence in hybridization; IHC, immunohistochemistry; LVEF, left ventricular ejection function; NA, not applicable; NR, not reported; PACS, Protocole Adjuvant dans le cancer du sein; PR, progesterone receptor; RT, radiotherapy.
[a]N9831 had a sequential arm but this was not included in the joint analysis.
[b]Only if tumor size >1cm.
[c]Only if at least one concomitant risk factor (grade >1, hormone receptor negative, tumor >2 cm, age <35y).
[d]Only if size >20 mm and PR negative.
[e]ER positive only.
[f]Initially local *HER2* testing was permitted, but the protocols were amended to require centralized testing.
Adapted from de Azambuja E, Piccart M. Adjuvant treatment of ERBB2 positive breast cancer. In: Morrow M, Harris JR, Lippman ME, Osborne CK, eds. *Diseases of the Breast*. 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2011. (Ref. 90.)

concurrently with trastuzumab (TCH). For both of the trastuzumab arms, the trastuzumab was given weekly during the chemotherapy and then every 3 weeks to complete 1 year. The trial had broad entry criteria and included both node positive and high-risk node negative (defined as having at least one of the following criteria: tumor size >2 cm, ER and PR negative, histologic and/or nuclear grade 2–3, or age <35 years) patients. A total of 3,222 patients were enrolled, of whom approximately 29% were node negative.

The primary endpoint of BCIRG- 006 was disease free survival. Recently, a protocol-specified analysis of the study was reported after 656 DFS events had occurred. Both trastuzumab containing arms demonstrated significantly improved DFS and overall survival relative to the AC/docetaxel control arm of the study. The 5-year disease-free survival rate was 75% for AC/docetaxel, 81% for TCH, and 84% for AC/docetaxel/trastuzumab (22). This corresponds to a hazard ratio for the comparison of TCH and ACTH with AC/docetaxel of 0.75; $p = .04$, and 0.64; $p < .001$ respectively. The 5-year overall survival rate was 87% for AC/docetaxel, 91% for TCH, and 92% for AC/docetaxel/trastuzumab. This corresponds to a hazard ratio for the comparison of TCH with AC/docetaxel of 0.77; $p = .04$, and AC/docetaxel/trastuzumab with AC/docetaxel of 0.63; $p < .001$ (22). Unlike the N9831/B31 and HERA studies, very few patients (1.6%) on the control arm of BCIRG 006 crossed over to receive trastuzumab, so this issue did not significantly affect the impact of trastuzumab on outcomes in this study. The differences in DFS and overall survival between TCH and AC/docetaxel/trastuzumab were not significant. The study had only limited power to detect large differences in outcome between the two trastuzumab-containing arms. While both trastuzumab-containing arms were better than the control, the anthracycline containing arm has a numeric advantage in terms of both DFS and OS. Importantly, the results do not prove equivalence of TCH to ACTH.

Two smaller randomized trials have also evaluated the adjuvant use of trastuzumab. Both the FinHer study and FNCLCC-PACS 04 study evaluated trastuzumab in the subset of patients with HER2-positive cancers (232 patients in FinHer, 528 in PACS 04) as part of larger studies comparing different chemotherapy regimens. FinHer was noteworthy for two reasons. First, the chemotherapy backbone consisted of a randomization to either vinorelbine (25 mg/m^2 weekly for 9 weeks) or docetaxel (100 mg/m^2 every 21 days), both followed by three cycles of FEC (fluorouracil 600 mg/m^2, epirubicin 60 mg/m^2, and cyclophosphamide 600 mg/m^2 every 21 days). Second, patients with HER2-positive cancers randomized to trastuzumab received weekly therapy for only 9 weeks, concurrent with either the vinorelbine or docetaxel. Despite the short duration, patients who received trastuzumab had an improved recurrence-free survival (RFS) at 3 years compared to those who were randomized to chemotherapy alone (89% vs. 78%; HR = 0.42; 95% CI, 0.21–0.83; $p = .01$) (23).

In PACS04, patients with node positive, HER2-positive cancers received either six cycles of FEC (fluorouracil 500 mg/m^2, epirubicin 100 mg/m^2, and cyclophosphamide 500 mg/m^2) or ED (epirubicin 75 mg/m^2 and docetaxel 75 mg/m^2)

every 3 weeks. A second randomization was to either observation or a year of trastuzumab (given every 3 weeks) starting after completion of the chemotherapy. In this study, the addition of trastuzumab was associated with only a minimal improvement in DFS (HR = 0.86, 95% CI, 0.61–1.22), which was not statistically significant (p = .41) (24).

BENEFIT OF TRASTUZUMAB IN THE NEOADJUVANT TREATMENT OF HER2-POSITIVE EARLY-STAGE BREAST CANCER

The clear benefit of trastuzumab in patients with metastatic disease sparked interest in evaluating trastuzumab in the neoadjuvant setting. While several small, single-arm studies demonstrated that preoperative treatment with the combination of trastuzumab and chemotherapy was feasible and active (25,26), the first randomized trial to show a benefit to trastuzumab was conducted by the MD Anderson Cancer Center. Buzdar and colleagues randomized patients with operable stage II–IIIA HER2-positive cancers to either four cycles of paclitaxel (225 mg/m^2 as a 24-hour infusion every 3 weeks) followed by four cycles of FEC (500 mg/m^2 fluorouracil on days 1 and 4, 500 mg/m^2 IV cyclophosphamide and 75 mg/m^2 epirubicin on day 1 only of a 3-week cycle) or the same chemotherapy regimen combined with weekly trastuzumab. The trastuzumab was started concurrent with the taxane and continued throughout the chemotherapy (24 weeks). The primary objective of the study was to compare the rate of pathological complete response (pCR, defined as no residual invasive cancer in the breast or axillary nodes) between the two arms. Although the study planned to enroll 164 patients, accrual was terminated after 42 patients were randomized because a large difference in pCR rates was observed. 26.3% of patients who received chemotherapy alone had a pCR compared to 65.2% of patients who received chemotherapy with trastuzumab (27). Despite the small sample size, this difference in pCR rates was significant (p = .016). A cohort of 22 patients was subsequently enrolled and treated in a uniform fashion with the same chemotherapy and trastuzumab regimen. The pCR of this cohort was 54.5% (28). After a median follow-up of 36 months, the 3-year disease-free survival for those patients randomized to chemotherapy alone was 85.3% while no patients randomized to the trastuzumab arm had recurred (p = .041 for the comparison between arms) (28).

The benefit of neoadjuvant trastuzumab was confirmed in the larger phase III NOAH (Neoadjuvant Herceptin) trial. In this study, 235 patients with HER2-positive locally advanced (T3N1 or T4 or N2/N3, or ipsilateral supraclavicular node involvement) breast cancer received a multiagent chemotherapy regimen consisting of doxorubicin 60 mg/m^2 and paclitaxel 150 mg/m^2 every 3 weeks for three cycles, followed by paclitaxel 175 mg/m^2 administered every 3 weeks for four cycles. Cyclophosphamide (600 mg/m^2), methotrexate (40 mg/m^2), and fluorouracil (600 mg/m^2) were then given on days 1 and 8 every 4 weeks for three cycles. Those patients randomized to the trastuzumab arm received the antibody every 3 weeks concurrent with the entire chemotherapy regimen. They also received trastuzumab postoperatively to complete a total of 1 year of trastuzumab therapy.

Similar to the results from the MD Anderson study, the addition of trastuzumab in NOAH led to a marked improvement in pCR rates—19% for patients who received chemotherapy alone compared to 38% for those who received chemotherapy and trastuzumab (29). With a median follow-up of 3.2 years, long-term outcomes were also improved with trastuzumab. Three-year event-free survival (defined as disease recurrence or progression, or death from any cause) was 71% (95% CI, 61–78; n = 36 events) among patients randomized to trastuzumab, vs. 56% (46–65; n = 51 events) for the patients who received chemotherapy alone (29). This difference was statistically significant with a hazard ratio of 0.59 (95% CI, 0.38–0.90; p = .013). Because of the clear benefit of trastuzumab demonstrated in the MD Anderson and NOAH neoadjuvant studies, as well as similar benefits seen in the adjuvant trials discussed earlier, all subsequent neoadjuvant trials included HER2-directed in all arms.

CARDIAC TOXICITY OF TRASTUZUMAB

In general, trastuzumab is well tolerated. In the randomized studies, rates of adverse events were similar in patients assigned to receive trastuzumab relative to that of the control group (18,20,22). However, as previously discussed, the pivotal metastatic study demonstrated significant evidence of cardiac toxicity with trastuzumab, particularly when combined with an anthracycline. Because of this observation, all of the adjuvant studies and many of the early neoadjuvant studies avoided concurrent use of trastuzumab with an anthracycline and required confirmation of an adequate left ventricular ejection fraction (LVEF) prior to a patient's initiating the trastuzumab. In addition, all of these trials included extensive cardiac monitoring. The data from these randomized studies thus provide valuable information regarding the cardiac effects of trastuzumab in patients with early-stage disease, including quantification of the absolute risk of cardiac toxicity, identification of treatment regimens that are more likely to be associated with cardiac effects, and characterization of risk factors that predict a higher likelihood of cardiac toxicity.

There is no question that trastuzumab, particularly when given in conjunction with an anthracycline-based regimen, does have the potential to cause cardiac toxicity in the adjuvant setting (summarized in Table 46-3), but the absolute incidence of significant toxicity is low and the rates vary substantially across the trials. While cross-trial comparisons are complicated by the varied definition of cardiac events used in the individual studies and possible differences in the patient populations, the highest rate of symptomatic cardiac events (NYHA class III/IV CHF) was generally seen in studies in which patients received an anthracycline within weeks of initiation of trastuzumab. In N9831, NSABP B31, and the BCIRG trial, the rates of significant cardiac toxicity when a taxane–trastuzumab regimen was administered immediately following AC were 2.9%, 4.1%, and 2.0% respectively (18,22). Patients on the TCH arm of BCIRG 006 had the lowest rate of cardiac toxicity (0.4%) (22). Interestingly, the rate of symptomatic cardiac events in patients randomized to trastuzumab in HERA (0.5%) appeared lower than that of the other trials despite the fact that 94% of patients on HERA received an anthracycline prior to the trastuzumab (20). There are several possible explanations for this observation. Of note, HERA required a LVEF of ≥55% to begin trastuzumab whereas most of the other studies required an LVEF of >50%. This difference may be particularly relevant given that several studies suggest that a baseline LVEF <55% increases the risk of trastuzumab-induced cardiotoxicity (30–32). Another difference is that because HERA required participants to complete chemotherapy and radiotherapy before randomization, there was a longer delay between completing chemotherapy and initiation of trastuzumab relative to the other studies. The majority of patients in HERA did not

TABLE 46-3

Cardiac Safety Results in Adjuvant Trastuzumab Trials

	HERA (20)		*NSABP B-31 (18)*		*NCCTG N9831 (30)*			*BCIRG 006 (22)*			*PACS-04 (24)*	
Treatment arms	Obs	1-yr H	AC→P	AC→PH	AC→P	AC→P→H	AC→PH	AC→D	AC→DH	DCb+H	Obs	1-yr H
Women at risk (n)	1,710	1,677	872	864	664	710	570	1,050	1,068	1,056	268	260
Follow-up (yr)	1		2.4		3			5.4			3.9	
Cardiac death or CHF NYHA class 3-4 (%)	0.1	0.54	0.8	4.1	0.3	2.8	3.3	0.7	2.0	0.4	0.4	1.5

AC, doxorubicin, cyclophosphamide; BCIRG, Breast Cancer International Research Group; Cb, carboplatin; CHF, congestive heart failure; D, docetaxel; H, Herceptin (trastuzumab); HERA, HERceptin Adjuvant; NSABP, National surgical Adjuvant Breast and Bowel Project; NYHA, New York Heart Association, Obs, observation; PACS, Protocole Adjuvant dans le cancer du sein; OS, overall survival; P, paclitaxel.
Note: No CHF class 3-4 and no cardiac deaths reported in the FinHer trial.
Adapted from de Azambuja E, Piccart M. Adjuvant treatment of ERBB2 positive breast cancer. In: Morrow M, Harris JR, Lippman ME, Osborne CK, eds. *Diseases of the Breast.* 4th ed. Philadelphia, PA: Lippincott Williams & Wilkins, 2011. (Ref. 90.)

receive a taxane, in contrast to the other large studies in which taxanes were given to all patients. There are however, no data that clearly implicate prior receipt of a taxane as a risk factor for trastuzumab induced cardiac toxicity. Lastly, it has been postulated that HERA's purely sequential design may have contributed to its low cardiac toxicity rate by extending the time interval between the anthracycline and initiation of trastuzumab. However, given the similar rates of significant cardiac events in the sequential (2.8%) and concurrent (3.3%) arms of N9831 (30), the only randomized comparison of the two approaches, it seems unlikely that the sequential design of HERA was the primary reason for its relative lack of serious cardiac toxicity.

Several studies have sought to identify patient characteristics that predict an increased likelihood of developing trastuzumab-induced cardiotoxicity. In a univariate analysis of data from the N9831 study, age ≥60, prior or current use of antihypertensive medications, and baseline LVEF <55% were all associated with increased risk of cardiac events within 3 years. (30) A similar analysis from the NSABP B-31 data again found age (50–59 years, HR = 2.43, ≥60, HR = 2.73), use of hypertension medications (HR = 2.1), baseline LVEF 50%–54% (HR = 6.7), and post-AC LVEF (55%–64% HR = 3.6, 50%–54% HR = 11.8) associated with increased cardiac risk. (31) A multivariate analysis has also been performed in the combined N9831/B-31 database with age >50 years and baseline LVEF identified as independent predictors of cardiac events. (32)

A recent report with extended follow-up (7 years) of NSABP B-31 provides insight into the timing and long-term outcomes of trastuzumab-induced cardiotoxicity. In this analysis, a total of 37 (4.0%) of 944 patients treated on the trastuzumab arm of the study experienced a significant cardiac event (defined as cardiac death or CHF with a decrease LVEF of greater than 10% to a value <55% or a decrease of greater than 5% to a value below the lower limit of normal) compared to 1.3% of patients who received chemotherapy alone (31). There was one cardiac death in each arm. The vast majority of cardiac events occurred during the first year of trastuzumab therapy, and only two events occurred more than 2 years from the initiation of trastuzumab. Thus, at this time, there is no clear evidence to suggest that trastuzumab therapy is associated with delayed-onset cardiotoxicity. In patients who do develop cardiotoxicity while on trastuzumab, it appears to be reversible in most cases. Of the 37 trastuzumab-treated patients who developed a significant cardiac event on B-31, 33 were no longer symptomatic when assessed 6 months after the event, although most remained on cardiac medications (31). When assessed at least 6 months after the cardiac event, 25 of the 37 patients had an LVEF that was lower than their initial baseline, all but 21 of these patients had recovered to at least 50% (31).

As discussed previously, all of the large randomized trials included extensive cardiac monitoring, typically with LVEF evaluations at baseline and approximately every 3 months while patients were receiving trastuzumab. The studies also employed strict stopping rules for trastuzumab therapy based on defined decreases in LVEF. This approach was developed before the benefits of trastuzumab in the adjuvant setting had been demonstrated. Given the low absolute rates of clinically significant cardiac toxicity, particularly in patients without risk factors for this toxicity, the substantial benefits of adjuvant trastuzumab, and the reversibility of most cardiac toxicity, it is not clear that such extensive cardiac monitoring and strict trastuzumab stopping rules are necessary. One can argue that the cardiac safety of adjuvant trastuzumab was established in the context of strict monitoring and dose interruption, but in the absence of symptoms, it is not clear that the best interests of patients are served by dose interruption for minor changes in the ejection fraction. Unfortunately, it is unlikely that this question will ever be answered in a randomized trial. In our view, cardiac function should be evaluated prior to initiating trastuzumab and at some regular intervals during therapy. Physicians should carefully consider the potential benefits of trastuzumab in the individual patient before discontinuing it in patients who are asymptomatic and do not have major reductions in their cardiac function. Patients with risk factors for trastuzumab-induced cardiac toxicity need more extensive monitoring.

It is intriguing that despite data from the pivotal metastatic trial demonstrating that concurrent therapy with an anthracycline and trastuzumab is associated with significant cardiotoxicity, several neoadjuvant studies treated patients with concurrent anthracycline and trastuzumab without substantial cardiac toxicity. In NOAH, participants received a total of 180 mg per square meter of doxorubicin, while in the MD Anderson study, a total of 300 mg per square meter of epirubicin was given. Two of the 117 patients treated with trastuzumab and anthracycline on the NOAH study and none of the 45 patients treated on the MD Anderson study

developed clinically significant cardiac toxicity (28,29). More recently, in the GeparQuattro and GeparQuinto studies, each of which included an arm that received a total of 360 mg per square meter of epirubicin with concurrent trastuzumab, only two of 752 (0.3%) patients and one of 307 (0.3%) patients developed clinical CHF, respectively (33,34). It is unknown if the relatively low rate of cardiotoxicity observed in these trials despite the delivery of concurrent anthracycline and trastuzumab is due to the use of epirubicin or <4 cycles of doxorubicin, the requirement of baseline EF ≥55% in most of the trials, or some other unknown factor. However, it does suggest that an absolute prohibition on concurrent anthracyclines and trastuzumab is not necessary and that in the appropriate circumstances this is a reasonable approach.

OPTIMIZING ADJUVANT TRASTUZUMAB THERAPY

Ultimately, a wide range of factors may influence the choice of adjuvant therapy for the patient with early stage HER2-positive breast cancer. One can imagine a time when there will be a number of anti-HER2 regimens that combine various targeted therapies, chemotherapy, and/or hormonal therapy. Decisions about treatment may depend on disease burden, biologic characteristics of the tumor, and patient preference. At this time, however, trastuzumab is the only anti-HER2 agent with demonstrated efficacy in the adjuvant setting, and once a decision has been made to administer trastuzumab, the questions remaining are: (i) should the administration be concurrent with chemotherapy; (ii) how long should trastuzumab be administered; and (iii) what is the most appropriate chemotherapy regimen to use in a given patient, taking into account effectiveness and toxicity.

Concurrent versus Sequential Trastuzumab Therapy

The study designs of the adjuvant trastuzumab trials varied as to whether the trastuzumab was given concurrent with chemotherapy or initiated only after the chemotherapy regimen was completed (see Table 46-2). Only one of the studies, N9831, included a randomized comparison of sequential versus concurrent therapy. When the study was initially reported (as part of the joint analysis with NSABP B-31), an unplanned interim analysis was performed when the number of DFS events observed on the sequential and concurrent arms was small. This initial analysis demonstrated a DFS benefit for concurrent trastuzumab relative to sequential therapy (HR = 0.64, 95% CI, 0.46–0.91; p = .00114) (35). In many ways, the result was perplexing given the robust benefit of sequential trastuzumab seen in the HERA trial.

More recently, an updated analysis of the concurrent versus sequential arms of N9831 was reported with a 6-year median follow-up. In this analysis, the 5-year DFS for the sequential arm was estimated at 80.1% (95% CI, 77.4%–82.9%) compared to 71.8% (95% CI, 68.6%–75.1%) for the control arm treated with chemotherapy alone (HR = 0.69; p < .001) (36). Although the concurrent arm had a numerically superior DFS compared to the sequential arm (84.4% vs. 80.1%, HR = 0.77; p = .02), this difference did not meet predefined criteria for statistical significance at this interim analysis (36). There were an insufficient number of deaths at the time of the analysis to compare survival between the arms.

In clinical practice, there seems to be little reason not to embrace a concurrent approach. While the only randomized comparison between sequential and concurrent trastuzumab therapy has failed to show an unequivocal benefit for the sequential approach, the trial (as noted above) did reveal a strong trend in that direction. Given this result, and the observation that concurrent therapy is not associated with any excess toxicity compared to sequential therapy, a strong case can be made that concurrent trastuzumab and chemotherapy should be the preferred approach.

Optimal Duration of Trastuzumab Therapy

All of the large randomized studies of adjuvant trastuzumab included at least 1 year of trastuzumab therapy. One year was arbitrary, but was made possible by the lack of significant chronic toxicities of trastuzumab. The small FinHer trial randomized patients to chemotherapy alone or with 9 weeks of trastuzumab, concurrent with the chemotherapy (docetaxel or vinorelbine). Despite this short duration of therapy, the benefits of trastuzumab initially observed in this study, RFS HR = 0.42 (p = .01) (23), were similar to that seen in the trials in which trastuzumab was given for 1 year. Although the subsequent report, at a median follow-up of approximately 5 years, was less promising (HR = 0.65, 95% CI, 0.38–1.12; p = .12) (37), the early results from FinHer called into question assumptions about the necessity of a year of trastuzumab treatment.

At the 2012 European Society for Medical Oncology (ESMO) Congress, results from the first randomized studies comparing different durations of trastuzumab therapy were presented. The HERA study included a randomization of 1 versus 2 years of trastuzumab therapy, and with approximately 1,550 patients in each arm and a median of 8 years of follow-up, there was absolutely no difference between the two arms; DFS of 75.8% and 76.0%, respectively (HR = 0.99, 95% CI, 0.85–1.14; p = .86) (38). Overall survival for the two arms was also essentially the same (HR = 1.05, 95% CI, 0.86–1.28; p = .63) (38). Of interest, the additional year of trastuzumab was associated with a modest increase in mild or asymptomatic cardiac toxicity, which was 4.1% in the 1-year arm and 7.2% in the 2-year arm, but no difference was seen in severe cardiac toxicity (0.8% vs. 1.0%) (38).

Initial data from the PHARE study shed further light on the question of duration of therapy. In this study, 3,384 patients who had received 6 months of trastuzumab were randomized to receive an additional 6 months of trastuzumab (total of 12 months) or no further therapy. The study included a heterogeneous population; 55% of the patients had node negative disease and 73% received both an anthracycline and a taxane. 58% of the patients started the trastuzumab concurrently with the chemotherapy and 42% received a sequential regimen (39). The trial was designed to test the non-inferiority of 6 versus 12 months of trastuzumab, and with a median follow-up of 42.5 months, the hazard ratio for DFS was 1.28 (95% CI, 1.05–1.56; p = .29) in favor of the 12-month arm (39). Although the results did not allow the investigators to conclude that 12 months was superior, non-inferiority of the 6-month regimen, which would have required that the upper boundary of the 95% confidence interval be no higher than a HR of 1.15, could not be established.

With the results of the HERA and PHARE studies, there is now fairly clear guidance on the optimal duration of trastuzumab therapy. HERA shows that extending trastuzumab therapy beyond a year is not beneficial. Although the PHARE study did not definitely demonstrate that 12 months was superior, the trend unquestionably favors 12 months. These data, coupled with the significant disease-free and overall survival benefit of 12 months of trastuzumab observed in the BCIRG006 and B31/N9831 studies, dictates that 12 months of trastuzumab is the standard of care. It is fortunate that the

decision to use 1 year of therapy in the initial randomized trials, which was completely arbitrary, has been borne out as likely the optimal approach.

Anthracycline vs. Non-Anthracycline Regimens

While ambiguity regarding optimal scheduling and duration of trastuzumab have been largely resolved by the recent clinical trial results discussed in the preceding sections, there is still substantial controversy regarding the optimal chemotherapy backbone to use with trastuzumab in the adjuvant setting. The central question is whether to include an anthracycline in the treatment regimen. The argument to exclude an anthracycline relates to the toxicity of this approach. Although the incidence of clinically significant cardiac toxicity is quite low with the use of an anthracycline followed by trastuzumab, it is higher than is seen with non-anthracycline-containing regimens. The absolute risk is particularly low in individuals who have no risk factors for cardiomyopathy. In addition, there is a small increase in the risk of acute leukemia or myelodysplasia in individuals treated with anthracyclines, though this risk appears to be less than 0.5% in almost all studies (40–42). Ultimately, it may be possible to eliminate anthracyclines from the treatment of most or all women, but at this time there are compelling reasons to include an anthracycline for the majority of patients with HER2-positive disease. First, as described previously, it is known that the anthracyclines are particularly active in HER2-positive disease. Second, almost all of the adjuvant regimens that have demonstrated a benefit from the addition of trastuzumab have included an anthracycline. Third, and perhaps most importantly, the one study that compared an anthracycline-containing regimen (AC-TH) to a regimen devoid of anthracycline therapy (TCH), demonstrated a nonsignificant trend in favor of the AC-TH regimen (22). While the study does not allow us to conclude that AC-TH is superior to TCH, it certainly does not provide sufficient evidence to conclude the two regimens are equivalent. Even if one includes all of the serious cardiac events and cases of leukemia/myelodysplasia along with the disease recurrences and deaths in each arm, AC-TH has fewer absolute events than TCH. At this time, the optimal approach seems straightforward. In a patient with a moderate to high risk of disease recurrence where one wants to optimize the adjuvant regimen, we favor an anthracycline-based regimen as long as the patient does not have risk factors for the development of cardiac toxicity. If she does, or if her risk of disease recurrence is relatively low, a very reasonable approach is to substitute TCH for AC-TH. We fully expect that adjuvant regimens for HER2-positive disease will change over the next 5 to 10 years, and as part of this evolution, it is likely that there will be fewer women receiving anthracyclines. For some or many women, it may be possible to eliminate chemotherapy altogether and use HER2-directed approaches alone; however, at this time, it is not possible to select women for such a treatment approach.

NOVEL AGENTS UNDER EVALUATION IN THE ADJUVANT AND NEOADJUVANT SETTING

The introduction of trastuzumab in the adjuvant and neoadjuvant setting has substantially improved outcomes for women with HER2-positive early breast cancer. A recent Monte Carlo simulation using SEER data estimates that the widespread use of adjuvant trastuzumab in the United States will decrease the number of patients with HER2-positive cancers who develop disease recurrence by approximately 38% or 2,800 patients per year (43). However, trastuzumab is not perfect—recurrences still occur despite treatment with an optimal trastuzumab regimen. The same Monte Carlo simulation estimates at least 4,500 patients still develop recurrence each year (43). In an effort to further reduce the number of women who develop metastatic disease, several novel HER2-targeted agents are being evaluated in combination with standard therapies in patients with early-stage HER2-positive cancers.

Lapatinib

Lapatinib, an oral small molecule inhibitor of the HER2 and EGFR tyrosine kinases, improves DFS when combined with capecitabine in patients with metastatic disease who have previously received trastuzumab-based therapy (86). Preclinical studies, as well as clinical data, suggest that the combination of lapatinib with trastuzumab has synergistic anti-tumor effects. In the adjuvant setting, lapatinib was first evaluated as monotherapy in the phase III TEACH trial in which trastuzumab naïve women who had previously received an adjuvant chemotherapy regimen were randomized to one year of lapatinib (1,500 mg daily) or placebo. Enrollment on this study closed in 2008 with a total of 3,147 patients randomized (44). Because the study did not place any restrictions on the time between completion of adjuvant chemotherapy and entry on the study, the trial population was heterogeneous with approximately 29% of patients enrolling more than 4 years after their initial diagnosis. After a median follow-up of approximately 48 months, there were 210 (13%) DFS events in the patients who received lapatinib and 264 (17%) in patients who received placebo (HR = 0.83, 95% CI, 0.7–1.0; p = .053) (44). Given the widespread use of trastuzumab in the adjuvant setting, the clinical relevance of this study is limited.

In the neoadjuvant setting, lapatinib has been directly compared to trastuzumab, and has also been evaluated in combination with trastuzumab. The phase III GeparQuinto study, led by the German Breast Group, randomized 620 patients to four cycles of EC (epirubicin [90 mg/m^2] and cyclophosphamide [600 mg/m^2] every 3 weeks), followed by four cycles of docetaxel (100 mg/m^2 every 3 weeks) with either trastuzumab or lapatinib (1,000–1,250 mg daily) (33). The trastuzumab and lapatinib were given throughout the entire chemotherapy course. Patients on this study had either clinical T3/4 tumors and/or clinically node positive disease with at least T2 tumors. Patients with sentinel node positive cancers were also eligible. The primary endpoint was pCR defined as no residual invasive or *in situ* cancer in the breasts or nodes. The pCR rate was 30.3% in patients who received trastuzumab-based therapy and 22.7% in those patients who received lapatinib (odds ratio [OR] 0·68 [95% CI, 0.47–0.97]; p = ·04) (33). Trastuzumab was also better tolerated with more rash, diarrhea, and treatment discontinuation (14% vs. 33.1%) in patients randomized to lapatinib.

NeoALTTO randomized 455 patients with T2 or larger HER2-positive cancers to a 6-week run-in of lapatinib (1,500 mg daily), trastuzumab (weekly), or the combination (lapatinib given at 1,000 mg daily) (45). After 6 weeks of that therapy, all patients received 12 weekly doses of paclitaxel (80 mg/m^2) with continuation of the same HER2-targeted regimen, followed by definitive surgery. The primary endpoint was pCR, defined in this study as no residual invasive cancer in the breast. Those patients randomized to the combination of lapatinib and trastuzumab had a significantly higher rate of pCR than those who received trastuzumab alone 51.3% versus 29.5%

(absolute difference 21·1%, 9·1–34·2, p = ·0001) (45). The pCR rate for patients in the lapatinib arm (24.7%) was numerically lower than that of the trastuzumab arm (29.5%), but unlike the GeparQuinto study, this difference was not statistically significant (absolute difference –4·8%, –17·6 to 8·2, p = ·34) (45).

A third neoadjuvant study, NSABP B-41, also compared trastuzumab and lapatinib regimens. In this study, women with operable HER2-positive breast cancer were randomized to four cycles of AC, followed by four cycles of paclitaxel (80 mg/m^2 on days 1, 8, and 15 of 28-day cycle) with either trastuzumab, lapatinib (1250 mg daily), or the combination (with lapatinib at 750 mg daily). In 519 evaluable patients, the rate of pCR (defined as absence of invasive disease in the breast) was similar for patients randomized to trastuzumab (52.5%) or lapatinib (53.2%) (46). Patients who received the combination had a somewhat higher rate of pCR (62%), but this did not meet statistical significance (p = .075 for the comparison with trastuzumab) (46). Higher rates of diarrhea were observed in the lapatinib-containing arms.

Together, the results of GeparQuinto, NeoALTTO, and NSABP B-41 are consistent with data from the metastatic setting that suggest that lapatinib based therapy is not superior to trastuzumab and may be inferior (47). More importantly, these data, which are consistent with what has been seen in the metastatic setting (48,49), indicate that combining two HER2 inhibitors with different mechanisms of action, an approach termed "dual-blockade," is associated with improved short-term efficacy. These observations will be tested definitively in the ALTTO study, a global phase III adjuvant study comparing 1 year of trastuzumab, lapatinib, and combinations of the two in conjunction with chemotherapy.

In addition to lapatinib, other small molecule tyrosine kinase inhibitors are being evaluated in the treatment of HER2-positive breast cancer. Neratinib, an inhibitor of the HER2, EGFR, and HER4 kinases, differs from lapatinib in that neratinib binds irreversibly to the target kinase. In preclinical studies, neratinib appears more potent than lapatinib (50), and in studies in the metastatic setting, neratinib has substantial single agent activity (51). Presumably because of its greater potency, neratinib has relatively high rates of moderate to severe diarrhea, which requires aggressive management (51).

Neratinib is currently being studied in a randomized phase III adjuvant trial, the ExteNET study, in which patients with HER2-positive early stage cancers who completed a year of trastuzumab-based therapy are randomized to an additional year of neratinib or placebo. Accrual to this study has been completed, and the analysis is ongoing.

Pertuzumab

Another approach to the "dual-blockade" paradigm of utilizing two anti-HER2 agents with nonoverlapping mechanisms of action is to combine trastuzumab with pertuzumab. Pertuzumab, like trastuzumab, is a humanized monoclonal antibody specific for the extracellular domain of HER2. Data from the phase III CLEOPATRA study in the first-line metastatic setting demonstrates that the addition of pertuzumab to a trastuzumab-taxane regimen markedly improves progression-free and overall survival in patients with HER2-positive cancers (52,53). In addition, a small phase II study showed the combination of pertuzumab and trastuzumab has clinical activity in patients whose cancer had progressed on a previous trastuzumab regimen (54).

These findings were extended to the early disease setting by the NeoSphere study, a phase II randomized neoadjuvant trial in which 417 women with HER2-positive cancers received four cycles of docetaxel (75 mg/m^2, escalating, if tolerated, to 100 mg/m^2) every 3 weeks, combined with trastuzumab (8 mg/kg loading dose, followed by 6 mg/kg every 3 weeks) or pertuzumab (840 mg loading dose, followed by 420 mg every 3 weeks), or the combination of the two antibodies. Patients in a fourth arm of the study received the combination of pertuzumab and trastuzumab without chemotherapy. The primary endpoint was pCR in the breast. Consistent with what was observed in the metastatic setting, the pCR rate in NeoSphere was significantly higher in patients receiving docetaxel with the combination of trastuzumab and pertuzumab (45·8% [95% CI, 36.1–55.7]) than in those patients who received docetaxel with either trastuzumab (29·0% [20.6–38.5]; p = .0141) or pertuzumab alone (24.0% [15.8–33.7]) (55). The addition of pertuzumab to trastuzumab and chemotherapy was not associated with any significant increase in toxicity (55).

Interestingly, while women randomized to pertuzumab and trastuzumab without the docetaxel had a lower rate of pCR (16.8% [10.3–25.3]) than any of the chemotherapy groups, one-sixth of the patients achieved a pathologic complete response with 12 weeks of combined antibody therapy alone (55). This observation suggests that there is a subset of patients with HER2-positive cancers that are exquisitely sensitive to HER2-directed agents and that such patients, if identified, might be treated with targeted therapy alone and spared the toxicity of chemotherapy. Why is there enhanced clinical activity with dual blockade? In the case of pertuzumab and trastuzumab, preclinical data suggest that synergism may result from the ability of pertuzumab, which binds to the dimerization arm of HER2 (domain II), to inhibit ligand-induced heterodimerization of HER2 with HER3 (56). In contrast, trastuzumab, which binds to the juxtamembrane region (domain IV) of HER2, is able to inhibit ligand-independent HER2/HER3 interactions (57).

Pertuzumab's ability to augment the effectiveness of trastuzumab in the metastatic and neoadjuvant settings, without substantially increasing toxicity, has led to interest in exploring the role of pertuzumab in adjuvant therapy. The APHINITY study, a phase III trial of patients with high risk HER2-positive early breast cancer randomizes patients to 1 year of pertuzumab or placebo in addition to a standard chemotherapy/trastuzumab regimen. This study completed accrual in 2013 and is awaiting maturation and analysis.

Based on the substantial improvement in pCR seen with the addition of neoadjuvant pertuzumab in the NeoSphere study, and in view of the survival benefit seen with pertuzumab in the CLEOPATRA trial, the United States FDA granted accelerated approval for the neoadjuvant use of pertuzumab in combination with chemotherapy and trastuzumab in September, 2013 (58,59). The indication is limited to patients with locally advanced, inflammatory, or early breast cancer greater than 2 cm in diameter and/or node positive. The FDA guidance suggests that based on the study design and safety data from NeoSphere and another neoadjuvant pertuzumab study, TRYPHENA (60), appropriate regimens to use with pertuzumab include 1) four preoperative cycles of pertuzumab in combination with trastuzumab and docetaxel followed by 3 postoperative cycles of FEC, 2) three preoperative cycles of FEC alone followed by 3 preoperative cycles of pertuzumab in combination with docetaxel and trastuzumab, or 3) six preoperative cycles of pertuzumab in combination with TCH.

It should be noted that at the current time, there are no data indicating that the use of pertuzumab in the early disease setting is associated with improvements in long term outcome measures such as DFS or OS. Thus, the conversion to full FDA approval of pertuzumab is contingent upon confirmatory data from the adjuvant APHINITY study described above. Given the current lack of proven long term benefit

for the use of neoadjuvant pertuzumab, it may be prudent to reserve the use of this agent for patients at high risk for disease recurrence.

Trastuzumab Emtansine

The most recent HER2-directed agent to be evaluated in the early disease setting is trastuzumab emtansine (T-DM1). T-DM1 is an antibody drug conjugate consisting of the potent anti-microtubule molecule DM1 (up to 270-fold more potent than paclitaxel) (61) conjugated via a non-cleavable linker to the trastuzumab monoclonal antibody. On average, there are 3.5 DM1 molecules per antibody. Even with the conjugation, the trastuzumab retains its affinity for HER2 and its effector functions including activation of ADCC. T-DM1 is thus able to deliver the cytotoxic DM1 selectively to the HER2-positive cancer cell, and also retain the anti-tumor functions of trastuzumab. In patients with metastatic HER2-positive breast cancer who were previously treated with trastuzumab, the phase III EMILIA study demonstrated that T-DM1 improved PFS and survival compared to capecitabine and lapatinib, and did so with significantly less toxicity. T-DM1's combination of potent activity and favorable toxicity profile has led to interest in evaluating this agent in the (neo)adjuvant setting. To date, only a pilot safety study with T-DM1 has been conducted in the (neo)adjuvant setting, and this revealed that the use of T-DM1 after standard anthracycline based chemotherapy was well tolerated (62). This study paves the way for a large, randomized adjuvant trial as well as randomized neoadjuvant studies to evaluate the role of T-DM1 in the early disease setting.

Although there is much interest in the pending adjuvant trial results with the new agents described above, the relatively favorable outlook for most patients with operable HER2-positive breast cancer may make it difficult for these novel therapies to demonstrate a clinically meaningful benefit. This issue is particularly important because most of these adjuvant studies used "add-on" designs in which the investigational agent was given in addition to standard therapy, rather than replacing it. This approach makes it especially important to show a substantial improvement in outcome to justify the extra toxicity from the additional therapy. It is also quite possible that several of these new HER2-targeted agents will show improvements in outcome when added to the current standard of care. Identification of molecular predictors of response to these individual agents will be critical to rationally select among these different options to optimize outcomes for an individual patient.

PREDICTIVE MARKERS OF TRASTUZUMAB BENEFIT AND RESISTANCE

Although the introduction of trastuzumab has improved outcomes of patients with HER2-positive early breast cancers, trastuzumab is not uniformly effective—recurrences still occur despite treatment with an optimal trastuzumab regimen, and only a subset of patients treated with neoadjuvant trastuzumab-based regimens achieve a pCR. These observations reflect some degree of either inherent or acquired resistance to trastuzumab-based therapy. If molecular markers could be identified that predict which patients' cancers are not fully sensitive to trastuzumab-based therapy, those patients could be provided additional or alternative therapies to overcome this resistance. Biomarkers are also needed to help select which alternative anti-HER2 agents would be most active for a given cancer. As noted above, this question is becoming increasingly important as the number of novel HER2-directed agents increases. Unfortunately, it has proven difficult to identify markers that definitively predict which patients will or will not benefit from trastuzumab or who might benefit from an alternative approach.

In the initial analyses of the large randomized adjuvant studies evaluating trastuzumab, it was clear that trastuzumab had similar benefits across the subgroups of breast cancer defined using standard clinical or histological criteria (e.g., hormone receptor status, nodal status, tumor size, patient age, or menopausal status) (18,20,22). Most of the recent efforts to identify predictive markers of trastuzumab benefit in the (neo)adjuvant setting have focused on individual components of the HER2 signaling pathway. Preclinical studies demonstrate that the transforming activity of HER2 is critically dependent on signaling through the PI3-kinase pathway, and that resistance to trastuzumab can be induced by constitutive activation of PI3-kinase (63,64). It was therefore hypothesized that activating mutations in *PIK3CA*, the gene coding for the catalytic subunit of PI3-kinase, or loss of PTEN, the suppressor of the PI3-kinase pathway, would be associated with resistance to trastuzumab. Consistent with this hypothesis, in retrospective analyses of small preoperative studies, and some metastatic datasets, alterations in the PI3-kinase pathway were associated with inferior outcomes in trastuzumab-treated patients (64–66). However, analysis of the N9831 and NSABP B31 studies failed to show an association between alterations in either PIK3CA or PTEN and benefit of trastuzumab (Reference (67) and Soon Paik, personal communication, 2012). Similarly, a comprehensive biomarker analysis focused on HER family members and the PI3-kinase pathway failed to show any significant association between a specific biomarker and differential benefit from trastuzumab or pertuzumab in the Neo-Sphere Study (68).

There has also been interest in evaluating the role of p95 as a predictor of trastuzumab benefit. p95, which is expressed in a subset of HER2-positive cancers, is a truncated form of the HER2 protein which lacks the extracellular domain, but retains kinase activity. p95 can be formed by proteolytic cleavage or synthesis of the protein from an internal translation initiation site. Because p95 lacks the extracellular portion of HER2, trastuzumab is unable to bind to it, and many therefore hypothesized that the subset of HER2-positive cancers with significant expression of p95 would exhibit resistance to trastuzumab. Consistent with this hypothesis, retrospective analyses of small series of archival primary HER2-positive cancers from patients treated with trastuzumab-based therapy in the metastatic setting found inferior outcomes in patients with p95 expressing cancers (69,70). However, a recent analysis of pretreatment tumor samples from 134 patients treated with trastuzumab-based neoadjuvant chemotherapy on the GeparQuattro study found that patients with p95 positive cancers actually had higher pCR rates than those with p95 negative cancers (59% vs 24%, $p < .001$) (71). A similar analysis of tumor samples from patients treated with neoadjuvant chemotherapy and trastuzumab on the CHER-LOB study also failed to demonstrate an inverse association between p95 expression and pCR; however, this study included only 29 evaluable patients (72). Given the small sample sizes and questions regarding the optimal method to assess p95 expression, these results do not definitively disprove the hypothesis that p95 expression is a clinically important mediator of trastuzumab resistance. Additional data, perhaps with alternative assays for p95 expression, are needed to address the role of p95 in resistance to trastuzumab.

In cancers that are both HER2-positive and express estrogen and/or progesterone receptors, resistance to HER2-directed therapy has been postulated to occur due to cross-talk between the HER2 signaling pathway and hormone receptors. Preclinical studies demonstrate that the estrogen receptor can interact with the HER2 signaling pathway through both genomic and nongenomic mechanisms (73,74). Consistent with these observations, tamoxifen or estrogen deprivation improves the effectiveness of HER2-targeted therapy in xenograft models (75). This interaction between the HER2 and estrogen receptor signaling pathways could be playing a role in the lower rates of pCR consistently observed in hormone receptor positive compared to hormone receptor negative HER2-positive cancers treated with preoperative HER2-directed therapy in the absence of endocrine treatment (e.g., reference 45,55). A recent neoadjuvant study of 12 weeks of trastuzumab and lapatinib, combined with hormonal therapy in hormone receptor positive, HER2-positive breast cancers demonstrated that this combination is feasible and was associated with a substantial rate of pCR (21%) (76). Randomized trials are needed to definitely evaluate whether there is a role for antiestrogens in overcoming resistance to HER2-directed therapy.

In preclinical models, trastuzumab is able to activate ADCC, and it has been suggested that this immune effect plays a significant role in mediating trastuzumab's clinical benefit. Because activation of ADCC requires binding of trastuzumab's Fc component to Fcγ receptors (FcγR) on the surface of immune effector cells, it has been hypothesized that polymorphisms in the FcγR gene that affect antibody binding affinity would influence the benefit of trastuzumab. Supporting this hypothesis, studies have demonstrated associations between higher affinity FcγR genotypes and better outcome in patients with lymphoma who received the CD20 specific monoclonal antibody rituximab and in patients with colorectal cancer treated with the EGFR targeted antibody cetuximab (77,78). In addition, a small retrospective study of 54 patients with metastatic HER2-positive breast cancer treated with trastuzumab found a significant association between FcγR genotype and improved patient outcomes (79). However, when FcγR polymorphisms were evaluated in approximately 1,200 patients from the BCIRG006 study, there was no correlation between FcγR genotype and DFS (80).

Thus, despite a number of potential mechanisms of resistance to trastuzumab identified in preclinical studies, none have been conclusively validated in the adjuvant or neoadjuvant setting. As we move forward, it may be more productive to use more comprehensive analytic approaches, rather than testing serial candidates. The ability to assess tumors comprehensively at the genomic level, using next generation sequencing platforms to perform whole genome or whole exome sequencing and/or RNA sequencing analyses may be illuminating. These approaches are currently being applied to the tissue samples from recent large preoperative studies.

Even in the absence of well-validated mechanisms of resistance to HER2-directed agents, one approach that has been successful in overcoming therapeutic resistance has been the strategy of combining two HER2-directed agents. As discussed previously, combining trastuzumab with lapatinib or with pertuzumab improves progression free and overall survival in the metastatic setting and pathologic complete response rates in neoadjuvant trials compared to the use of a single HER2-directed agent (16,45,68,81). The benefits of this dual-blockade approach may be attributable to the ability of these combinations to inhibit more comprehensively signaling from HER2 homodimers and heterodimers of HER2 with other HER family receptors.

MANAGEMENT OF SPECIAL POPULATIONS

Adjuvant Therapy in Patients with Small (<2 cm) Node Negative HER2-Positive Cancers

Although HER2 positivity is associated with more advanced stage disease at diagnosis, a sizable proportion of patients present with stage I disease (T1N0). The optimal management strategy for patients with this subset of cancers is not clear, particularly for patients with node negative cancers that are one centimeter and smaller. All of the large studies evaluating trastuzumab in the adjuvant setting were restricted to patients with high-risk cancers, typically defined as node positive or node negative with higher risk features. Small, node negative cancers were generally not included in these studies, and as a result, we lack data from randomized trials on the outcomes of patients with small HER2-positive cancers treated with trastuzumab-based regimens. The chemotherapy backbone of most of the adjuvant studies was designed for patients at high risk of recurrence and typically included regimens with multiple agents and prolonged duration of therapy (e.g., ACTH, TCH). These regimens are clearly effective, but are also associated with a significant side effect burden. They may well represent excessive treatment for patients with a low burden of disease, yet until recently, there were not data available for less intensive chemotherapy regimens.

A critical question relates to the natural history of small HER2-positive cancers in the absence of treatment, or with hormonal therapy alone (for those with hormone receptor positive disease). If the recurrence risk is low enough—for example as low as most HER2 negative T1a,bNO cancers—then perhaps chemotherapy, with or without HER2-targeted therapy, may not be needed for many of these cancers.

Several recent retrospective studies have provided data to address this question. The MD Anderson group analyzed 965 patients with T1a,bN0 cancers who did not receive adjuvant chemotherapy or trastuzumab. With 74 months' median follow-up, there were significantly more recurrences in patients with HER2-positive cancers than those with HER2-negative cancers (5-year RFS 77.1% vs. 93.7%; $p < .001$) and HER2 status was a significant independent risk for distant recurrence in a multivariable analysis (HR = 5.3, 2.23–12.62, $p < .001$) (8). An Italian study evaluated 150 patients with HER2-positive T1a,bN0 cancers as well as matched patients with HER2-negative cancers. In this study, a subset of the patients received adjuvant chemotherapy, but no patient received trastuzumab. Overall, the 5-year DFS rates (92% for HER2-positive vs. 99% for HER2-negative) were higher than those seen in the MDACC study, but in multivariable analysis there was a trend for worse outcomes in the HER2-positive group (HR = 2.4, 0.9 to 6.5; $p = .09$) (9). An analysis of a tissue microarray dataset from British Columbia included 117 patients with T1N0 HER2-positive cancers, only a small minority of whom received systemic adjuvant chemotherapy. In these patients, with a median follow-up of 12.4 years, the 10-year RFS was 71.6%, and breast cancer–specific survival (BCSS) was 81.3% (82). Looking specifically at patients with T1b (0.6–1.0 cm) HER2-positive cancers who did not receive systemic adjuvant therapy, the 10-year RFS was 68.4%, but this was in a very small population (82). In a Finnish study of patients with HER2-positive T1N0 cancers; the 9-year RFS was approximately 72% (83).

These data show a relatively broad range of outcomes for patients with small node negative HER2-positive cancers, and the studies are limited by small sample sizes and heterogeneous treatment. However, it does seem clear

that there is at least a modest risk of recurrence associated with these cancers (at least those that are greater than 0.5 cm), and therefore some type of adjuvant therapy is appropriate for most patients. Currently, there is no universally accepted standard for the adjuvant treatment of these patients. Although node negative cancers <1 cm were not included in the randomized adjuvant trials, data from the trials suggests that the benefits of trastuzumab are independent of tumor size or nodal status (20,22). For example, in HERA, approximately 15% of the trial population had T1c (between 1.1 and 2.0 cm), node negative cancers. In this subset, the benefit of trastuzumab (HR = 0.53, 0.26–1.07) was similar to that of the entire population (HR = 0.64, 0.54–0.76) (84). Given these observations, and the highly favorable toxicity profile of trastuzumab, it would seem logical to incorporate trastuzumab into the treatment regimen for this population. However, it also seems reasonable to try to reduce the chemotherapy component of the regimen in view of the lower overall recurrence risk of these patients.

It has been postulated that one approach to providing an effective regimen for this population while minimizing the toxicity of therapy would be to utilize HER2-targeted therapy without chemotherapy (85). It is clear from data in the preoperative setting that treatment with dual-blockade targeted therapy regimens such as trastuzumab/pertuzumab (55) and trastuzumab/lapatinib (76) without chemotherapy are extremely active (as evidenced by pCRs in neoadjuvant studies) in a subset of HER2-positive cancers. The main limitation of this approach is that currently there are no established biomarkers to identify which HER2-positive cancers are likely to be sensitive to this approach.

Another approach has been taken by investigators from the Dana-Farber Cancer Institute. They hypothesized that utilizing a relatively well-tolerated single agent chemotherapy regimen in combination with trastuzumab would exploit the synergy observed when trastuzumab is given concurrently with chemotherapy, while avoiding the toxicity associated with combination chemotherapy regimens. To test this hypothesis, they initiated a single-arm phase II study, the APT trial, in which a planned 400 patients with node negative HER2-positive cancers less than 3 cm in size received 12 weekly infusions of paclitaxel (80 mg/m^2) and 1 year of trastuzumab with the trastuzumab starting concurrent with paclitaxel. Because a randomized study in this population is difficult due to the expected low event rate, a single-arm design was utilized with the goal of demonstrating a very low recurrence rate in patients who received this regimen. The design has a high probability (95%) of declaring the regimen worthy of further study if the true 3-year failure rate is 5% or less.

The initial results of the APT study were presented at the 2013 San Antonio Breast Cancer Symposium (86). A total of 406 patients were enrolled; 9% of patients had T2 cancers, 42% had T1c cancers, 31% had T1b cancers, and 19% had T1a cancers. With a median follow-up of 3.6 years, there were 10 disease free survival events, of which only 2 were distant recurrences. The overall 3-year DFS was 98.7% (95% CI: 97.6% to 99.8%) (86). The favorable outcome was seen regardless of tumor size (95% CI: 96.0% to >99.9% for tumors >1cm and 98.4% to >99.9% for tumors ≤ 1cm) or hormone receptor (HR) status (95% CI: 97.0% to >99.9% for HR-positive cancers and 97.7% to >99.9% for HR-negative cancers). The paclitaxel/trastuzumab regimen was generally well tolerated with 2 cases (0.5%) of symptomatic CHF and 13 patients (3.2%) with an asymptomatic LVEF decline that led to an interruption of trastuzumab. 11 of these patients were able to resume trastuzumab without further complications. 14 patients (3.4%) had grade 3 neuropathy.

Outside of a trial, treatment of patients with T1 lesions with negative lymph nodes needs to be individualized. Consideration of a trastuzumab-based regimen is reasonable for most patients with T1b and T1c cancers. In general, it is prudent to avoid an anthracycline-based regimen in these "low risk" patients, and some clinicians use TCH in this setting. Unfortunately, TCH is associated with substantial short-term toxicity. Given the recent data from the APT study, which demonstrated an extremely low rate of distant recurrence and a favorable tolerability profile (86), the paclitaxel/trastuzumab regimen can be considered an appropriate standard of care for such patients. For T1a tumors, particularly those that are hormone receptor positive, the prognosis is quite favorable in the absence of systemic chemotherapy and it is appropriate to consider using hormonal therapy alone for patients with HR expressing cancers and no therapy for very small HR-negative cancers.

Adjuvant Therapy of HER2-Positive Cancers in the Elderly

While the incidence of HER2-Positive breast cancer in older populations is not well studied, an Italian study of 1,085 women with early-stage breast cancer found that 16% of the cancers were HER2-positive (3+ by IHC), suggesting that the percentage of HER2-positive cancers in this age group is similar to that of the general population (87). The optimal treatment for this group is not well established. A study of patients with stage I–III, HER2-positive disease aged ≥60 treated at academic centers within the National Comprehensive Cancer Network (NCCN) found that the rates of initiation of trastuzumab-based adjuvant chemotherapy were 79% for women in the 60–69 age group and 54% for women ≥70 (88). These data suggest that in practice, there appears to be reduced utilization of trastuzumab in this population. It is worth exploring the basis for this reduced utilization. One factor may be concerns over a lack of data on trastuzumab's effectiveness in this population. It is clear that the elderly were underrepresented in the randomized adjuvant trials of trastuzumab. Only approximately 16% of patients participating in HERA and NSABP B31/N9831 were aged ≥60. PACS 04 and FinHer excluded patients >65 years, and BCIRG 006 only characterized patients as younger or older than 50 years. However, despite the underrepresentation, there is fairly clear evidence that trastuzumab is effective in older patients. In the B31/N9831 combined analysis, the addition of trastuzumab was associated with a significant improvement in DFS in patients aged ≥60 (HR = 0.41, 0.24–0.68). In a recent pooled analysis of the available data from the randomized trials of patients aged ≥60, a significant reduction in DFS events was observed with the addition of trastuzumab (HR = 0.53, 0.36–0.77) (89). These data suggest that trastuzumab has similar benefits in older patients as it does in the general population. A second concern with the use of trastuzumab is possible toxicity, specifically cardiac effects. As detailed previously (see the Cardiac Toxicity of Trastuzumab section), multivariable analysis of data from the B31/N9831 dataset identified age >50 years as an independent predictor of cardiac events (32). The absolute incidence of serious cardiac events in patients aged ≥60 who received trastuzumab was 5.3% in NSABP B-31 and 6.6% in N9831 (89). A third concern is increased prevalence of comorbidities in older women that influence their competing risks of mortality, which has to be considered on a case-by-case basis.

Given the available data, it is appears that women over the age of 60 derive as much benefit from trastuzumab as younger patients, but are subject to modestly higher risks (in absolute

terms) of cardiac toxicity from this agent. These factors need to be considered, along with the patient's comorbidities, when planning adjuvant therapy for the older patient with HER2-positive disease. Availability of lower toxicity regimens with single agent chemotherapy or targeted therapy alone, as discussed above for patients with small HER2-positive cancers, would be appealing for older patients as well.

MANAGEMENT SUMMARY

- Patients with moderate to high risk HER2-positive breast cancer (node positive, or node negative with high-risk features) should generally receive chemotherapy and 1 year of trastuzumab.
  - Appropriate chemotherapy regimens include an anthracycline/taxane/trastuzumab regimen or TCH.
  - Current data support initiating trastuzumab concurrently with taxane chemotherapy.
- There is no standard of care for patients with small (<2 cm) node negative cancers, as these patients were not well represented in the randomized trials. Treatment needs to be individualized for these lower-risk patients.
  - The combination of weekly paclitaxel and trastuzumab is associated with an extremely low recurrence rate in a large single arm study. This regimen represents a reasonable standard for many, if not most, patients with T1b/T1c cancers.
  - T1a cancers, particularly those that are hormone receptor positive, have a favorable prognosis in the absence of chemotherapy and it is appropriate to consider using hormonal therapy alone for such patients with hormone receptor expressing cancers and no therapy for very small hormone receptor negative cancers. If a chemotherapy and trastuzumab regimen is administered, the weekly paclitaxel and trastuzumab approach is optimal.
- Randomized long-term data on the optimal neoadjuvant regimen are limited. A pertuzumab/trastuzumab/chemotherapy regimen is associated with a high pCR rate and is recommended for the neoadjuvant treatment of patients with higher risk disease. For the neoadjuvant treatment of lower risk patients, and in situations in which pertuzumab is not available, it is reasonable to use one of the standard regimens used in the adjuvant setting (e.g., anthracycline/taxane/trastuzumab or TCH).
  - In general, unless a patient demonstrates progressive disease or unacceptable toxicity during neoadjuvant therapy, one should complete the full planned course of therapy prior to surgery.
- Trastuzumab and pertuzumab, in combination with one of several chemotherapy regimens, is an effective approach in patients with locally advanced HER2-positive breast cancer.
- Patients receiving trastuzumab based therapy should have LVEF evaluated prior to initiating trastuzumab and then at regular intervals during trastuzumab therapy.

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CHAPTER 47

Adjuvant Systemic Therapy: Bone-Targeted Treatments

Robert E. Coleman

CHAPTER CONTENTS

Bone is the most common site for distant recurrence in breast cancer and is the first location for recurrence in about one-third of patients who relapse. The incidence of bone metastases in metastatic breast cancer is 60% to 80% (1). The development of skeletal metastases involves complex interactions between cancer cells, osteoblasts, and osteoclasts and both hematopoietic and endothelial stem cells within the bone microenvironment. The presence of tumor in bone ultimately results in activation of osteoclasts, leading to an increased rate of bone resorption. Additionally, bone marrow derived stem cells are of fundamental importance in the development of metastases at other sites, preparing the environment for tumor cells to establish a metastasis (2). Drug that are able to target bone, notably the bisphosphonates but also inhibitors of receptor activator of nuclear factor kappa-B ligand (RANKL), a key regulator of bone cell function, provide an additional strategy to prevent metastasis within bone and, potentially, at extraskeletal sites.

Bisphosphonates are potent inhibitors of osteoclastic bone resorption, with proven efficacy in reducing tumor-associated skeletal complications in advanced cancer (3). More recently, clinical studies have investigated the adjuvant use of these drugs in breast cancer, with evaluation of their impact on bone density, metastases, and survival. Additionally, numerous preclinical experiments have shown that the development of bone metastases can be inhibited by either the bisphosphonates or RANKL inhibition, through both bone-mediated and possible direct antitumor mechanisms (4). Synergy between potent aminobisphosphonates such as zoledronic acid with chemotherapy has been demonstrated in mouse models, although the clinical relevance of these observations remains uncertain (5).

The data available to date suggest an increasing role for adjuvant bisphosphonates in the treatment of early-stage breast cancer although, as is discussed below, benefits appear to be confined to the postmenopausal setting (6). A strong need exists for continued clinical and laboratory investigation of these drugs in the adjuvant breast cancer setting.

RATIONALE: THE BIOLOGY OF BONE METASTASES

Healthy bone is in a constant state of remodeling, a process that is essential to preserve the structural integrity of bone and to minimize the risk of fragility fractures. Bone-derived osteoblasts and osteoclasts work together through the influence of cytokines and other humoral fractors to couple formation and resorption. Osteoblasts, derived from fibroblast precursors, produce collagen matrix and contribute to bone formation. Osteoclasts are multinucleated giant cells derived from the macrophage-monocyte lineage, and are the major mediator of bone degradation or resorption. In normal health and bone remodeling, the relationship between osteoblastic bone formation and osteoclastic bone resorption are balanced. However, bone diseases including malignancy disturb this delicate balance and result in a loss of the normal structural integrity of the skeleton.

The process of breast cancer metastasis includes tumor cell seeding, tumor dormancy, and subsequent metastatic growth. The primary tumor releases cells that pass through the extracellular matrix, penetrate the basement membrane of angiolymphatic vessels, and then are transported to distant organs via the circulatory system. Circulating breast cancer cells have a particular affinity for bone. These circulating cells can adhere to the vessels and sinusoids of the bone marrow, invading into the marrow and intertrabecular spaces with the help of adhesion molecules. Tumor cells have been shown to exhibit chemotactic responses to areas of bone undergoing resorption (7). Disseminated tumor cells have been reported in the bone marrow of 30% to 40% of early-stage breast cancer patients at the time of diagnosis (8). Most disseminated tumor cells die, but the bone marrow microenvironment may act as a reservoir for malignant cells and the site for dormant tumor cells that only result in relapse many years after the diagnosis of early breast cancer. Tumor cells have the capacity to produce a wide range of cytokines and growth factors that may increase the production of RANKL and macrophage colony-stimulating factor (M-CSF) from osteoblasts leading to activation of osteoclasts and disturbance of the balance of new bone formation and bone resorption. These

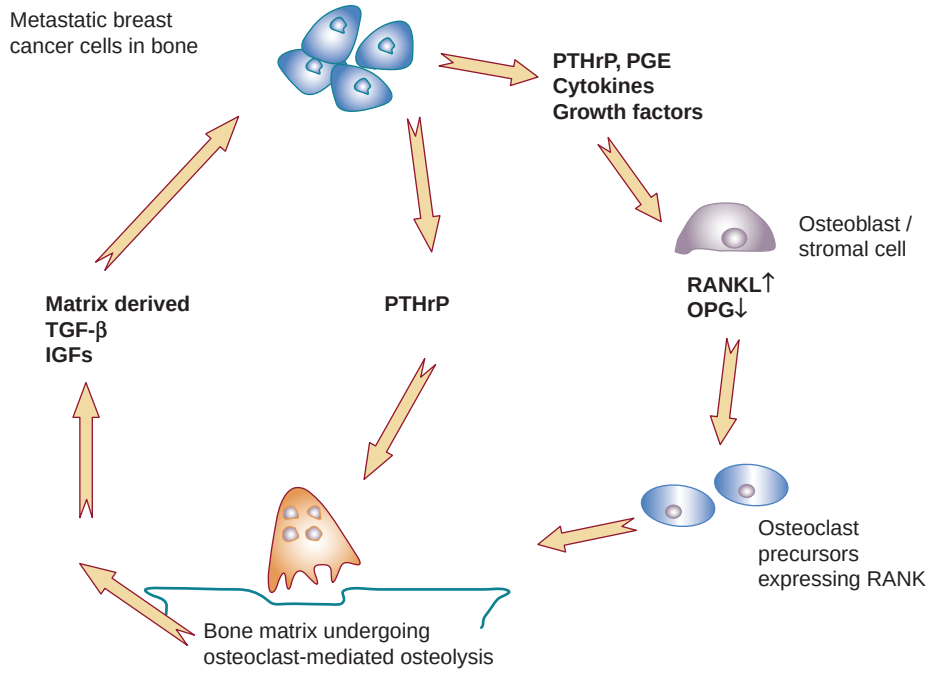

FIGURE 47-1 **This illustration highlights the interaction between breast cancer cells and the bone microenvironment.** A variety of cancer-derived growth factors, including parathyroid hormone-related protein (PTHrP), prostaglandins (PGE), and cytoikines, stimulate osteoclastic activity. Other osteoclast-stimulating cytokines, such as receptor activator of NF-κB ligand (RANKL) and macrophage colony-stimulating factor (M-CSF), are indirectly released through interactions between cancer cells and osteoblasts, macrophages, and other cells within the bone environment. Bone provides a favorable niche for the cancer cell because it is a repository for tumor-stimulating growth factors, such as transforming growth factor β (TGFβ) and insulin-like growth factor (IGF-1), which are released with bone resorption.

multiple interactions between metastatic tumor cells and the bone microenvironment may contribute to the development of metastases both within and outside bone.

Käkönen and Mundy (9) have described a "vicious cycle" that occurs when cancer cells are present adjacent to the bone matrix (Fig. 47-1). Products produced by the tumor induce breakdown of bone, causing release of factors into the local environment that may cause stimulation and further growth of malignant cells, which in turn leads to yet further bone resorption. At the microscopic level, osteoclasts are visible between cancer cells and the bone surface that is being destroyed (10). Osteoclasts are activated by cytokines produced directly or indirectly by the tumor cell, including parathyroid hormone related peptide (PTHrP), prostaglandins, and interleukins (11). As bone matrix is broken down, a rich supply of mitogenic factors is released, including insulin-like growth factor (IGF-1), platelet-derived growth factor (PDGF), and transforming growth factor β (TGFβ). These factors can lead to increased growth and proliferation of the breast cancer metastases (6,11). The overall effect is the creation of a self-sustaining vicious cycle with multidirectional interactions between cancer cells, osteoclasts, osteoblasts, and the bone microenvironment.

BISPHOSPHONATES: AGENTS AND MECHANISM OF ACTION

Bisphosphonates are effective in treating conditions in which there is excessive bone resorption and osteoclast activity, including Paget's disease of bone, osteoporosis, fibrous dysplasia, and hypercalcemia of malignancy. Bisphosphonates have a proven role in reducing skeletal complications in breast cancer patients with bone involvement, and a potential emerging role in the prevention of breast cancer metastases.

Bisphosphonates are analogs of endogenous pyrophosphate, in which a carbon atom replaces the central oxygen atom (Fig. 47-2). As with pyrophosphate, bisphosphonates bind strongly to hydroxyapatite on the bone surface. Unlike pyrophosphate however, which is rapidly split

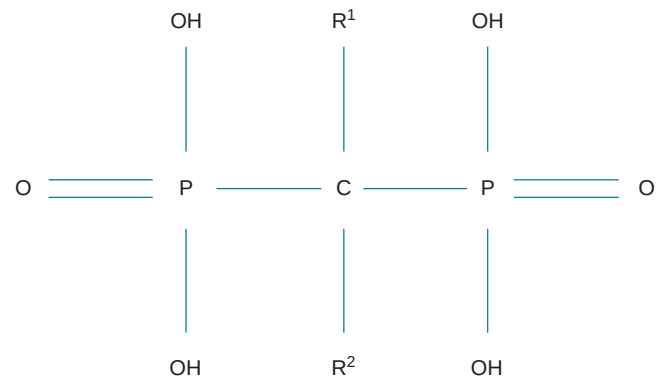

FIGURE 47-2 **The basic chemical structure of bisphosphonates includes a central carbon and two variable side chains (R).** Variations in the side chains alter the potency and side effects of the drugs.

by the hydrolytic enzymes of osteoclasts, bisphosphonates are stable owing to the central carbon substitution that makes them resistant to hydrolysis. This substitution also allows two additional side chains of variable structure that affect the pharmacologic properties of these agents. One of the side chains usually contains a hydroxyl moiety, which allows high affinity for calcium and bone mineral. The structural variation in the other side chain produces differences in the antiresorptive properties and toxicities (12).

Within the family of bisphosphonates, there are more similarities in pharmacologic effects than differences, although side effect profiles, rates of oral absorption, and potency do differ. Although differences in their molecular mechanism of action exist, all therapeutic bisphosphonates have a final inhibitory effect on osteoclast function. Bisphosphonates have a powerful affinity for bone; 40% to 70% of an intravenous administration binds rapidly to the bone surface, preferentially at sites of increased bone formation or resorption with the remainder excreted in the urine. The half-life of bisphosphonates in circulation is less than an hour (13). However, the half-life in bone is very long with biological effects of the most potent agents such as zoledronic acid still evident years after administration of a single dose (14). Once deposited on the bone surface, bisphosphonates are ingested by osteoclasts engaged in bone resorption. These agents interfere with bone resorption by producing a direct toxic apoptotic effect on osteoclasts, and by inhibiting their differentiation and maturation.

Bisphosphonates fall into two classes, based on whether this second side chain is nitrogen-containing or not. First-generation bisphosphonates, such as clodronate and etidronate, do not contain nitrogen. These agents substitute into the production of adenosine triphosphate, which then becomes a toxic adenosine triphosphate analogue that poisons the osteoclast (12). Nitrogen-containing bisphosphonates, such as pamidronate, alendronate, risedronate, ibandronate, and zoledronic acid, interfere with cell signaling and block the prenylation of small signaling proteins that are essential for osteoclast function and survival (12).

Several bisphosphonates are available worldwide for various conditions, with variable antiresorptive potency and route of administration (Table 47-1). The clinical impact of the differences in relative potency between bisphosphonates is not well documented, because only a few direct clinical trial comparisons have been conducted. Although all bisphosphonates can theoretically be administered either orally or intravenously, the oral bioavailability of any bisphosphonate is extremely limited and so for some only intravenous formulations have been developed. The dose and frequency of administration varies depending on the clinical indication, with doses used to treat bone metastases being about 10-fold higher than those used to treat osteoporosis. For example, the zoledronic acid dose approved for treating bone metastases is 4 mg intravenously every 3 to 4 weeks. When used in the treatment of osteoporosis, it is approved as a 5-mg dose once yearly. Ibandronate, available in both oral and intravenous forms, is given 50 mg orally daily or 6 mg intravenously monthly for bone metastases, compared with 150 mg orally monthly or 3 mg intravenously every 3 months for osteoporosis. In the United States, ibandronate is approved only for the osteoporosis indication. Doses of bisphosphonates under investigation in the adjuvant breast cancer setting for prevention of metastases have ranged from full bone metastasis treatment doses to somewhat lower doses or less frequent administrations more similar to the osteoporosis treatment schedules.

TABLE 47-1

Bisphosphonates: Antiresorptive Potency and Route of Administration

Bisphosphonate	*Relative Antiresorptive Potency*	*Route of Administration*
Etidronate	1	Oral, IV
Clodronate	10	Oral
Tiludronate	10	Oral
Pamidronate	100	IV
Alendronate	1,000	Oral
Risedronate	5,000	Oral
Ibandronate	10,000	Oral, IV
Zoledronic acid	100,000	IV

IV, intravenously.

BISPHOSPHONATES AS ADJUVANT THERAPY IN EARLY-STAGE BREAST CANCER

Preclinical data have provided biologic plausibility for a role of bisphosphonates in inhibiting the development of bone metastases. *In vitro* studies have demonstrated that bisphosphonates can inhibit critical steps in development of metastases in the bone, including adhesion and invasion (15). Animal tumor model systems have shown that bisphosphonates can inhibit development of bone metastases, reduce tumor burden in the bones, and improve survival in nude mice injected with human breast cancer cells (5,16,17). Although most animal models suggest that the primary antitumor effect of bisphosphonates is manifested in the bone, some data indicate also an effect of bisphosphonates on extraskeletal metastases. The potential mechanisms involved are summarized in Figure 47-3A. Laboratory experiments have shown also that bisphosphonates can have an impact on cancer cells through antiangiogenic, anti-invasive, and immunomodulatory mechanisms (18–20). Additionally, nitrogen-containing bisphosphonates can directly induce tumor cell apoptosis, inhibit tumor cell proliferation, and synergistically with cytotoxic chemotherapy agents commonly used in breast cancer treatment (5,16,21). The high doses of bisphosphonates that have been used in many laboratory studies suggesting direct anticancer activities are incompatible with the clinical doses and schedules approved for the treatment of cancer patients. Whether a direct antitumor effect of bisphosphonates plays a clinically significant role in the treatment or prevention of cancer in humans remains unproved.

Although bone-targeted treatments have had a profound effect on skeletal morbidity and quality of life in advanced breast cancer, clear improvements in survival of advanced cancer patients have not been seen. The studies may have been underpowered to detect survival advantages or, more likely, reflect the futility of modifying the bone microenvironment to influence the large burden of disease present with overt metastases. However, in the adjuvant setting, where the disease burden is microscopic and potentially more receptive to cellular changes in the bone marrow, the anticancer effects of bone-targeted treatments seen in the preclinical models are more likely to be mirrored in patients.

Phase II exploratory studies in women with early-stage, high-risk breast cancer have reported that monthly

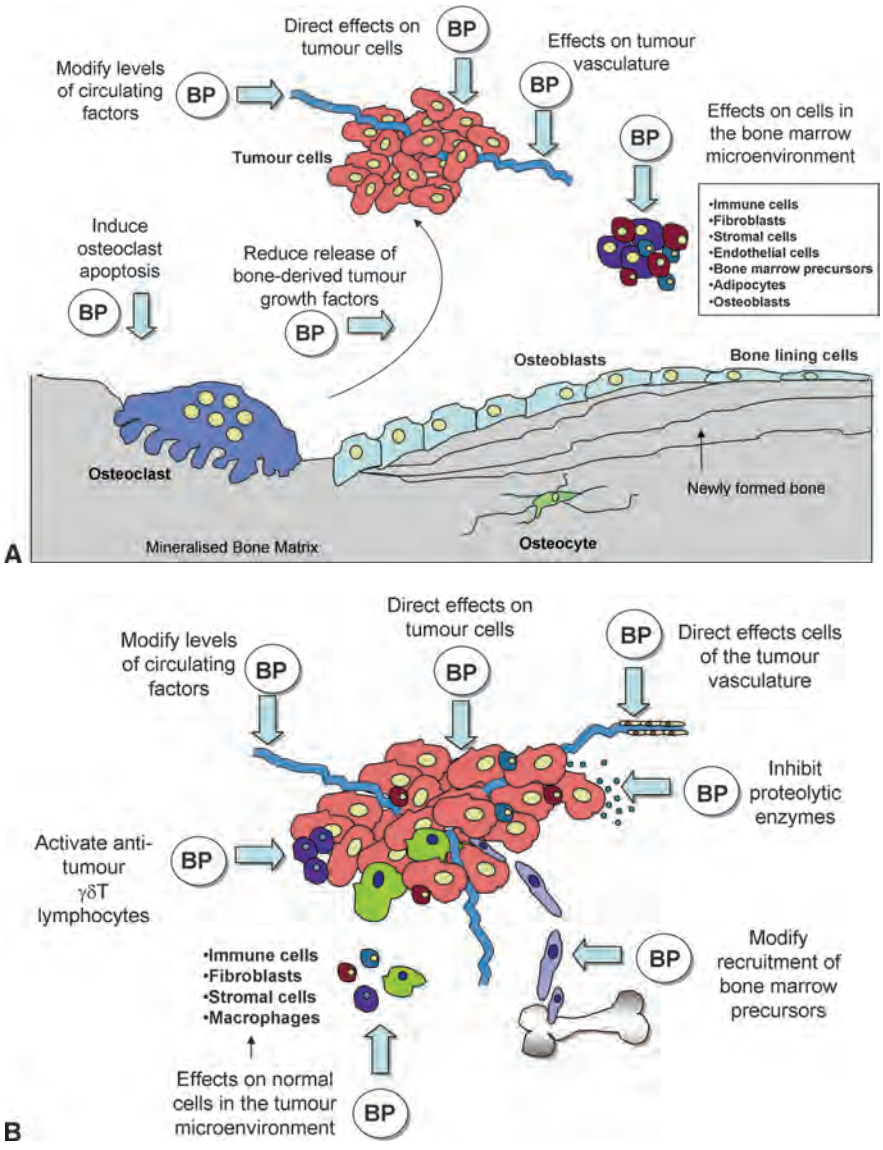

FIGURE 47-3 Potential antitumor effects of bisphosphonates within **(A)** and outside **(B)** bone. BP, bisphosphonates.

zoledronic acid, in combination with standard anticancer therapy, was able to increase the clearance of disseminated tumor cells (DTC) and reduce the number and persistence of DTC in bone marrow compared with standard therapy alone (22–24). The zoledronic acid-mediated reduction in DTC persistence might be one of the mechanisms underlying the observed clinical benefits in the studies described below. However, further studies are needed to determine whether the disease-modifying benefits seen in some patient subsets correlate with decreases in DTC levels.

The early adjuvant clinical trials evaluated oral bisphosphonates with three using daily oral clodronate (25–27) and a fourth daily oral pamidronate (28). Clodronate is approved for the treatment of metastatic bone disease in many parts of the world (except the United States) while the development of oral pamidronate was abandoned due to poor absorption and gastrointestinal toxicity at the high doses required for effects on bone metabolism.

The adjuvant trials evaluating oral clodronate provided promising but conflicting results (25–27). In the first study, 302 women with breast cancer and DTC detected using immunocytochemistry in a bone marrow aspirate (but no overt metastases) taken at the time of diagnosis were randomized to receive either clodronate (1,600 mg/day) or no bisphosphonate for 2 years. Additionally, patients received standard adjuvant systemic therapy (25). Patients who received clodronate had a lower incidence of bone metastases ($p = .003$), and a significantly longer bone metastasis-free survival ($p < .001$). A final analysis at 8.5 years of follow-up continued to show a significant improvement in overall survival for patients given clodronate, although the significance in disease-free survival (DFS) no longer persisted (29).

A larger, randomized, placebo-controlled, multinational trial was conducted in which 1,079 patients with early-stage breast cancer were randomized to receive either clodronate (1,600 mg/day) or placebo for 2 years in addition to standard systemic therapy (26). Patients were assessed for bone metastases at 2 and 5 years, and as clinically indicated. The final analysis showed that oral clodronate significantly reduced the risk of bone metastases at 2 years (hazard ratio [HR] 0.546; $p = .03$) and 5 years (HR 0.692; $p = .04$). A significant reduction was also seen in mortality (HR 0.768, $p = .048$). Follow-up showed a continued separation of the survival curves between years 5 and 10 (26). This reduction

was largely restricted to patients who were postmenopausal at diagnosis of breast cancer.

The third study of oral clodronate was a randomized, open-label study investigating 3 years of adjuvant clodronate therapy (1,600 mg/day) in 299 patients with lymph node–positive breast cancer (27). This study showed no reduction in bone metastases in the clodronate treated arm, and, at least at the time of the initial report, a worrisome increase in visceral metastases and a reduction in overall survival at 5 years for patients receiving clodronate. At the final analysis after 10 years, survival was similar in both groups (30). This small study also had some imbalances in important prognostic factors that may explain the apparent adverse effects with clodronate. Nevertheless, this study had a disproportionate effect on the perception of adjuvant clodronate as an adjuvant treatment and regulatory approval based on the other two positive studies was not achieved. The Danish study with oral pamidronate also failed to show any significant effect on disease outcomes, perhaps due to the poor absorption and patient adherence to treatment (28).

It was not until the first published results of the Austrian Breast and Colorectal Cancer Study Group (ABCSG) 12 trial in 2009 (31) that the potential role of adjuvant bisphosphonates was really appreciated by the breast cancer community and the old "seed and soil" theory of metastasis described in the 19th century by Sir Stephen Paget (32) regained influence in the search for further improvements in the outcome of patients with early breast cancer. The ABCSG 12 trial enrolled 1,803 premenopausal women with estrogen-receptor-(ER-) positive breast cancer. All patients received ovarian suppression for 3 years with goserelin. Patients were randomized in a 2 × 2 design to receive tamoxifen versus anastrozole, and zoledronic acid (4 mg every 6 months) or not.

At the first efficacy analysis, reported after 137 events (70 distant relapses) with approximately 60 months of follow-up, no difference was seen in outcome with respect to the endocrine therapy randomization. There was, however, a statistically significant improvement in DFS for the patients who received zoledronic acid (HR 0.64; $p = .01$). Patients who received zoledronic acid had fewer recurrences at all sites including visceral metastases. Additionally, locoregional recurrence was also less frequent with zoledronic acid. These results were maintained at a later analysis after a median follow-up of 62 months (33). Moreover, after further follow-up (median = 84 months) a persistent benefit in DFS more than 3 years after completion of treatment (HR = 0.71, $p = .011$) suggested a sustained "carryover" benefit from adding zoledronic acid to endocrine therapy (34). In addition at this most recent analysis, there were sufficient deaths in this generally good prognosis population of patients to show that treatment with zoledronic acid also significantly improved overall survival (OS) compared with the control group (HR = 0.61, $p = .033$). Interestingly, and of relevance when the results of the other adjuvant studies are discussed later, this most recent analysis of ABCSG-12 showed that the benefits of zoledronic acid appeared to be confined to women over the age of 40 at diagnosis in whom ovarian suppression with goserelin can be expected to reliably fully suppress estrogen and other reproductive hormone production. In women aged 40 years or younger ($n = 413$), no statistically significant difference in DFS was observed between the zoledronic acid-treated and control groups (HR = 0.87, $p = .53$). However, among women aged 40 years or more at study entry ($n = 1,390$), zoledronic acid resulted in a 34% reduction in the risk of DFS events compared with the control group of patients (HR = 0.66, $p = .013$). Zoledronic acid was also associated with a statistically significant improvement in OS in this older subset of patients (HR = 0.57, $p = .042$) (34).

The ZOledronic acid and FemarA Synergy Trials (European ZO-FAST, North American Z-FAST, and worldwide EZO-FAST) were designed to investigate the effects of zoledronic acid on bone mineral density (BMD) during adjuvant therapy with aromatase inhibitors (35–37). Postmenopausal women with ER+ early breast cancer were treated with letrozole and either immediate zoledronic acid 4 mg every 6 months, or delayed zoledronic acid mandated following a low-trauma fracture or significant decline in BMD. The effects of zoledronic acid on DFS and OS were secondary end points. In ZO-FAST ($n = 1,065$), the immediate zoledronic acid group had a statistically significant 34% reduction in the risk of DFS events versus the delayed zoledronic acid group (HR = 0.66, $p = .038$), with a reduction in breast cancer recurrence both within and outside bone (35). Disease modifying effects in Z-FAST and EZO-FAST were less clear. These studies are smaller and the number of DFS events few. However, in Z-FAST a nonsignificant improvement in DFS was seen (36), while in EZO-FAST, early information on recurrence, showed a nonsignificant disadvantage from treatment with zoledronic acid (37). Taken together the three studies would suggest an approximate 25% improvement in DFS with use of immediate 6 monthly zoledronic acid alongside an aromatase inhibitor for ER+ postmenopausal breast cancer.

The trial titled Does Adjuvant Zoledronic Acid Reduce Recurrence in Stage II/III Breast Cancer? (AZURE) is the largest adjuvant trial of zoledronic acid, and included a broad population of patients with stage II or III breast cancer, unrestricted by menopausal status or ER status. Patients received standard chemotherapy and endocrine therapy and were randomly assigned to receive an intensive regimen of zoledronic acid or a control group. Patients allocated to the zoledronic acid arm received 4 mg intravenously every 3 to 4 weeks for 6 doses to exploit any possible synergy with chemotherapy, and then every 3 to 6 months until 5 years or first evidence of distant metastases (38).

In the overall population, zoledronic acid did not significantly increase DFS compared with standard therapy alone (HR = 0.98, $p = .79$). However, preplanned subgroup analyses identified that menopausal status of the patients at study entry was an important modifier of zoledronic acid treatment effects. For pre- or perimenopausal patients, there was no appreciable difference in DFS (HR = 1.15, $p = .11$) or OS (HR = 0.97, $p = .81$) with zoledronic acid treatment versus standard therapy alone. However, in patients who were postmenopausal for at least 5 years before study entry, zoledronic acid significantly reduced the risk of DFS events by 25% (HR = 0.75, $p = .02$) and the risk of death by 26% (HR = 0.74, $p = .04$). Interestingly, although the effects of ZOL on distant skeletal recurrence did not differ significantly by menopausal groups (heterogeneity test $\chi^2_1 = 0.14$, $p = .70$), for the other components of invasive DFS there was a statistically significant large difference in treatment effect according to menopausal status, with benefit in postmenopausal women and harm in all other women (heterogeneity test $\chi^2_1 = 14.00$, $p \leq .001$). Treatment effects in AZURE were not influenced by ER status.

Recently, the National Surgical Adjuvant Breast and Bowel Project (NSABP) study B-34 has reported results of a placebo-controlled trial of oral clodronate 1,600 mg daily (39). In the total study population after a median follow-up of 8.4 years, oral clodronate had no significant effect on DFS or OS. However, similar to the findings in AZURE, a significant reduction in distant metastasis was seen in patients over age 50 (a surrogate for postmenopausal status) treated with clodronate (HR = 0.62; $p = .003$). Again the benefit was greatest in preventing recurrence at extraskeletal sites.

TABLE 47-2

Summary of Populations, Treatment Schedules, and Primary Outcomes in Key Trials Evaluating the Adjuvant Use of Clodronate or Ibandronate in Early-Stage (Stages I–III) Breast Cancer

	Trial (reference)		
Characteristic	*CLODROPLAC (26)*	*NSABP B-34 (39)*	*GAIN (40)*
Population	1,069 women pre- and postmenopausal women with stage I–III early breast cancer receiving standard chemotherapy and/or hormonal therapy.	3,323 women pre- and postmenopausal women with stage I–III early breast cancer receiving standard chemotherapy and/or hormonal therapy.	3,023 women pre- and postmenopausal women with stage II–III early breast cancer receiving one of two intensive chemotherapy regimens.
Treatment	Patients were randomly assigned to receive standard adjuvant treatment with or without oral clodronate (160 mg daily) for 2 years.	Patients were randomly assigned to receive standard adjuvant treatment with oral clodronate (1,600 mg daily) or placebo for 3 years.	Patients were randomly assigned to receive adjuvant chemotherapy with or without oral ibandronate (50 mg daily) for 2 years.
Primary outcomes	Clodronate group had a reduced risk of bone metastases (HR = 0.692, p = .043) and improved OS (HR = 0.768, p = .048).	DFS did not differ between ITT groups: HR 0.91, 95% CI 0.78-1.07; p = .27. In women aged 50 years or older on study entry clodronate improved RFI (0.75, 0.57–0.99; p = .045), BMFI (0.62, 0.40–0.95; p = .027), and NBMFI (0.63, 0.43–0.91; p = .014), but not OS (0.80, 0.61–1.04, p = .094).	No differences in DFS or OS in ITT population. In patients who were aged 60 or older a trend for improved disease outcomes was observed.

CLODROPLAC, Royal Marsden trial of oral clodronate versus placebo in stage I–III early breast cancer; NSABP B-34, National Surgical Adjuvant Breast and Bowel Project—Breast protocol 34; GAIN, German adjuvant ibandronate study: All p values quoted are two-sided; HR, hazard ratio; CI, confidence intervals; DFS, disease-free survival; OS, overall survival; RFI, relapse-free interval; BMFI, bone metastasis-free interval; NBMFI, nonbone metastases-free interval; ITT, intention to treat.

Finally, the German adjuvant ibandronate study (GAIN) randomized 3,023 women with breast cancer and involved axillary lymph nodes to one of two chemotherapy regimens plus either oral ibandronate 150 mg daily or a control group. With a short median follow up of 31 months, no significant differences in DFS (HR = 0.94, p = .59) or OS (HR = 1.04, p = .80) between the ibandronate and placebo treated groups were seen (40). There was a trend in favor of ibandronate in postmenopausal women or those over the age of 60, but insufficient events have occurred for reliable subgroup analyses.

A summary of the major randomized trials of adjuvant bisphosphonates reported to date is provided in Tables 47-2 and 47-3. The results from NSABP B-34 (39) and the previous clodronate study by Powles et al. (26) suggest that the beneficial effects of bisphosphonates in solid tumors may be less dependent on the type of agent chosen and more on the hormonal status of the patient. The ongoing South West Oncology Group (SWOG) clinical trial SWOG-0307 (NCT00127205) comparing zoledronic acid, ibandronate, and clodronate has recently completed accrual and will address the relative efficacy of oral clodronate (1,600 mg daily) versus oral ibandronate (50 mg daily) versus zoledronic acid (4 mg intravenously monthly for 6 months, then every 3 months), all for 3 years in both pre- and postmenopausal women.

There are also ongoing adjuvant studies with denosumab, a monoclonal antibody with high specificity for RANKL that has been shown to be more effective than zoledronic acid in preventing skeletal morbidity from bone metastases in advanced breast cancer (41). ABCSG-18 (NCT00556374) is a placebo-controlled study of denosumab 60 mg 6 monthly in postmenopausal women receiving an aromatase inhibitor, while the D-CARE study (NCT01077154) is evaluating a more intensive schedule of denosumab 120 mg, administered initially monthly for 6 months and then every 3 months thereafter in both pre- and postmenopausal women with stage II or III breast cancer. Accrual to D-CARE completed in 2012, but results are not anticipated before 2016.

The interactions between reproductive hormones and the paracrine TGFβ growth factors may provide an explanation for the differences seen according to ovarian function in the response to bisphosphonates. At menopause, serum oestradiol and inhibin decline over several years and follicle-stimulating hormone (FSH) levels rise. In the absence of inhibin, the TGFß ligand activin becomes the dominant signaling molecule in bone. Inhibin binds to the activin type II receptor and activates the SMAD family of proteins that are known to have important effects on both bone and cancer cell functions. Both activin and TGFβ will support homing of disseminated tumor cells to bone by increasing the chemokine CXCL4, and stimulating osteoclastic bone resorption leading

TABLE 47-3

Summary of Populations, Treatment Schedules, and Primary Outcomes in Key Trials Evaluating the Adjuvant Use of Zoledronic Acid in Early-Stage (Stages I–III) Breast Cancer

	Trial (reference)		
Characteristic	*ABCSG-12 (31,33,34)*	*ZO-FAST (35)*	*AZURE (38)*
Population	1,803 premenopausal women with endocrine-receptor-positive early-stage breast cancer receiving goserelin to induce menopause (3.6 mg every 28 days).	1,065 postmenopausal women with early-stage breast cancer receiving letrozole (2.5 mg per day for 5 years).	3,360 pre- and postmenopausal women with early-stage breast cancer receiving standard chemotherapy and/or hormonal therapy.
Treatment	Patients were randomly assigned to receive anastrozole (1 mg per day) or tamoxifen (20 mg per day) with or without zoledronic acid (4 mg every 6 months) for 3 years.	Patients were randomly assigned to receive immediate zoledronic acid (4 mg every 6 months) or delayed zoledronic acid (initiated only for fracture or high risk thereof).	Patients were randomly assigned to receive zoledronic acid 4 mg every 4 weeks × 6, then every 3 months × 8, then every 6 months until 5 years or until first evidence of distant metastases.
Primary outcomes	Zoledronic acid group had a 29% relative risk reduction for DFS (HR DFS event = 0.71, 95% CI = 0.55–0.92; p = .011) (54). Benefit largely restricted to women aged 40 years or older at study entry.	Immediate zoledronic acid group had a 34% relative risk reduction for DFS (HR of DFS event = 0.66, 95% CI = 0.44–0.97; p = .038) (57)	No differences in DFS or OS in ITT population. In patients who were postmenopausal for at least 5 years before study entry, zoledronic acid group had a 25% relative risk reduction for invasive DFS (HR of DFS event = 0.75, 95% CI = 0.59–0.96; p = .02) and the risk of death by 26% (HR of death = 0.74, 95% CI = 0.55–0.98; p = .04).

All p values quoted are two-sided. ABCSG-12, Austrian Breast and Colorectal Study Group-12; ZO-FAST, Zoledronic acid and FemarA Synergy Trial; AZURE, Does Adjuvant Zoledronic Acid Reduce Recurrence in Stage II/III Breast Cancer?; HR, hazard ratio; CI, confidence intervals; DFS, disease-free survival; OS, overall survival; ITT, intention to treat.

to greater availability of bone derived growth factors. In premenopausal women, the cycling endocrine effect of estrogen, progesterone, and inhibin has the potential to inhibit activin and TGFß signaling. In a postmenopausal woman, the loss of inhibin, estrogen, and progesterone will reduce inhibition of the TGFß superfamily, and thus the relative biological activity of activin and TGFß will increase (42,43).

Quite how the variable effects of reproductive hormones on the bone microenvironment explain the differential effects on extraskeletal recurrence according to menopausal status remains unclear. However, elegant experiments have demonstrated the ability of breast cancer cells to reseed from bone to other distant sites and back to the breast (44), perhaps suggesting that the bone microenvironment is the key coordinator in the metastatic process, determining the fate of cancer cells not only within bone but also at other distant sites.

Whether doses used in metastatic disease are required for prevention or alternatively that lower doses will suffice is unknown. It is unclear whether adjuvant bisphosphonates should be given continuously and orally, whether intravenous therapy is preferable, and whether less intensive intravenous regimens will turn out to be as effective as more intensive regimens. The optimal duration of adjuvant bisphosphonate therapy is also unknown.

BONE HEALTH IN PATIENTS WITH BREAST CANCER

Most women with breast cancer are at risk for osteoporosis, owing to either their breast cancer therapy or their age (45). The use of bone-targeted agents in preventing bone loss is a subject of increasing clinical importance in breast cancer patients. Aromatase inhibitors, increasingly used in postmenopausal breast cancer patients, have a detrimental impact on bone mineral density and increase fracture rates (46,47). In the premenopausal setting, ovarian suppression and chemotherapy-induced ovarian failure can lead to rapid, profound loss of bone density (48). Accelerated bone loss brings with it an increased fracture risk, which affects quality of life, treatment costs, and potentially survival (46,48). The American Society of Clinical Oncology (ASCO) 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer stated that oncology specialists need to take an expanded role in managing bone health in breast cancer patients (49).

Women with early-stage breast cancer should be evaluated for fracture risk. Counseling on nutrition and lifestyle for bone health is advised for all patients, and appropriate calcium and vitamin D supplementation is recommended. Vitamin D supplementation is particularly important as

only a minority of women with breast cancer have sufficient levels of vitamin D (50). Pharmacological therapy to prevent bone loss should be considered on an individualized basis based on bone mineral density and other fracture risk factors (including age, body mass index, personal and family history of fracture, smoking, alcohol consumption, and corticosteroid use). Evidence from randomized trials indicates that several intravenous and oral bisphosphonates can be effective in preventing bone loss and accelerated bone turnover in breast cancer patients receiving endocrine or chemotherapy (35–37,51–59). The comparative efficacy of these bisphosphonates has not been defined.

In premenopausal women, studies have shown that clodronate (53), risedronate (54), alendronate (55), and zoledronic acid (51) prevent and reduce bone loss caused by chemotherapy-induced menopause, ovarian suppression with LHRH analogues, and tamoxifen (which has a net negative effect on bone in the premenopausal setting in contrast to its positive effect in the postmenopausal setting).

The ABCSG-12 study prospectively examined the effects on bone density caused by ovarian suppression combined with tamoxifen or anastrozole, with or without zoledronic acid (4 mg every 6 months) in premenopausal women (51). In addition to the improvement in DFS described above (31,33,34), the addition of zoledronic acid inhibited loss of bone mineral density in both the tamoxifen and anastrozole arms and stabilized it at baseline levels. Without zoledronic acid, significant bone loss occurred; the mean reductions in bone mineral density at 3 years were 8% and 16%, with tamoxifen and anastrozole, respectively.

The Cancer and Leukemia Group B (CALGB) recently reported first results of C79809, a randomized trial of zoledronic acid (4 mg every 3 months) in premenopausal women who developed ovarian failure owing to adjuvant chemotherapy (58). The mean percentage change in lumbar spine bone mineral density at 12 months was +2.6% in the group receiving zoledronic acid, and –6.4% in the control group ($p<.0001$). Zoledronic acid added minimal toxicity and prevented the accelerated bone loss occurring in young women who developed ovarian failure from adjuvant chemotherapy.

In postmenopausal women receiving aromatase inhibitor therapy, studies have evaluated the impact of risedronate (57) and zoledronic acid on bone density (35–37). In the Z-FAST and ZO-FAST studies, comparing immediate versus delayed zoledronic acid (4 mg every 6 months), the powerful bone protective effects of twice yearly treatment on BMD were clearly demonstrated. In both of these studies, the differences in lumbar spine and total hip BMD at 5 years between patients receiving immediate or delayed treatment were approximately 9% and 6%. Less than 20% of patients on the delayed treatment arm met the protocol-specified criteria for starting zoledronic acid for T-score changes or fractures, however, and no significant differences in fracture rates were seen. Early reports of smaller randomized trials of risedronate and ibandronate in postmenopausal women receiving aromatase inhibitor therapy have also shown favorable impacts on bone mineral density (57,59).

A recent trial reported results for the RANK ligand inhibitor denosumab (60 mg subcutaneously every 6 months) versus placebo given to women receiving aromatase inhibitors in early-stage breast cancer (60). Rapid and significant gains in BMD at both the axial (spine and hip) and peripheral (wrist) sites were seen with denosumab, compared with slight bone loss in the placebo-treated patients.

As in the setting of postmenopausal bone loss and osteoporosis, bisphosphonates and denosumab are effective in preventing cancer treatment-associated loss of bone mineral density. Many issues need to be clarified to determine optimal management of bone loss in women with breast cancer. Whether early implementation of bisphosphonates will have an impact on long-term fracture rates remains a critical question. Is there harm incurred in delaying therapy until patients meet criteria for significant increased fracture risk? That very much depends on whether the benefits of bisphosphonates on disease recurrence are accepted. If they are, an argument can be made for all postmenopausal women to receive a bisphosphonate, irrespective of fracture risk. If not, treatment should be restricted to those at a relatively high absolute risk of fracture (46,48). To date we have no direct comparison of agents or delivery routes to guide in drug selection. It will also be important to determine which early-stage breast cancer patients are at most risk of clinically significant bone loss, and who will benefit most from early addition of bisphosphonates for preservation of bone mineral density.

SAFETY AND ADVERSE EFFECTS OF BISPHOSPHONATES

As a group, bisphosphonates are generally well tolerated at both osteoporosis and bone metastases treatment doses. Few serious adverse effects have been reported in clinical trials when given either orally or intravenously. Gastrointestinal toxicity in the form of dyspepsia is the most common side effect for oral agents. Esophageal inflammation and ulceration are described as rare but serious adverse effects (61). The efficacy of oral bisphosphonates is compromised by poor absorption. Generally, only a low percentage of an oral dose is absorbed from the gastrointestinal tract and intake of any food or beverage further diminishes absorption to negligible levels. Patients are therefore advised to take their oral medication in the morning on an empty stomach and wait 30 to 60 minutes before eating to maximize absorption.

Intravenous bisphosphonate administration can be associated with acute-phase reactions, which include flu-like symptoms, such as bone pain, transient arthralgia and myalgia, nausea, and fever. These reactions typically occur only after the first or second infusion, and symptoms usually resolve within 48 hours. The symptoms typically respond well to antipyretic and nonsteroidal anti-inflammatory drugs, and are not an indication to discontinue treatment. Hypocalcemia is another reported complication of bisphosphonate therapy. Clinically relevant hypocalcemia is rare, and generally may be prevented with the addition of supplemental calcium and vitamin D. FDA-approved labeling for pamidronate and zoledronic acid recommends periodic monitoring of serum calcium, electrolytes, phosphate, and magnesium. Hypocalcemia is also an important potential adverse effect of denosumab. However, denosumab has the advantage that acute phase responses are much less frequent and renal monitoring is not required.

Bisphosphonates have a potential for renal toxicity. The pharmacokinetics vary from agent to agent, and between oral and intravenous formulations, but all bisphosphonates are excreted via the kidneys. Clinical trials with pamidronate and zoledronic acid have shown renal toxicity, especially in patients with preexisting renal impairment (62). Increased dose, frequency, and speed of infusion are all related to the risk of renal toxicity; reducing the dose and slowing the infusion decrease toxicity. It is recommended that serum creatinine be monitored before each dose of these drugs. For patients with renal impairment or reduced creatinine clearance, it is recommended that the dose be reduced.

Osteonecrosis of the jaw (ONJ) has been reported to occur in cancer patients treated with intravenous bisphosphonates

(63,64). This entity is defined as an area of exposed, nonhealing bone in the maxillofacial region. The most common predisposing factors appear to be the type and total dose of bisphosphonate, a history of dental surgery (such as tooth extraction), and dental trauma (65). The true incidence of this problem is still not known, especially in the adjuvant setting. It appears to be most commonly associated with zoledronic acid when used at bone metastasis treatment doses, and is rarely seen with oral bisphosphonates used at osteoporosis treatment doses. It is recommended that before initiating bisphosphonate therapy, particularly intravenous administration, patients should receive a dental examination and appropriate preventive dentistry (66). While on therapy, patients should maintain excellent oral hygiene and avoid, if possible, invasive dental procedures. In the AZURE adjuvant breast cancer trial, with a median follow-up of 73.9 months, 26 cases of ONJ were reported, all in the zoledronic acid treated patients, representing a cumulative incidence of 2.1% (95% CI 0.9–3.3%). The median number of zoledronic acid administrations before onset of ONJ was 13 (range 1–19) and median time from randomization to onset was 863 days (range 21–2,767) (67). With the 6 monthly administration used in ABCSG 12 and ZO-FAST, the cumulative incidence of ONJ appears to be lower at less that 1%.

CONCLUSIONS

Bisphosphonates are a promising group of compounds in the adjuvant breast cancer setting. This class of drugs has two potential roles in the treatment of early-stage breast cancer patients: prevention of metastasis with resultant improved disease-free and overall survival, and prevention and treatment of osteoporosis.

Preclinical studies provide good proof of principle for the role of bisphosphonates in preventing the growth and development of bone metastases. There is also increasing evidence of clinically relevant anticancer response to bisphosphonates in disease outside the skeleton. Recent adjuvant studies in breast cancer patients have shown efficacy in a low-estrogen environment (postmenopausal women, and premenopausal women treated with GnRH agonists), with improvements in both local and distant DFS. Ultimately, we would like to determine which adjuvant breast cancer patients might benefit most from the addition of bisphosphonates to maximize benefit and minimize costs and risk. Tumor or patient characteristics, biomarkers, and bone marrow micrometastases may predict who is at highest risk for bone recurrence.

Breast cancer patients can have an added benefit from bisphosphonates, unrelated to the reduction of bone metastases, in the form of preservation of bone density. Several recent trials in early-stage breast cancer patients have demonstrated that bisphosphonates (and denosumab) are effective in treating and preventing bone loss associated with cancer treatment. Optimal timing of initiation of bisphosphonates to suppress loss of bone density, whether early in the treatment course or after bone loss has occurred, has not been established. The major studies of bisphosphonates in cancer treatment-induced bone loss have not yet shown clinically significant differences in fracture rates.

In addition to bisphosphonates and densoumab, several new classes of agents with antiosteoclastic activity are in various stages of investigation for treatment of bone metastases, prevention of bone metastases, and prevention and treatment of osteoporosis. These include radium-223, src kinase inhibitors, and cathepsin-k inhibitors. The relative efficacy and toxicity profiles of these agents compared with bisphosphonates and denosumab will be of great future interest.

MANAGEMENT SUMMARY

- The use of bisphosphonates or denosumab in the adjuvant setting has not been approved by the regulatory agencies. However, the use of bisphosphonates in women with early-stage breast cancer with the intention of reducing bone metastases is currently supported by the available clinical data for women who have passed through menopause or who are receiving ovarian suppression therapy.
- Adjuvant bisphosphonates are not recommended in women with ongoing ovarian function. Treatment in the presence of premenopausal levels of reproductive hormones may increase the risk of recurrence.
- Before initiating bisphosphonates, baseline dental examinations should be performed, to identify and treat oral problems that could lead to the need for dental surgery. It is important that patients maintain good oral hygiene, undergo regular dental examination, and be advised on appropriate measures for reducing the risk of osteonecrosis of the jaw.
- When giving intravenous bisphosphonates, it is advised that serum creatinine be checked before infusion. The dose of bisphosphonate may need to be adapted to renal function.
- All breast cancer patients on high-dose bisphosphonates or denosumab should be advised to take calcium and vitamin D supplementation to avoid the risk of hypocalcemia. Periodic monitoring of serum calcium, electrolytes, phosphate, and magnesium should be performed.
- Women with early-stage breast cancer should be evaluated for their bone density and risk of fracture. Nutritional vitamin D supplementation and lifestyle interventions should be advised for all women. Early-stage cancer patients at risk of developing cancer treatment-induced bone loss should be monitored by bone mineral density and considered for bisphosphonate treatment.

DISCLOSURES

Robert Coleman has received consultancy and speaker fees from Amgen and Bayer and given expert testimony on behalf of Novartis.

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CHAPTER 48

Pharmacogenomics of Systemic Therapy

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CHAPTER CONTENTS

INTRODUCTION TO PHARMACOGENETICS AND PHARMACOGENOMICS

Over the past half century, a large number of studies on the genetic diversity of human drug response have shown that a person's unique genetic makeup is a major determinant of idiosyncratic adverse drug reactions and therapeutic failure (1). This field, designated pharmacogenetics or pharmacogenomics, is defined as the study of inherited genetic polymorphisms (mostly single nucleotide polymorphisms [SNPs]) in genes that code for proteins responsible for a drug's pharmacokinetic (absorption, distribution, metabolism, and excretion) and pharmacodynamic (target interaction and signaling alterations) properties. The first groundbreaking pharmacogenetic studies identified gene variants that had profound effects on gene function and these variants had major effects on patient drug response. The advent of high throughput and cost effective DNA sequencing technologies have ushered in the new era of "pharmacogenomic" investigations which use a multi-gene or whole genome approach to identify the germline genetic causes of inter-patient variable drug response.

Pharmacogenetics and pharmacogenomics are shaping the future of personalized medicine, the concept of tailoring the type and dose of drug based on a patient's unique genetic makeup. This approach promises to have a significant impact in the field of oncology, in which the currently available drugs exhibit substantial variability in their pharmacokinetics and pharmacodynamics and only a limited number of generic therapeutic strategies are employed for all patients. The concept of personalized medicine embraces the goal of "finding the right drug at the right dose for the right patient."

For the most part, the practice of personalized medicine in breast cancer treatment has been based on using the somatic changes acquired by the cancer during the malignant process to select a therapeutic strategy most likely to be of benefit. Perhaps the two best examples of this approach are the use of estrogen receptor (ER) over-expression and HER-2 over-expression for the selection of anti-estrogen and anti-HER-2 therapies, respectively. A superior understanding of the estrogen-sensitive biology of the tumor (2) has meant that the treatment of breast cancer has led the treatment of many other cancers. The use of tumor-based markers such as the estrogen and progesterone receptors to guide endocrine therapy, first with tamoxifen worldwide and now with the aromatase inhibitor class of drugs, is the standard of care worldwide (3). These advances have been supplemented by the advent of HER2 based therapy in the form of trastuzumab aimed at tumors that express the HER2 receptor (4). The targeting of therapy based on tumor estrogen, progesterone, and human epidermal growth factor receptor 2 expression has recently been supplemented by the use of RNA expression-based biomarkers that can be used to predict the benefits of chemotherapy with the best example being the clinically used Oncotype Dx™ 21 gene array assay (5).

While approaches based on tumor biology have clearly resulted in improvements in recurrence free survival, the morbidity and mortality associated with breast cancer remain unacceptably high, and the toxicity of current therapies results in unacceptably low levels of compliance. As a result, the need for further improvements in targeting and treatment remains high, and the possibility that inherited variants in genes that control the metabolism, distribution and elimination of drugs, and that code for their targeted receptors and signaling pathways might be important predictors of drug effects and toxicity in breast cancer. The availability of high throughput genomic technologies that are able to screen for hundreds of thousands of individual variants at once has provided insights into the pathogenesis of breast cancer (6), and is now poised to identify inherited genetic associations with responses to specific therapies.

It seems particularly important to explore the inherited germline for clues to therapeutic response, when it is clear

that the treatments now available have been tested and validated in primarily Caucasian populations. Our ability to treat breast cancer in African-Americans, in whom the incidence of breast cancer is 20% lower than that in Caucasians, but the mortality is 20% higher, would appear more limited. Similarly, the notably increasing rates of lethal breast cancer in Asian populations (7) demands serious attention to the question of whether we can ignore differences in response to therapy that might be based not on tumor biology, but on the inheritance of factors that might alter drug efficacy and toxicity. There is widespread precedent for the concept of pharmacogenomics in other fields of medicine where, for example, it is recognized that 7% of the population experience little analgesic benefit from codeine because they lack the ability to metabolize codeine to morphine via the CYP2D6 enzyme (8), or experience an increased risk of intracranial bleeding while being treated with warfarin due to variants in the *CYP2C9* or *VKCOR* genes (9). In addition, a number of pharmacogenomic tests are already available in other areas of cancer treatment.

PHARMACOGENOMICS IN MEDICAL ONCOLOGY

Thiopurine S-methyltransferase and the Metabolism of Mercaptopurines

Perhaps one of the best studied examples for the application of pharmacogenomic strategies to prevent adverse drug reactions is the polymorphism of the thiopurine S-methyltransferase (*TPMT*) gene (9). *TPMT* catalyses the S-methylation of thiopurine drugs such as mercaptopurine and its prodrug azathioprine. These drugs are successfully used to treat acute lymphoblastic leukemia (ALL), and gastroenterologists prescribe thiopurine drugs as second-line (off-label) therapy for Crohn's disease and ulcerative colitis. Because methylation by *TPMT* is the predominant pathway for inactivation of thiopurines, patients with *TPMT* deficiency accumulate active thioguanine nucleotides and this can lead to severe and life-threatening hematological toxicity. *TPMT* activity in erythrocytes is trimodally distributed among Europeans, European-Americans, and African-Americans and this distribution corresponds well to the genotypes or the respective presence of 2, 1, or 0 functional *TPMT* alleles. Twenty mutant alleles of *TPMT* have been associated with low *TPMT* activity and 3 of these variants (*TPMT*2, TPMT*3A* and *TPMT*3C*) account for approximately 95 % of low *TPMT* activity phenotypes. Approximately 1 in 150–300 individuals is homozygous for inactive *TPMT* alleles, approximately 10% of patients are heterozygous and have intermediate activity and approximately 90% are normal or high methylators in a Northern European Caucasian population (10).

Because of the strong genotype–phenotype concordance and the severe toxicity associated with high concentrations of thioguanine nucleotides, several cancer centers routinely genotype patients for *TPMT* mutant alleles and use genotype-derived algorithms for dosing. Intermediate metabolizers receive approximately 65% and poor metabolizers 5% to 10% of standard doses of mercaptopurine (11). Dose reductions in patients with variant *TPMT* alleles lead to similar or superior survival compared to patients with wild-type alleles.

Of major concern is a report of an increased incidence of secondary brain tumors after radiotherapy in children with decreased *TPMT* activity phenotypes and/or high concentrations of thioguanine nucleotides in blood cells (12). The implications for therapeutic decisions regarding prophylactic radiotherapy in ALL, therefore, must be further investigated.

Uridine Diphosphate glucuronosyltransferase (*UGT*) 1A1 and the Metabolism of Irinotecan

Results from several recently published trials suggest that patients who are homozygous for a *UGT* gene variant known as *UGT1A1*28* (the "7/7" genotype) are at greater risk for irinotecan-induced severe diarrhea or neutropenia (13). Irinotecan is a camptothecin analogue and acts on cancer via inhibition of topoisomerase. The disposition of irinotecan is complex and involves numerous metabolic enzymes and transport proteins. SN-38 is the active metabolite of irinotecan and is eliminated via *UGT1A1* conversion to SN-38G, an inactive glucuronide cleared via biliary excretion. Reduced activity of *UGT1A1* is linked to an approximately four fold increased risk of severe toxicity, including dose-limiting diarrhea and neutropenia. Significant correlations between patients carrying one or two copies of the *UGT1A1*28* allele and reduced *UGT1A1* expression and reduced SN-38 glucuronidation are now been well documented.

More than 50 mutations in *UGT1A1* have been reported, many of which are found in patients with Gilbert's syndrome, a form of mild nonhemolytic unconjugated hyperbilirubinemia. The most common mutant gene is *UGT1A1*28*, which contains 7 dinucleotide repeats in the TATA box of the promoter ($A(TA)_7TAA$) instead of the normally 6 repeats, and leads to approximately 70% reduction of transcriptional activity. Many rare mutations also lead to Gilbert's syndrome, and individuals with this syndrome are predisposed to SN-38 initiated toxicity. Although, as always, a number of additional factors influence the toxicity of SN-38 in the intestine and bone narrow, assessment of the presence of the *UGT1A1*28* allele in patients prior to irinotecan treatment may allow lower starting doses or change to alternative therapies. Although there are pharmacogenetic studies that support this position, it is also clear the association of this toxicity with *UGT1A1* genotype is irinotecan dose-dependent (14). As a result, many oncologists prefer to simply adjust the irinotecan dose and avoid *UGT1A1* genotyping.

PHARMACOGENOMICS STUDIES IN BREAST CANCER

The study of pharmacogenomics in breast and other cancers has been impaired in part by the lack of availability of germline DNA from properly consented patients in the majority of large prospective clinical cancer trials. This is in contrast to other medical disciplines, where the collection of blood, buccal swabs, or saliva to allow extraction of germline DNA has been routine for many years. This obstacle in cancer trials has been overcome, in part, by the key demonstration that effective germline genotyping can be carried out on DNA extracted from paraffin blocks (15). The technical ability to genotype germline DNA from paraffin opens up the possibility of testing pharmacogenomic hypotheses in a large number of clinical studies that have available archived paraffin-embedded specimens with associated well annotated clinical outcomes data. As a result, significant progress has been made in studies designed to examine germline genetic associations with both the efficacy and toxicity of treatments for breast cancer (16).

Genetic Variants Associated with Toxicity of Agents Used to Treat Breast Cancer

Cyclophosphamide Activation by Cytochrome P450 Enzymes

A majority of chemotherapeutic regimens that have been used to treat all stages of breast cancer have used cyclophosphamide as an integral component. Cyclophosphamide

is a prodrug that requires metabolic activation by cytochrome P450 (CYP) enzymes to 4-hydroxycyclophosphamide. Multiple CYPs have been implicated in this activation, including CYP2A6, 2B6, 2C19, 2C9, 3A4, and 3A5 (17). Interestingly, CYP2C19 appears to be the predominant enzyme responsible for cyclophosphamide activation, particularly at low drug concentrations. CYP2C19 is a genetically polymorphic enzyme that is expressed primarily in the liver and that has been shown to be responsible for the metabolism of a wide range of important therapeutic agents (18). The genetic variants in *CYP2C19*, which have now been studied in a wide range of human populations, results in complete absence of enzyme activity in 3% to 5% of Caucasians and in 15% to 25% of Asian populations. In addition, the *CYP2C19*17* allele, which is present in 18% of Caucasians and Africans, and 4% of Asians, codes for a significantly more active enzyme, and interestingly, has been associated with a decreased risk for breast cancer (19). It is reasonable to hypothesize that those individuals who do not carry active *CYP2C19* alleles may experience less prodrug activation and, therefore, decreased cyclophosphamide efficacy and treatment related side effects. Furthermore, those individuals who carry the more active *CYP2C19*17* allele may experience exaggerated drug response at standard doses.

Thus, in a study conducted in lupus nephritis patients taking cyclophosphamide monotherapy, it was found that *CYP2C19*2* is a predictor of premature ovarian failure and progression to end-stage renal disease (20). These findings have been validated by other investigators; however, not all studies to date have been able to reproduce the association (21). While the precise mechanism of this effect is unclear, these observations suggest that a line of *in vitro* and clinical investigations are necessary to determine the cause of ovarian toxicity, and thus to prevent it in women at risk, an example of "reverse" translational research. Although these studies suggest that there is clinical relevance to the role of *CYP2C19* in the use of cyclophosphamide in other settings, studies to test whether these variants in *CYP2C19* or variants in other candidate genes are associated with cyclophosphamide outcomes in breast cancer are not available at present.

Vincristine Inactivation by Cytochrome P450 Enzymes

While cyclophosphamide is used in a large number of adjuvant regimes used in breast cancer, the use of vincristine is confined to the metastatic setting. After many years during which the metabolism of vincristine was poorly understood, it has recently been shown that vincristine is primarily metabolized by a highly genetically polymorphic enzyme: *CYP3A5* (22). This enzyme has two common polymorphisms (*CYP3A5*3* and *CYP3A5*6*) that cause alternative splicing and protein truncation resulting in the absence of functional *CYP3A5* enzyme production in patients with the homozygous variant genotype. Interestingly, *CYP3A5* is more frequently expressed in livers of African-Americans (60%) than in Caucasians (33%) due to ethnic differences in the *CYP3A5*3* and **6* alleles frequencies (23). In a clear demonstration of the potential clinical relevance of this variability, Caucasians recently have been shown to be notably more vulnerable to vincristine-related neurotoxicity than African-Americans (24). Four percent of total doses administered to Caucasian patients were reduced due to vincristine-related neurotoxicity compared to 0.1% given to African-Americans ($p < .0001$), and 1.2% of all protocol-indicated doses for Caucasians were held due to severe vincristine-associated toxicity compared to 0.1% of doses for African-Americans ($p < .01$). The association between vincristine-induced neurotoxicity and *CYP3A5* genotype was confirmed in a prospective study of children with precursor B cell acute lymphoblastic leukemia (25). Together, these studies suggest that the unpredictable neurotoxicity that patients experience with vincristine may actually be predictable, and that *CYP3A5* genotype may contribute. However, further studies are required to determine whether *CYP3A5* genotype will have clinical utility for predicting side effects associated with vincristine and other chemotherapeutic agents metabolized by the *CYP3A5* drug metabolism pathway.

Tamoxifen Pharmacogenomics

Mortality from breast cancer has been declining over the last two decades. Much of this decline is due to the widespread application of endocrine therapy, of which there are two major types: (i) selective estrogen receptor modulators (SERMs) including tamoxifen; and (ii) aromatase inhibitors (AI) including anastrozole, letrozole, and exemestane. These drugs have clearly played a substantial role in decreasing breast cancer mortality rates, especially when used in the adjuvant setting (26). Tamoxifen has also been shown to prevent breast cancer (27). Approximately 60% to 70% of newly diagnosed breast cancers are estrogen receptor (ER)-positive, but only 60% of these will respond to therapy. It is not currently possible to identify which patients with ER-positive cancers will respond to endocrine therapy nor is it possible to determine whether a specific treatment (tamoxifen or an AI) will be more effective for an individual patient. Currently, a great deal of research has been focusing on using pharmacogenomic strategies to personalize breast cancer endocrine therapy. It has been proposed that variants in genes that encode proteins involved in drug and steroid metabolism, and in genes that code for components of the estrogen signaling pathways can predict response to, and side effects from, endocrine therapy.

Tamoxifen is the most widely studied breast cancer drug from a pharmacogenomic perspective. It is an essential part of standard adjuvant and palliative systemic therapy for patients with ER-positive breast cancers. Adjuvant tamoxifen significantly decreases relapse rates and mortality in pre- and postmenopausal patients, and the therapeutic benefit resulting from 5 years of adjuvant tamoxifen is maintained for more than 10 years after diagnosis (28). Tamoxifen is a valid therapeutic option next to AIs in postmenopausal patients with endocrine responsive disease; it is considered the standard care for premenopausal patients, for prevention of invasive breast cancer in women at high risk including those who have had ductal carcinoma *in situ*, and for the treatment of male breast cancer. It is important to note that, although the clinical benefit of tamoxifen has been evident for more than three decades, up to 50% of patients receiving adjuvant tamoxifen relapse or die due to tumor resistance or lack of response to the drug. In addition, while tamoxifen is a very effective drug, as with all potent medications, it also has side effects. Because the difference in efficacy between tamoxifen and the aromatase inhibitor class of drugs is in the 2 to 4% range, we are in great need of biomarkers that are able to predict the efficacy of specific endocrine treatments, and that help identify individual patients who are most likely to experience specific side effects that are not predictable *a priori*.

Efforts to identify genomic biomarkers for tamoxifen effects have been significantly aided by improved understanding of tamoxifen metabolism that has helped identify candidate genes involved in the actions of the drug. Tamoxifen itself has weak anti-estrogen properties and is converted into much more potent anti-estrogenic metabolites. It has, therefore, been proposed that tamoxifen, like cyclophosphamide, is a prodrug and that inherited variations in drug metabolizing enzymes (mainly CYP450s) might alter tamoxifen's anticancer activity and side effects.

Data on the metabolism of tamoxifen carried out in the 1980s in rats indicated that the drug is extensively metabolized by the cytochrome P450 system and that it is primarily demethylated to *N*-desmethyl tamoxifen or hydroxylated (29). It was shown that the 4-hydroxylated metabolite was approximately 100 times more potent as an anti-estrogen than the parent tamoxifen and its primary metabolite *N*-desmethyltamoxifen, and it was subsequently believed that 4-hydroxy-tamoxifen was *the* active metabolite. As a result, this metabolite was synthesized by a number of companies and remains the most widely used substitute for tamoxifen in many laboratory studies. Another hydroxylated metabolite, 4-hydroxy-*N*-desmethyl tamoxifen is created in humans, but not in mice (30) by the hydroxylation of *N*-desmethyl tamoxifen, and this has more recently been clearly documented to be the most abundant species in human serum at steady state (31). Stearns et al. reported that the serum concentrations of this metabolite, now designated endoxifen, were notably lower in patients who were co-prescribed paroxetine, a potent *CYP2D6* inhibitor, and in patients with *CYP2D6* gene variants that result in no functional enzyme production (32).

CYP2D6 is one of the most intensively studied human drug metabolizing enzymes with known genetic variants (33). *CYP2D6* is the key metabolic route for over 20% of clinically used drugs including many antidepressants, neuroleptics, antiarrhythmics and other commonly used drugs. It is absent in 7% of Caucasians as the result of genetic variants that do not code for active enzyme. Patients who are homozygous for two null *CYP2D6* alleles are considered poor metabolizers (PM) compared to patients with one or more wild-type *CYP2D6* alleles (intermediate metabolizers [IM] and extensive metabolizers [EM], respectively). A high prevalence of IM in Asian populations results in lower average *CYP2D6* activity in these patients, and the presence of multiple copies of the *CYP2D6* gene results in high or ultrarapid metabolizers (UM) in approximately 5% of Caucasians, but more than 20% of East African populations in Ethiopia and Saudi Arabia (33).

To confirm a clinically important involvement of the *CYP2D6* enzyme in tamoxifen metabolism, Desta et al. (34), conducted a comprehensive evaluation of the metabolism by the cytochrome P450 system, and demonstrated that the metabolism of *N*-desmethyltamoxifen to endoxifen is carried out almost exclusively by *CYP2D6*. The human metabolism of tamoxifen is now well understood. It involves the conversion of the parent drug to two well documented active metabolites: 4-hydroxy-tamoxifen, which is formed directly from tamoxifen by 4-hydroxylation catalyzed by at least three enzymes, and the independent conversion of tamoxifen to *N*-desmethyl tamoxifen by cytochrome P450 3A, followed by secondary metabolism to endoxifen catalyzed exclusively by *CYP2D6* (34).

Endoxifen is believed to be tamoxifen's clinically active metabolite because it binds to ER with 100-fold greater affinity than tamoxifen and *N*-desmethyl-tamoxifen, and its serum concentration is 6 to 10-fold higher than 4-hydroxy-tamoxifen (31). *CYP2D6* is the primary and rate-limiting enzyme responsible for the formation of endoxifen and patient *CYP2D6* genotype correlates with endoxifen serum concentrations (32). These studies were the basis for the hypothesis that *CYP2D6* genotype may predict response to tamoxifen.

In an examination of a randomized, controlled prospective trial, Goetz et al. successfully isolated intact DNA from paraffin blocks from 223 of 256 eligible patients, and found that women with the *CYP2D6 *4/*4* genotype (the most common null variant found in Caucasians) had worse relapse-free time (RF-time; $p = .023$) and disease-free survival (DFS; $p = .012$), but not overall survival ($p = .169$) and did not experience moderate to severe hot flashes relative to women heterozygous or homozygous for the wild-type allele (35). In the multivariate analysis, women with the *CYP2D6 *4/*4* genotype still tended to have worse RFS (hazard ratio [HR], 1.85; $p = .176$) and DFS (HR, 1.86; $p = .089$). It was concluded that breast cancer patients with estrogen receptor-positive disease and who have the *CYP2D6 *4/*4* genotype tend to have a higher risk of disease relapse and a lower incidence of hot flashes, consistent with the previous observation that *CYP2D6* is responsible for the metabolic activation of tamoxifen to endoxifen.

The initial tamoxifen/*CYP2D6* publication spurred a growing number of studies evaluating the possible association between *CYP2D6* genotype and response to tamoxifen therapy (reviewed by Hertz [36]). These studies have generated a great deal of controversy over whether *CYP2D6* genotyping should be used clinically to identify patients less likely to respond to tamoxifen (36). Most of the studies conducted thus far have been confounded by relatively small numbers of patients, lack of comprehensive genotype data, lack of detailed clinical outcome data, and patient selection biases. Furthermore, no studies have controlled for differences in rates of adherence to tamoxifen therapy which may, in fact, be lower in patients with the highest endoxifen levels (37). A large study combined two previously published patient cohorts with additional patients from a registry study and concluded that *CYP2D6* genotype does predict response to tamoxifen (38). This was considered by many the definitive study establishing the value of CYP2D6 status. However, evidence against the clinical use of *CYP2D6* testing was generated recently from two prospective-retrospective studies published from the Breast International Group (BIG) 1-98 and Arimidex, Tamoxifen, Alone or in Combination (ATAC) clinical trials, which failed to show an association between *CYP2D6* genotype and clinical outcomes in tamoxifen-treated patients (39,40) The strengths of these two studies include the large number of patients analyzed, the long-term and detailed clinical follow-up set within registration clinical trials, and the inclusion of control groups (patients receiving AI). To date, these two studies provide the highest level evidence available, suggesting that *CYP2D6* genotype does not influence tamoxifen activity and that genetic testing is not indicated for women with ER-positive breast cancer considering adjuvant tamoxifen therapy.

The interaction between antidepressants and tamoxifen has also received considerable attention as a result of this work, as it is clear that *CYP2D6*-inhibiting SSRIs such as paroxetine and fluoxetine lower endoxifen concentrations (31,32). It has been demonstrated that venlafaxine, a weak inhibitor of *CYP2D6*, does not appreciably lower the concentrations of active tamoxifen metabolites, affording women with breast cancer the possibility of taking an effective antidepressant that is also able to treat hot flashes, and has little chance of altering the risk of recurrence.

Post-menopausal women being treated with endocrine therapy for breast cancer clearly now have a number of alternative therapies available to them. These include tamoxifen and the aromatase inhibitors anastrozole, letrozole, and exemestane. The choice of which therapy should be used in which woman should obviously be guided by the potential benefits for each woman and the attendant risks of specific therapies in each woman, but also by the tolerability of specific therapies, as it is clear that compliance with tamoxifen or the aromatase inhibitor class of drugs can influence outcomes. While it was hoped that *CYP2D6* genotype would have clinical utility for determining whether a patient should be prescribed tamoxifen, the data are not yet conclusive. However, it is recommended that, if possible, women taking tamoxifen should avoid *CYP2D6*-inhibiting drugs (a list of common *CYP2D6* inhibitors is provided in

TABLE 48-1

Common Drugs That Inhibit CYP2D6

Strong Inhibitors
Paroxetine (Paxil®)
Fluoxetine (Prozac®)
Bupropion (Wellbutrin®)
Quinidine (Cardioquin®)

Moderate Inhibitors
Duloxetine (Cymbalta®)
Diphenhydramine (Benadryl®)
Thioridazine (Mellaril®)
Amiodarone (Cordarone®)
Cimetidine (Tagamet®)

Weak or Noninhibitors
Venlafaxine (Effexor®)
Citalopram (Celexa®)
Escitalopram (Lexapro®)
Sertraline (Zoloft®)

Table 48-1). In situations where women are committed to a *CYP2D6*-inhibiting antidepressant by years of effective treatment that is not easily substituted for by another drug, then it is recommended that they stay on the effective antidepressants. Of note, these recommendations do *not* apply to women in the premenopausal setting, in whom the aromatase inhibitors are not effective alternatives to tamoxifen, and for whom there is only limited data on the clinical consequences of *CYP2D6* genomics.

Pharmacogenomics in the Use of Anti-angiogenic Agents in Breast Cancer

The possibility that host genomics might influence outcome is perhaps greatest in situations where the host response to the tumor might be modified. This is obviously the case in the physiology of tumor angiogenesis, where the host's ability to confer a sustaining blood supply to a solid tumor is widely recognized as variable, and a target of therapy. This has most recently been made clear by the approval of bevacizumab, an anti-vascular endothelial growth factor antibody to treat breast cancer. Bevacizumab was approved as the result of the data from a number of trials, including a trial designated as E2100, in which women with metastatic breast cancer were treated with either paclitaxel alone, or paclitaxel with bevacizumab. The results of this trial indicated that bevacizumab prolonged disease-free survival from 5.9 to 11.8 months, but did not alter overall survival. Using techniques similar to those developed for CYP pharmacogenetics testing, researchers were able to obtain sufficient high quality DNA to conduct germline genetic testing from paraffin blocks to allow genotyping for candidate gene that are in the angiogenesis response pathway. When these techniques were applied to paraffin blocks obtained during the E2100 trial, they were able to show that women who carried either of two promoter single nucleotide polymorphisms in the *VEGF* gene experienced notably longer overall survival (41). Women who carried the –2578 *AA* variant experienced a 10 month increase in median overall survival (p = .023), relative to the control arm, while women who carried the –1154 *AA* variant survived for 20 months longer (p = .001) than those in the control, paclitaxel alone arm. While these data require validation, the size of the effects is large, and the cost of bevacizumab therapy argues that it may make not only clinical sense, but economic sense to conduct pharmacogenetics testing before treatment with bevacizumab in this setting and many others.

FUTURE IMPACT OF PHARMACOGENOMICS IN BREAST CANCER

The pioneering studies in the field of pharmacogenetics investigated clear-cut genotype–phenotype relationships, and were, therefore, possible with relatively small numbers of patients. In contrast, predicting response to breast cancer therapy is much more complex, and much larger studies are required to dissect the more subtle effects that some genetic polymorphisms may have in cancer pharmacology. Furthermore, the relevant treatment outcomes may take many years to become manifest in this context. Although the science of pharmacogenomics is more than 50 years old, it is only recently that pharmacogenetics variants have been tested as possible biomarkers of response to therapy in breast cancer. Women with breast cancer have benefited tremendously from improved understanding of tumor biology and we now routinely stratify therapy based on the presence of estrogen, progesterone, HER2 and expression array data. There is great potential for similar stratification of therapy using germline pharmacogenomics, and ongoing studies in the areas of chemotherapy, endocrine therapy, and anti-angiogenic therapy make clear that this is now not only an active area of investigation, but one in which there is great potential to identify women most likely to respond to very expensive biologic therapies as well as treatments that have become more routine. This is now clear to many investigators, and so the pace of presentation of pharmacogenetic studies in breast cancer is accelerating rapidly.

MANAGEMENT SUMMARY

At present, we are in the early stages of determining whether any of the pharmacogenomic tests currently being evaluated will aid in therapeutic decision-making in breast cancer. While there has been a great deal of excitement about the potential use of *CYP2D6* genotype for determining tamoxifen therapy, to date the available clinical data argues against the use of *CYP2D6* genotyping. Until higher levels of evidence become available for *CYP2D6* and the other genetic tests discussed earlier, they should all be considered as pharmacogenomics research hypotheses that require further validation in studies providing the high level of evidence required in order to show the markers' clinical utility. Current specific recommendations are:

- *CYP2D6* genotype in the premenopausal setting. Women with hormone receptor-positive breast cancer do not have multiple alternative therapies for endocrine therapy beyond tamoxifen as neither raloxifene nor the aromatase inhibitors are effective in this context. *CYP2D6* genotyping is *not* recommended in this setting given the lack of clinical data supporting the test. Similarly, in the breast cancer prevention setting, *CYP2D6* genotyping is *not* recommended.

- *CYP2D6* genotype in the postmenopausal setting. Women with hormone receptor-positive breast cancer have multiple potential alternative therapies that include tamoxifen and three aromatase inhibitors. While the ideal sequence and duration of these therapies in individual women is still a subject of research, *CYP2D6* genotyping is *not* recommended in this setting given the lack of clinical data supporting the test.
- Avoiding *CYP2D6* inhibitors in women prescribed tamoxifen. Given the high level of evidence provided by the BIG 1-98 and ATAC studies which failed to detect an association between *CYP2D6* genotype and benefit from tamoxifen, it stands to reason that concomitant use of *CYP2D6* inhibitors will not influence tamoxifen efficacy. However, from a clinical drug-drug interaction standpoint, it is recommended that *CYP2D6* inhibitors be avoided whenever possible because the *CYP2D6* drug metabolism pathway is involved in the metabolism of approximately 25% of all drugs.
- In terms of anti-angiogenic therapy, we have one large prospective trial in women with metastatic breast cancer (E2100) to rely upon for pharmacogenomic data, so it remains premature to make firm recommendations at this time. If data from this trial are validated, then we will be able to quickly identify a group of women who stand to derive considerable benefit from this effective but expensive treatment, and another group who do not and who should, therefore, not be treated.

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CHAPTER 49

Implications of Obesity in Breast Cancer

Ayca Gucalp, Patrick G. Morris, Clifford A. Hudis, and Andrew J. Dannenberg

CHAPTER CONTENTS

INTRODUCTION

Obesity is a major risk factor for the development of some of the leading preventable causes of death in the United States including cardiovascular disease, diabetes mellitus, and stroke. In addition, epidemiologic studies link obesity with an increased incidence of common epithelial malignancies including postmenopausal hormone-receptor-positive and triple-negative breast cancers (TNBC). Obesity is also recognized as a poor prognostic factor among survivors of breast cancer irrespective of menopausal status and breast cancer subtype. The underlying mechanisms for these phenomena remain incompletely understood. Growing evidence suggests that complex interactions between multiple pathways regulating estrogen synthesis, insulin resistance, adipokine and cytokine production, and chronic systemic inflammation may collectively explain the link between obesity and breast cancer pathogenesis. Increasing adiposity also poses additional technical challenges in the detection of breast cancer and in its effective local and systemic treatment. This chapter reviews the epidemiologic data linking obesity and breast cancer, the underlying biological mechanisms, and the important practical implications of this condition on the diagnosis and management of this disease. Finally, we examine potential interventions and strategies to reduce the unfavorable impact of obesity on the diagnosis and treatment of breast cancer.

EPIDEMIOLOGY OF OBESITY

Obesity has been classified by the World Health Organization as a global epidemic (1). The number of overweight and obese individuals in the United States has doubled since 1990, and it is projected that the prevalence of obesity will be greater than 50% in 39 states by the year 2030 (Fig. 49-1) (2).

One commonly used measure of extent of body fat is body mass index (BMI), calculated by dividing an individual's weight in kilograms by the square of his or her height in meters (1). For adults, BMI is categorized into the following four standard groups: underweight less than 18.5 kg/m^2, normal 18.5 to 24.9 kg/m^2, overweight 25.0 to 29.9 kg/m^2, and obese 30 kg/m^2 or more (1). Although BMI is reproducible, inexpensive, and easy to measure and calculate, it is nonetheless only a surrogate measure of body fat. The correlation between BMI and percentage of body fat varies by age, ethnicity, gender, and muscle mass. For example, BMI routinely overestimates the adiposity of trained athletes and underestimates the true percentage of body fat of older individuals with less lean muscle mass (1).

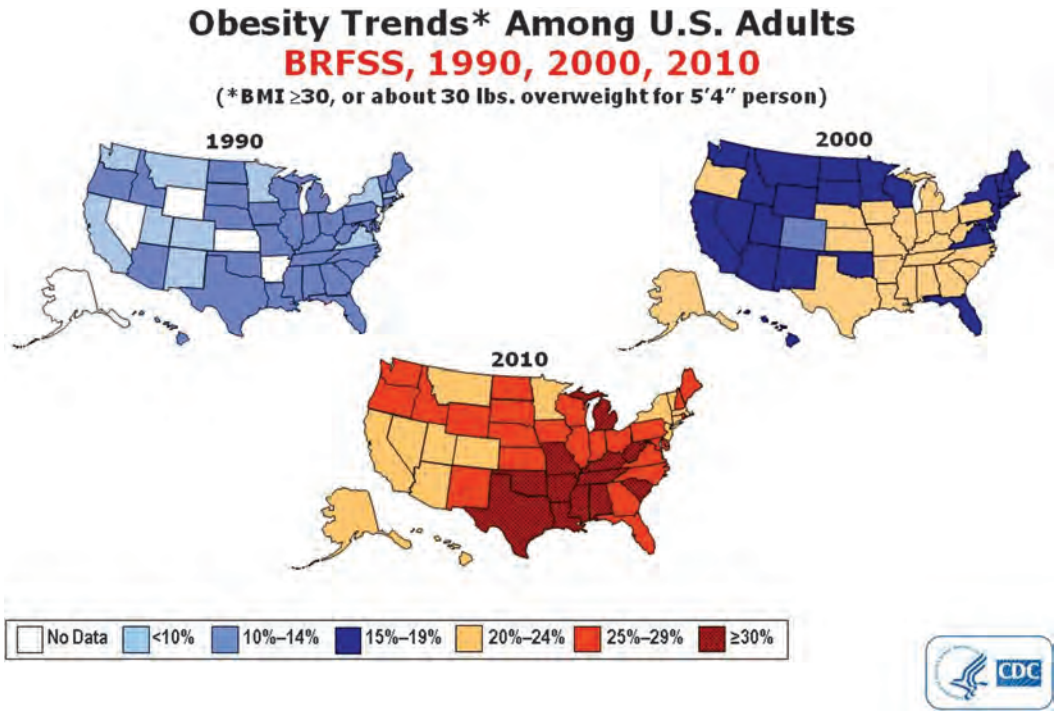

FIGURE 49-1 Obesity trends among U.S. adults. (From Behavorial Risk Factors Surveillance System, the Centers for Disease Control and Prevention.)

EPIDEMIOLOGIC LINK BETWEEN OBESITY AND BREAST CANCER

Postmenopause

Many observational studies have demonstrated that increasing BMI is a risk factor for postmenopausal hormone-receptor-positive breast cancer. This is the most common subtype of breast cancer. Of note, breast cancers are considered "hormone sensitive" when they expresses the estrogen receptor (ER) and/or progesterone receptor (PR). However, gene expression profiling has allowed us to subdivide hormone-receptor-positive breast cancers into those that are likely sensitive to hormone therapies ("luminal A") and those that are usually not ("luminal B"). Hence, hormone receptor status is an imperfect surrogate for hormone sensitivity. Of course, the absence of these receptors is very predictive of hormone insensitivity.

In a meta-analysis of eight prospective cohort studies, increasing BMI was directly correlated with breast cancer risk in postmenopausal women (3). Compared to those with a BMI less than 22.5 kg/m^2, women with a BMI in the overweight to obese range had an increased relative risk (RR) of 1.36 to 1.62 of developing breast cancer (Table 49-1) (3).

Premenopause

The effect of overweight and obesity on breast cancer risk in premenopausal women is less clearly defined. More precisely, it appears likely that the influence of weight may differ based on an individual patient's underlying risk. Cecchini et al. reported the pooled analysis of two large, randomized breast cancer prevention trials (Breast Cancer Prevention Trial [P1] and the Study of Tamoxifen and Raloxifene [STAR]), which included nearly 32,000 women at high risk of developing the disease. In comparison to premenopausal women with normal BMI, overweight (hazard ratio [HR] 1.59, 95% CI 1.05–2.42) and obese women (HR 1.70, 95% CI 1.10–2.63) had an increased risk of developing invasive breast cancer (4).

Several studies have also suggested an association between adult obesity and the development of TNBC, which lacks expression of the ER, PR, and human epidermal growth factor receptor 2 (*HER2*). In the Women's Health Initiative (WHI), a longitudinal study of postmenopausal women, in which over 5,000 invasive breast cancers were diagnosed, the highest quartile of BMI (31.5 or higher) was associated with a 1.39-fold (95% CI 1.22–1.58) increase in the risk of ER-positive breast cancer when compared to women with a BMI in the lowest quartile (less than 23.75) but a similar magnitude of risk of TNBC was also seen (HR 1.35, 95% CI 0.92–1.99), although this latter result was not statistically significant (5).

Impact on Treatment Outcomes

Studies examining the prognostic effect of overweight or obesity after a breast cancer diagnosis have consistently demonstrated poorer clinical outcomes for women with

TABLE 49-1

Relative Risk of Breast Cancer Development by Body Mass Index

Body Mass Index Category (kg/m^2)	*Relative Risk*	*95% Confidence Interval*
<22.5	Reference	Reference
25.0–27.4	1.45	1.08–1.95
27.5–29.9	1.62	1.17–2.24
≥30	1.36	1.00–1.85

Data from Key TJ, Appleby PN, Reeves GK, et al. Body mass index, serum sex hormones, and breast cancer risk in postmenopausal women. *J Natl Cancer Inst* 2003;95:1218–1226.

an elevated BMI. In a recent meta-analysis, Protani and colleagues examined 43 studies with sample sizes ranging from 100 to more than 420,000, and included women diagnosed with breast cancer from 1963 to 2005. The authors demonstrated that obese women consistently experienced higher breast cancer–specific (HR 1.33, 95% CI 1.19–1.50) and all-cause mortality (HR 1.33, 95% CI 1.21–1.47) in comparison to their nonobese counterparts (6). Obesity has also been associated with several other poor clinical outcomes including increased risk of contralateral breast cancer and second primary breast cancers (7).

OBESITY-RELATED PATHWAYS AND BREAST CANCER PATHOGENESIS

Several lines of evidence suggest that obesity-induced tumor development, invasion, and progression are mediated by a complex interplay between both estrogen dependent and independent pathways (Fig. 49-2). Following the decline of ovarian function at menopause, estrogen production predominantly occurs by the peripheral conversion of androgen precursors to estrogens in extragonadal sites such as adipose tissue. The rate-limiting step in this process is catalyzed by the enzyme aromatase, encoded by the *CYP19* gene. Breast cancer incidence increases with age and it is in the setting of lowered circulating estrogen levels that the highest rates of hormone sensitive breast cancer are diagnosed. This seemingly paradoxical phenomenon is thought to be partially due to two related factors: increased adipose tissue and elevated aromatase expression in adipose tissue (8).

In addition to peripheral fat stores, the majority of the normal female breast is composed of white adipose tissue (WAT). WAT is an active endocrine organ producing various hormones, growth factors, and cytokines. Complex interactions between adipocytes and immune cells, such as activated macrophages, have been shown to promote chronic inflammation in the tumor microenvironment as well as insulin resistance. Through multiple interactive pathways involved in energy metabolism and immune function, adipose tissue is thought to contribute to breast cancer development and progression (Fig. 49-2).

Insulin Resistance

Obesity is associated with insulin resistance, characterized by impaired glucose tolerance and elevated systemic levels of insulin and insulin-like growth factor-1 (IGF-1), which have both been associated with breast cancer risk and worse prognosis (9). In a cohort of 512 patients with early-stage breast cancer, elevated fasting insulin levels were associated with both distant recurrence (HR 2.0, 95%

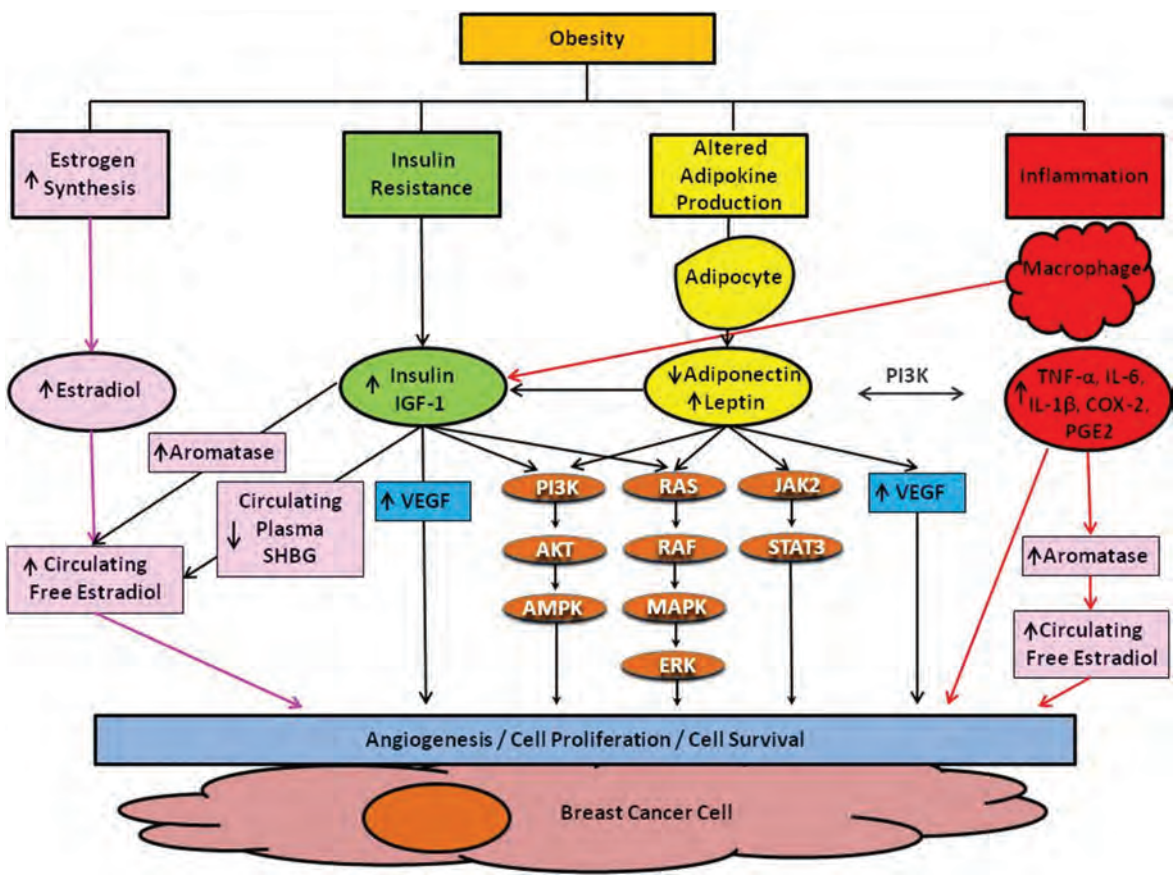

FIGURE 49-2 Pathways linking obesity with breast cancer. SHBG, sex hormone-binding globulin; IGF-1, insulin-like growth factor 1; VEGF, vascular endothelial growth factor; PI3K, phosphatidylinositol 3-kinase; ERK, extracellular signal-regulated kinase; MAPK, mitogen-activated protein kinase; JAK2, Janus kinase 2; STAT3, signal transducer and activator of transcription 3; AMPK, 5' adenosine monophosphate-activated protein kinase; TNF-α, tumor necrosis factor alpha; IL-6, interleukin-6; IL-1β, interleukin-1β; COX-2, cyclooxygenase-2; PGE2, prostaglandin E2.

CI 1.2–3.3) and all-cause mortality (HR 3.1, 95% CI 1.7–5.7) (9). It is theorized that insulin mediates breast carcinogenesis by stimulating signaling through activation of insulin/IGF-1 receptors that can be overexpressed on human breast cancer cells. Downstream activation of the Ras-Raf-MAPK and PI3K/Akt pathways ultimately leads to tumor cell proliferation and inhibition of apoptosis. Additionally, IGF-1 and insulin have been shown to stimulate aromatase activity in adipose tissue. Moreover, increasing insulin levels can affect sex hormone biosynthesis leading to increased androgen production by the ovaries and decreased hepatic production of sex hormone-binding globulin (SHBG) that normally antagonizes some negative effects of circulating estrogens.

Altered Adipokine Production

Adipokines, a group of proteins synthesized and secreted from adipose tissue, are also implicated in the interaction between obesity and breast cancer. Decreased serum adiponectin and elevated leptin levels have been associated with obesity and type 2 diabetes mellitus. Similar disturbances in these adipokines have also been associated with increased breast cancer risk (10) and worse prognosis (11). Although the mechanisms underlying these phenomena are incompletely understood, adiponectin is thought to exert its effects through the activation of multiple downstream signaling pathways including AMPK, PI3K/mTOR, and the transcription factor, nuclear factor-kappaB (NF-κB), which have also been implicated in breast cancer development (12). In addition, adiponectin has been shown to inhibit the growth of multiple breast cancer cell lines (13).

In contrast, leptin is thought to affect different aspects of breast tumorigenesis such as cell growth, angiogenesis, and metastasis and is to known to act mainly through activation of the JAK/STAT, MAPK/ERK, and PI3K/Akt signaling pathways leading to increased cell migration, invasion, and cell survival. Leptin-induced proliferation has been associated with overexpression of c-myc and cyclin D1which are important in cell cycle regulation (12). Finally, leptin has also been reported to have both proinflammatory and angiogenic properties, which may be important for breast carcinogenesis.

Obesity-Induced Chronic Systemic Inflammation: The Obesity-Inflammation-Aromatase Axis

Obesity causes chronic subclinical inflammation in adipose tissue (14). In obese women, increased levels of proinflammatory mediators such as tumor necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) are commonly found in the circulation and may contribute to breast cancer progression and mortality. Interactions between adipocytes and immune cells promote this proinflammatory response through toll-like receptor- (TLR)-mediated signaling pathways and the activation of NF-κB. In mouse models of obesity and in overweight and obese humans, macrophages infiltrate visceral and subcutaneous adipose tissue and form characteristic crown-like structures (CLS) around dead adipocytes. In both dietary and genetic models of obesity, CLS occur in the adipose tissue of the mouse mammary gland as well as in visceral fat (15). Similarly, in women undergoing mastectomy, the presence of CLS of the breast (CLS-B) was associated with increased BMI. Importantly, the presence of CLS-B is associated with NF-κB-dependent upregulation of multiple proinflammatory mediators such as interleukin-1β (IL-1β), cyclooxygenase-2 (COX-2), prostaglandin E2 (PGE2), and TNF-α, which leads to increased transcription of *CYP19,* the gene encoding aromatase (16,17). These elevated levels of proinflammatory molecules and aromatase expression and activity are paralleled by upregulation of PR, an ER target gene. Aromatase activity correlates more strongly with the CLS-B index ($\rho = .88$, $p < .001$), a marker of extent of inflammation, than with BMI ($\rho = .5$, $p = .02$). This finding underscores the fact that obesity-related inflammatory mediators are critical for the induction of aromatase. Collectively, these results establish the existence of an obesity-inflammation-aromatase axis in breast tissue, which is likely to be one mechanism by which obesity influences breast carcinogenesis.

CLINICAL IMPLICATIONS

Obesity poses several practical challenges in regard to diagnosis, surgical management, and systemic treatment for breast cancer. In addition to the physical limitations that are associated with an elevated BMI, there may be psychosocial barriers to providing optimal care for the obese patient. Several studies have shown that obese patients are more likely to delay seeking medical care and are also less likely to receive preventive testing such as breast examinations and mammography when they do present for routine health maintenance (18). Consistent with these observations, overweight and obese women often present with tumors that are higher stage (larger size and higher number of involved lymph nodes) than lean women (19).

DIAGNOSTIC IMAGING

Obesity poses challenges for screening mammography and other imaging modalities (20). In mammography, increasing BMI has been associated with a higher false-positive rate (the detection of radiographic abnormalities that subsequently turn out to be benign). In reviewing over 100,000 screening mammograms, Elmore and colleagues demonstrated that obese women had an increased risk of having a false-positive mammogram result compared to nonobese women (odds ratio [OR] 0.79, 95% CI 0.74–0.84) (21). This study, as well as others, also demonstrated increased rates of recall for additional imaging for obese women compared with underweight and normal-weight women, as well as increased biopsy rates (21).

SURGERY

Although obesity may not have a negative impact on less invasive breast procedures such as lumpectomy, it has been associated with higher rates of complications after more invasive procedures such as mastectomy and breast reconstruction surgery. The National Surgical Quality Improvement Program Patient Safety in Surgery prospectively collected postoperative morbidity and mortality data on 1,660 and 1,447 women undergoing mastectomy and axillary procedures respectively. In this study, obesity was a significant independent predictor of wound infection, the most common adverse event, on multivariate analysis ($p < .001$).

Furthermore, the risk of postoperative lymphedema has been shown in several large cohort studies to be higher among women who were obese (22). With respect to breast reconstruction, increasing BMI is an independent risk factor for the development of surgery-related complications. In a retrospective series of nearly 1,200 breast reconstructions, Mehrara and colleagues reported that obesity was a major predictor of postoperative complications overall in both univariate and multivariate analysis and across all complication types (minor, major, early, and late) (23). Chang et al. reported similar findings among women who underwent free transverse rectus abdominis myocutaneous (TRAM) flap breast reconstruction (24). Finally, in women undergoing tissue expander

and implant reconstruction a BMI greater than 30 kg/m^2 was associated with nearly a twofold increase in perioperative complications (OR 1.8, 95% CI 1.1–3.0, p = .02) (25).

RADIATION

Obesity has important implications for the delivery of adjuvant radiotherapy following breast surgery. As a practical matter, increasing BMI may preclude the use of radiation therapy for the morbidly obese patient as standard equipment used in the planning and delivery of radiation has established weight limitations. Additionally, increased toxicity after radiation therapy has been observed in obese women. In a case control study of 200 patients who received adjuvant radiotherapy after lumpectomy or mastectomy, Allen and colleagues identified BMI as an independent predictor of radiation pneumonitis in multivariate analysis (p < .01) (26). It is hypothesized that this association may be due, in part, to increased dose delivery to the lung based on body habitus, an increased incidence of comorbid pulmonary conditions among overweight and obese patients, and elevations in circulating proinflammatory mediators, which have been documented in both obese individuals and those at risk for pneumonitis. Obesity is an independent risk factor for the development of ipsilateral arm edema following radiation therapy (27). Factors related to patient size, such as breast volume, are also strongly associated with poor cosmetic outcomes (28) and skin toxicity (29).

SYSTEMIC THERAPY

Obesity can also interfere with the effective delivery of systemic therapy. Investigators have identified many contributing factors to explain the suboptimal outcomes observed with chemotherapy and endocrine interventions in overweight and obese women which fall into two main categories: inadequate dosing and reduced efficacy.

CHEMOTHERAPY

Historically, cytotoxic chemotherapeutic agents have been dosed based on body surface area (BSA). Unfortunately, for drugs with fat solubility and consequently a higher volume of distribution, the use of BSA may result in relative underdosing of overweight and obese patients. Additionally many physicians "cap" the total administered dose for some drugs in obese patients by using a maximum weight in order to minimize toxicity. On average, overweight and obese women are at an increased risk for dose reductions or treatment delays. In a study of 20,799 early-stage breast cancer patients, BSA greater than 2 m^2, which approximates to an obese BMI, was an independent risk factor for the delivery of relative dose intensity less than 85%, a threshold that has been associated with decreased clinical benefit (30).

Adjuvant Chemotherapy

Less favorable outcomes following adjuvant chemotherapy have been reported among overweight and obese women. Several studies including a pooled analysis of three large, randomized trials coordinated by the Eastern Cooperative Oncology Group evaluating various adjuvant therapy regimens have demonstrated that obesity is associated with inferior outcomes (7). In one of these three studies (E1199) obesity was strongly associated with decreased disease-free survival (HR 1.24, 95% CI 1.06–1.46, p = .0079), overall survival (HR 1.37, 95% CI 1.13–1.67, p = .0015), and breast cancer–specific survival (HR 1.40, 95% CI 1.11–1.76, p = .0042) in multivariate analyses. Importantly, this negative prognostic effect of obesity was demonstrated despite the use of modern anthracycline and taxane-based chemotherapy regimens in this study. This suggests that despite advances in systemic therapy, obese patients remain at risk of worse clinical outcomes.

Neoadjuvant Responses

In the preoperative or "neoadjuvant" setting, an inverse relationship between BMI and the efficacy of cytotoxic chemotherapy has been reported in several studies. In a large cohort of nearly 1,200 patients who received preoperative chemotherapy, overweight and obese individuals were less likely to achieve a pathological complete response than nonobese patients (OR 0.67, 95% CI 0.45–0.99) (31). However, actual administered doses were not verified in this study and thus it is unclear whether the decreased response to chemotherapy was a result of some degree of inadequate dosing in this setting. As mentioned earlier, concern over increased toxicity has led many clinicians to adopt a practice of limiting doses in overweight and obese patients and, consistent with this practice, several studies have demonstrated lower rates of toxicity in obese women compared to patients of normal weight, including fewer hospital admissions (BMI over 35; OR 0.61, 95% CI 0.38–0.97) and fewer neutropenic events overall (BMI over 25; OR 0.49, 95 % CI 0.37–0.66) (32). Conversely, low body mass index (BMI) (less than 23 kg/m^2) was associated with a higher risk of febrile neutropenia (OR 4.4, 95% CI 1.65–12.01). All of these observations could reflect the impact of unreported dose-capping by clinicians or the routine use of hematopoietic growth factor support in obese patients receiving adjuvant chemotherapy.

Practical Considerations for Chemotherapy

With increasing attention being paid to the impact of obesity on chemotherapy dosing and its influence on treatment efficacy and toxicity, the American Society of Clinical Oncology issued clinical practice guidelines for the optimal dosing of obese patients (33) (Table 49-2).

TABLE 49-2

Adapted from the American Society of Clinical Oncology Clinical Practice Guidelines for Chemotherapy Dosing for Obese Adult Patients with Cancer

- Actual body weight should be used when dosing both oral and intravenous cytotoxic chemotherapy doses for all patients including those who are overweight and obese particularly in the curative setting.
- For morbidly obese patients (BMI of 35 kg/m^2 or more), full weight-based dosing is also recommended.
- Dose reduction for adverse events should be consistent for all patients and full weight-based doses for subsequent cycles should be attempted provided the toxicity has resolved.
- The use of fixed-dose cytotoxic chemotherapy should be limited to specific agents with established maximum doses secondary to toxicity such as vincristine, bleomycin, and carboplatin.

Data from Griggs JJ, Mangu PB, Anderson H, et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol* 2012;30:1553–1561.

These recommendations state that actual body weight should be used when dosing both oral and intravenous cytotoxic chemotherapy for almost all patients, including those who are overweight and obese particularly in the curative setting.

ENDOCRINE THERAPY

Traditionally, endocrine therapies such as tamoxifen and aromatase inhibitors have not been dosed according to weight or BSA. However, a post hoc analysis of the Arimidex, Tamoxifen Alone or in Combination (ATAC) study demonstrated a higher rate of distant plus local recurrences (HR 1.39, 95% CI 1.06–1.82) in women with high BMI (over 35 kg/m^2) versus BMI less than 23 kg/m^2 at baseline. In the multivariate analysis, treatment with anastrozole was shown to be significantly less effective in postmenopausal women in the highest BMI quintile when compared to women in the lowest quintile (HR 1.53, 95% CI 1.01–2.32, p = .001) (34). In contrast, in this study (34) and others tamoxifen was equally effective across all BMI groupings. One possible explanation for the reduced efficacy of certain endocrine therapies in obese women is the inadequate suppression of elevated estrogen levels, commonly seen in overweight and obese patients, by aromatase inhibitors like anastrozole. This hypothesis is supported by work by Folkerd and colleagues which demonstrated a direct correlation between circulating estradiol levels and increasing BMI (ρ = .57, p < .001) (35). Results of this study are consistent with another report by Ewertz et al. which suggested a difference (not statistically significant in this report) in survival outcomes for obese versus normal-weight patients treated with either letrozole or tamoxifen (HR = 1.22; 95% CI 0.93–1.60 and HR = 1.18; 95% CI 0.91–1.52, respectively) (36). Randomized prospective trials are warranted in this setting to further elucidate whether dose adjustments or the preferential use of more potent aromatase inhibitors can improve outcomes for overweight and obese patients. If obesity is found to activate ER signaling by both ligand-independent and ligand-dependent mechanisms, higher doses of aromatase inhibitor or more potent agents may not yield added clinical benefit. If so, alternate treatments may be required.

OBESITY-DIRECTED INTERVENTIONS

Obesity is a modifiable risk factor. Therefore, interventions such as lifestyle changes and the development of agents that target obesity-related pathophysiological pathways have the potential to have an impact on breast cancer incidence, morbidity and mortality.

BEHAVIORAL INTERVENTIONS

Weight Loss and Exercise

The maintenance of a BMI less than 25—either through physical activity, diet modification, or a combination of the two—has been associated with improved outcomes for women diagnosed with breast cancer in multiple observational studies. For example, in the Nurses' Health Study approximately 3,000 women with early stage breast cancer were followed for a median of 8 years and serially surveyed to assess the relationship between reported activity levels and breast cancer–related outcomes. Women who reported engaging in at least 3 to 5 hours of physical activity per week, equivalent to walking at an average pace (2.0–2.9 mph), derived the greatest benefit in terms of breast cancer–related morality (RR 0.50, 95% CI 0.31–0.82) (37).

The effect of dietary modifications on breast cancer–related outcomes is an area of active research. The Women's Intervention Nutrition (WINS) Study randomized 2,437 women between 1994 and 2001 to evaluate the influence of dietary fat reduction on relapse-free survival in patients with early stage breast cancer. The dietary fat intake in the investigational arm (involving registered dietitians implementing a low-fat eating plan with individual goals and regular counseling sessions) was significantly lower than in the control arm at one year (33.3 fat grams/day (95% CI 32.3–34.5) versus 51.3 fat grams/day (95% CI 50.0–52.7, p < .001) and this difference was maintained over the course of 5 years of follow-up. On average, women in the intervention arm lost approximately 6 pounds and, at a median follow up of 60 months, had a lower risk of relapse than those in the control arm (HR 0.76, 95% CI 0.60–0.98). Interestingly, the dietary modifications had the greatest effect on relapse-free survival in the ER-negative subset (HR 0.58, 95% CI 0.37–0.91) suggesting that obesity may promote breast cancer pathogenesis via estrogen independent mechanisms, in addition to estrogen-dependent pathways (38). Because the lower-fat diet was associated with weight loss, the WINS is not able to resolve the contribution of a particular diet as opposed to calorie restriction and weight loss specifically. In contrast, the Women's Healthy Eating and Living (WHEL) study failed to demonstrate a lower risk of recurrence among breast cancer survivors randomized to a low-fat, high-fiber, high intake of fruits and vegetables diet (39). Notably, unlike the WINS study, the women randomized to the intervention diet did not have similar resultant weight loss. Hence, one possible explanation for the difference in effect on breast cancer outcomes observed in these two studies may be that weight loss may be more important than the type of dietary intervention strategy.

In an effort to better characterize the causal relationships between obesity and breast carcinogenesis, many studies have evaluated the effect of diet and weight loss on circulating biomarkers implicated in obesity-related pathways. Campbell and colleagues reported the results of a randomized controlled trial examining the effect of aerobic exercise versus calorie reduced diet either alone or in combination on sex hormone levels in postmenopausal women with a BMI over 25 kg/m^2. Women randomized to the combination arm of exercise and reduced calorie diet demonstrated a reduction in circulating estradiol levels by 20.3% (p < .001) and an increase in SHBG by 25.8% (p < .001) (40). Statistically significant reductions in serum levels of insulin, highly sensitive CRP, and leptin were also observed with diet-induced weight loss as was increased adiponectin levels. Several studies have reported similar favorable changes after weight loss in these, as well as other, inflammatory biomarkers that have been implicated in breast cancer development and progression. These results have established the association between weight loss and improved breast cancer outcomes and circulating biomarker levels and confirmed the feasibility of effecting durable lifestyle changes and weight loss through dietary and exercise interventions. Collectively, these findings can serve as the blueprint for future prospective trials focused on evaluating the effect of lifestyle changes on breast cancer outcomes and the parallel development of predictive biomarkers of benefit.

Pharmacologic Agents

As our understanding of the biological underpinnings linking obesity with breast carcinogenesis evolves, so does research to develop novel therapeutic agents to target metabolic

and inflammatory pathways known to be dysregulated in overweight and obese women with breast cancer.

Metformin

Retrospective data suggest that metformin, an oral antidiabetic agent, is associated with reduced cancer incidence and mortality. A meta-analysis of 11 studies demonstrated that metformin was associated with a reduction in all cancer incidence or mortality, reported as a summary relative risk (SRR), in comparison to other antidiabetic agents (SRR 0.69, 95% CI 0.61–0.79). A nonsignificant decrease in breast cancer risk was observed (41). It is hypothesized that in the setting of obesity, metformin may act indirectly to reduce cancer risk or progression via AMPK-mediated inhibition of hepatic gluconeogenesis resulting in lower levels of circulating insulin, a hormone suggested to play a role in carcinogenesis. A second more direct effect is also postulated whereby metformin activates AMPK in tumor cells. This causes downstream inhibition of mammalian target of rapamycin (mTOR) resulting in decreased protein synthesis, tumor cell proliferation, and increased apoptosis. Prospective neoadjuvant "window of opportunity studies" in which patients are administered metformin from the time of their diagnostic core biopsy up until their surgical resection have demonstrated a reduction in circulating insulin levels as well as alterations in gene expression, decreased proliferative index, and increased apoptosis (42). Currently, several prospective phase II and III trials are accruing patients to further investigate the anticancer effects of metformin.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

Nonsteroidal anti-inflammatory drugs (NSAIDs) inhibit the cyclooxygenase activity of COX-1 and 2, important enzymes in the biosynthesis of prostaglandins which play an important role in carcinogenesis. Although both epidemiologic studies and prospective randomized clinical trials have demonstrated that use of NSAIDs is associated with risk reduction for colorectal cancer, the data for breast cancer remain inconsistent. Recently, Zhang and colleagues explored the relationship between NSAID use and breast cancer risk within the Nurses' Health Study, which includes detailed and routinely updated information about NSAID use. In this cohort, approximately 4,700 invasive breast cancers were diagnosed over a period of 28 years and no significant difference in breast cancer incidence was demonstrated between regular aspirin users and nonusers. This lack of benefit was also reported both among users of nonaspirin NSAIDs and acetaminophen and did not vary based on either baseline patient or tumor characteristics or drug administration schedule (43). However, given the emerging data regarding the role of inflammation in the pathogenesis of breast cancer, the use of NSAIDs in more highly selected populations, such as the obese, remains an attractive area of active research (8).

Statins

Preclinical data suggest that statins (HMG-CoA reductase inhibitors) may have an antineoplastic role based on their pleiotropic effects on various cells and tissue. However, clinical data regarding the association between the use of statins and breast cancer risk are inconsistent. A meta-analysis of 24 observational studies failed to demonstrate a significant benefit in terms of breast cancer risk reduction for either short-term or chronic statin use (44). This may in part be due to the observational nature of these studies and the inherent biases associated with this type of analysis as well as difficulties acquiring complete and accurate cancer-related outcome data, since these studies were largely designed with primary cardiac and vascular endpoints. Moreover, preclinical studies suggest that only lipophilic statins are able to traverse the cell membrane and affect cell proliferation, invasion, and apoptosis. Therefore, well-planned randomized prospective trials are necessary to more clearly evaluate the role of these agents in breast cancer prevention and treatment.

Docosahexaenoic Acid (DHA)

Docosahexaenoic acid (DHA), an omega-3 fatty acid in fish oil, can suppress inflammation by multiple mechanisms including inhibition of TLR4-activated signaling pathways that induce TNF-α and COX-2. Diets rich in fish oil have been associated with a reduced risk of a number of malignancies including breast cancer. Consistent with other targeted therapies, specific dietary factors including omega-3 fatty acids may be beneficial only in subsets of patients. Therefore, trials to evaluate the anti-inflammatory and potentially antineoplastic effects of DHA are currently underway in multiple cancers including breast cancer, with a focus on higher risk cohorts where the impact may be demonstrable.

CONCLUSION

The effect of obesity on breast cancer development and natural history is complex and is becoming increasingly important, as a larger proportion of the population has elevated BMIs. Overweight and obesity are associated with an increased risk of ER-positive breast cancer in postmenopausal women, and may be associated with increased risk for other subtypes of the disease, specifically the triple-negative phenotype. Following a diagnosis of breast cancer, increasing BMI is associated with worsened breast cancer specific outcomes. Increasing adiposity presents a series of challenges for the optimal clinical management of breast cancer in terms of detection, local therapy (surgery and radiotherapy), and systemic treatment. Diet and exercise may attenuate the adverse prognostic impact of obesity to some degree, but novel therapeutic strategies are urgently needed to combat the complex interaction between the obesity epidemic and breast cancer. These strategies will need to focus on the specific pathophysiology of obesity, as it relates to breast cancer, rather than simply on BMI alone. Hence, as prospective clinical trials are designed and developed in this arena we must consider, similar to other targeted therapies, that the efficacy of these novel agents may be patient specific in identifiable ways. In the future, a more individualized approach to obesity may allow us to both prevent breast cancer and treat it more effectively, despite the special challenges presented by obesity and overweight.

MANAGEMENT SUMMARY

- Obesity is associated with an increased risk of ER-positive breast cancer in postmenopausal women and possibly triple-negative disease.
- Increasing body mass index (BMI), a commonly used metric of obesity, is associated with a series of challenges for the optimum detection and management of breast cancer, including increased surgical complications, and difficulties in the delivery of safe and effective radiotherapy and systemic therapy.

- Guidelines from the American Society of Clinical Oncology suggest that clinicians should generally use actual body weight when calculating both oral and intravenous cytotoxic chemotherapy doses, including for patients who are overweight and obese.
- Clinicians and other health care professionals should encourage regular physical activity, adherence to a healthy balanced diet, and weight management during all phases of breast cancer care.
- Novel approaches based on the underlying pathophysiology of overweight and obesity are urgently needed and clinical trial participation should be encouraged.

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CHAPTER 50

Lifestyle Issues in Breast Cancer Survivors

Jennifer A. Ligibel and Rowan T. Chlebowski

CHAPTER CONTENTS

Evidence increasingly suggests that lifestyle factors such as diet, physical activity, and body weight may play an important role in breast cancer survivors. Observational studies suggest that obesity, inactivity, and possibly differences in dietary intake may influence breast cancer prognosis (1,3). Studies have also demonstrated that interventions targeting weight, diet, and physical activity lead to better quality of life and fewer disease and treatment-related side effects in breast cancer survivors (4,5). Preliminary evidence suggests that lifestyle change may also improve prognosis in early stage breast cancer (6), but much work still needs to be done to validate this and to determine which types of lifestyle change are most important. This chapter outlines the observational evidence regarding lifestyle and breast cancer outcomes, with emphasis on recent reports, and presents an overview of lifestyle intervention studies in breast cancer survivors.

BODY WEIGHT AND BREAST CANCER

More than 50 observational studies have looked at the relationship between weight at the time of breast cancer diagnosis and clinical outcomes (1,7–10). Studies have focused on different populations, used different weight measures, and have been conducted in different eras. Despite these differences, the majority of these studies have demonstrated an increased risk of breast cancer recurrence and mortality in individuals who are obese at the time of breast cancer diagnosis as compared to leaner individuals. A recent meta-analysis by Protani et al. (1) included 43 studies looking at the relationship between weight at diagnosis and outcomes; the report demonstrated a 33% increase in breast cancer–specific and overall mortality in individuals who were obese (body mass index [BMI] 30 kg/m^2 or over) at the time of breast cancer diagnosis compared to individuals who were not obese (BMI less than 30 kg/m^2). The relationship between poor prognosis and obesity was seen in both pre- and postmenopausal women, and was also independent of type of weight measurement (BMI vs. other measure), year of report, and type of study (observational cohort vs. treatment trial).

Potential Influence of Treatment Factors

Although the Protani meta-analysis showed a relationship between poor prognosis and obesity both in the setting of clinical trials and observational cohort studies, it is notable that only 7 of the 45 reports included in the analysis collected data in the setting of a clinical trial, and few other reports included in the analysis adequately controlled for systemic adjuvant therapy (1). Recent attention has focused on optimizing adjuvant therapy for obese cancer patients, as concerns regarding toxicity have led many oncologists to cap or otherwise adjust chemotherapy doses in obese patients. Studies have shown that these a priori dose reductions in obese patients lead to inferior outcomes (11,12). For example, in Cancer and Leukemia Group B 8541 (12), a randomized trial of adjuvant anthracycline-based chemotherapy in women with node-positive breast cancer, obese women who received less than 95% of expected weight-based doses of chemotherapy for their first cycle of therapy had an increased risk of cancer recurrence as compared to obese women who received full weight-based chemotherapy (adjusted risk ratio [ARR] 0.73, 95% confidence interval [CI] 0.53–1.00). Obese women treated with full weight-based doses of chemotherapy had a similar risk of recurrence as compared to leaner women (ARR 1.02, 95% CI 0.83–1.26). Findings such as these prompted the American Society of Clinical Oncology to issue guidelines for the treatment of obese patients (13), which recommended full weight-based dosing of chemotherapy for all patients, regardless of body weight.

Body Weight and Breast Cancer Outcome (in Cooperative Group Trials)

Given the potential influence of treatment factors on the relationship between obesity and poor breast cancer prognosis, data from clinical trials, where treatments are uniform, doses are recorded, and outcomes are well documented, are especially relevant. A number of recent reports (Table 50-1) examine the relationship between obesity and breast cancer prognosis in the setting of modern adjuvant therapy trials. These studies continue to show a fairly consistent relationship between obesity at the time of breast cancer diagnosis and increased risk of recurrence and death in women with early-stage breast cancer treated with aromatase inhibitors (10,14,15) and modern anthracycline- and taxane-based chemotherapy regimens (7–9).

The relationship between BMI at the time of breast cancer diagnosis and outcomes has been evaluated in three large adjuvant aromatase inhibitor trials. In each of these, the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial, the Breast International Group (BIG) 1-98 trial, and the Austrian Breast Cancer Study Group (ABCSG) 12 trial, obesity was associated with a significantly higher risk of breast cancer recurrence. However, in the ATAC and ABCSG 12 studies, obesity was associated with poor outcomes only in patients treated with anastrozole and not in patients treated with tamoxifen. In contrast, the BIG 1-98 trial, which randomized women to letrozole or tamoxifen, demonstrated a modest relationship between obesity and worse overall survival in the study population as a whole (OR 1.19, 95% CI 0.99–1.44), but did not see a difference in the relationship between etiology of obesity and poor outcomes in women treated with letrozole versus those treated with tamoxifen (p = .74). The difference in outcomes in obese aromatase inhibitor-treated women in these studies is not clear, but could potentially be a reflection of the relative potencies of the drugs (16). One report from the ALIQUOT study suggested that suppression of estradiol was more complete in obese women treated with letrozole as compared to anastrozole, although it is not clear whether these differences are clinically meaningful (17,18).

Obesity at diagnosis has also been linked to a higher risk of recurrence in individuals treated in the context of recent adjuvant chemotherapy trials. Three recent trials—the Eastern Cooperative Oncology Group (ECOG) 1199 trial, the ADEBAR study, and CALGB 9741—have all evaluated the relationship between BMI at diagnosis and outcomes in women treated with adjuvant anthracyclines and taxanes. In all three studies, individuals who were obese at the time of breast cancer diagnosis had an increased risk of breast cancer recurrence and/or mortality as compared to leaner women. In E1199, this finding was seen only in women with hormone-receptor-positive tumors, whereas in CALGB 9741, obesity was a poor prognostic factor in both estrogen-receptor-positive and estrogen-receptor-negative tumors. These reports provide provocative information regarding

TABLE 50-1

Obesity and Breast Cancer Prognosis in Recent Adjuvant Chemotherapy and Hormonal Therapy Randomized Trials

Study	*N*	*Study Treatment*	*Patient Population*	*Results*
ABCSG 12 (15)	1,684	Ovarian suppression + tamoxifen or anastrozole	Premenopausal women	-Anastrozole: BMI ≥25 kg/m^2 vs. <25 kg/m^2: • HR recurrence 1.60 (95% CI 1.06–2.41) • HR death 2.14 (95% CI 1.17–3.92) -Tamoxifen: No increased risk of recurrence or death seen in overweight women
ATAC (14)	4,939	Tamoxifen, anastrozole, or combination	Postmenopausal women	-BMI ≥35 kg/m^2 vs. <23 kg/m^2: • HR for recurrence 1.39 (95% CI 1.06–1.82) -Anastrozole significantly less effective in women with BMI >30 kg/m^2 vs. <28 kg/m^2 (p = .01)
BIG 1-98 (10)	4,760	Letrozole or tamoxifen	Postmenopausal women	-BMI ≥30 kg/m^2 vs. BMI <25 kg/m^2: • HR OS 1.19 (95% CI 0.99–1.44) -Efficacy of letrozole not dependent on BMI
ADEBAR (8)	1,500	5-FU, Epirubicin, cyclo-phosphamide vs. epirubicin, cytoxan-docetaxel	Pre and postmeno-pausal women	BMI ≥30kg/m2 vs. BMI > 25 and <30 kg/m^2: -Significantly worse DFS (p = .0075)
E1199 (7)	3,484	Doxorubicin, cyclo-phosphamide and taxane	Pre- and postmeno-pausal women	-HR positive tumors: BMI ≥30 vs. <30 kg/m^2 • HR recurrence 1.24 (95% CI 1.06–1.46) • HR death 1.37 (95% CI 1.13–1.67) -HR negative and HER-2 positive tumors: No association between obesity and prognosis
C9741 (9)	1,909	Doxorubicin, cyclophosphamide and paclitaxel	Pre- and postmeno-pausal women	-In multivariate analyses, each unit increase in BMI associated with 1.5% increase risk of recurrence and death • BMI 32 vs 22: HR for RFS 1.22 (p = .01) -No interaction between HR status and relationship between BMI and outcomes

the potential role of obesity in altering breast cancer outcomes even in patients receiving contemporary anticancer adjuvant treatment.

Weight Gain after Diagnosis and Breast Cancer Outcome

The association between obesity and poor prognosis in early-stage breast cancer is especially worrisome given the weight gain seen in many women following diagnosis where, even with anthracycline-based adjuvant regimens, weight gain of 2 to 6 kg is commonly reported (19). A number of older studies suggest that weight gain after breast cancer diagnosis is associated with poor prognosis, but recent reports have been less consistent. A report from the Nurses' Health Study found that nonsmoking women with early-stage breast cancer who gained 2.0 kg/m^2 or more (median weight gain of 17 pounds) had higher risk of breast cancer recurrence, breast cancer death, and all-cause mortality than did women who did not gain weight (20). Other recent reports, including an analysis of the Life After Cancer Epidemiology Study Cohort (21), have not shown a relationship between weight gain and breast cancer prognosis.

Weight-Loss Studies in Breast Cancer Survivors

Despite the consistent evidence that obesity at the time of breast cancer diagnosis is a poor prognostic factor, there are no data from randomized trials demonstrating that purposeful weight loss after diagnosis will lead to improvements in prognosis. Many experts have speculated that the difference in findings of two large-scale dietary intervention trials (6,22) (see description below in dietary section), one of which induced weight loss and the other of which did not, provides evidence that weight change after diagnosis will lower the risk of cancer recurrence and related mortality, but large-scale trials are needed to test this hypothesis.

A number of smaller-scale trials have been performed in breast cancer populations demonstrating the feasibility and benefits of weight-loss interventions (23). The largest weight-loss study in breast cancer survivors to date, the Lifestyle Intervention Study for Adjuvant Treatment of Early Breast Cancer (LISA) trial, randomized 338 postmenopausal women with hormone-receptor-positive breast cancer to an educational control group or to a 2-year, telephone-based weight-loss intervention focused on calorie restriction, a low-fat diet, and increased physical activity. Intervention participants lost approximately 4.5 kg more than the control group at 6, 12, 18, and 24 months and reported a significant improvement in physical functioning scores as compared to control participants (5). A number of other weight-loss studies, including the ENERGY, SUCCESS-C, DIANA-5, and CHOICE trials, will provide additional information regarding the efficacy and benefits of weight-loss interventions in breast cancer survivors.

PHYSICAL ACTIVITY AND BREAST CANCER

A number of reports over the last several years have examined the relationship between physical activity and breast cancer outcomes (2). A recent systematic review identified 17 studies evaluating the association between physical activity patterns before and/or after cancer diagnosis and breast cancer–specific and overall mortality (2). Studies largely focused on recreational physical activity, although a few evaluated occupational and household activity as well. Most of the data were collected from prospective cohorts of healthy individuals who subsequently developed cancer or from cohorts of cancer survivors. Physical activity was assessed using a variety of interviewer-administered or questionnaire-based instruments; all of the data were self-reported. Only a few of the studies accounted for BMI, tumor stage, or treatment variables.

The review found consistent evidence that higher levels of physical activity both before and after breast cancer diagnosis were associated with a lower risk of breast cancer–specific and overall mortality (Fig. 50-1). No study reported

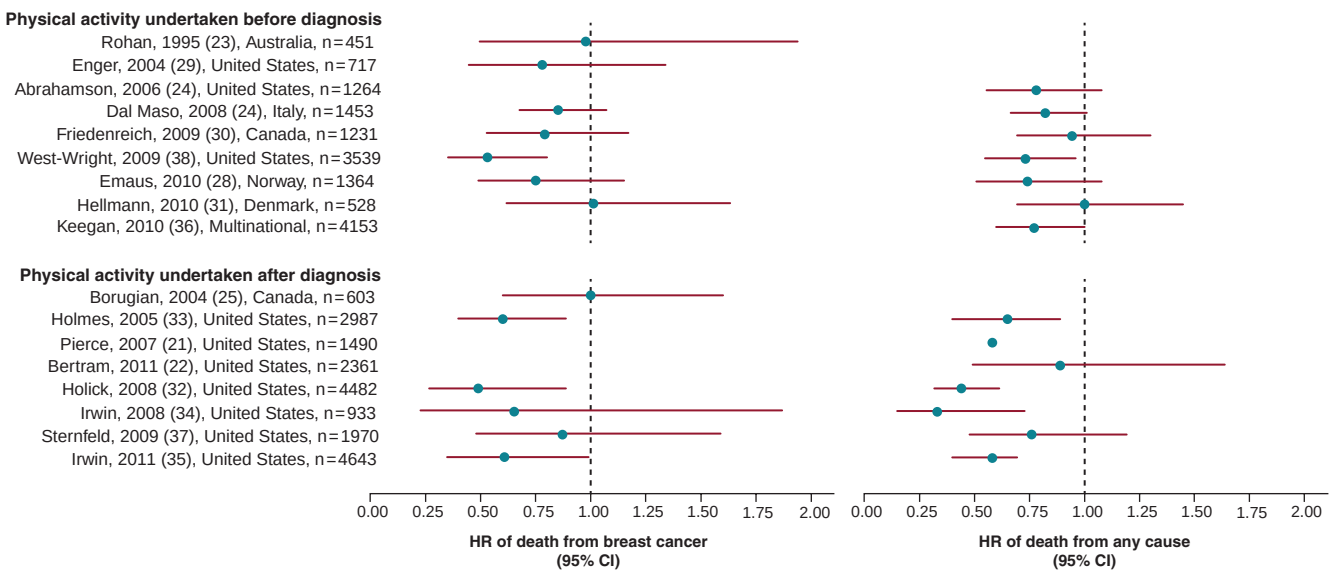

FIGURE 50-1 Forest plot of risk estimates from observational studies of physical activity and mortality outcomes in breast cancer survivors. (Redrawn from Ballard-Barbash R, Friedenreich CM, Courneya KS, et al. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J Natl Cancer Inst* 2012;104[11]:815–840. doi:10.1093/jnci/djs207.)

an increased risk of cancer-specific or overall mortality with increased levels of physical activity. Thirteen of 16 reports evaluating the relationship between physical activity and breast cancer–specific mortality demonstrated a 13% to 51% lower risk of mortality in physically active individuals. Similarly, 12 of 14 studies evaluating the relationship between physical activity and all-cause mortality found lower rates of mortality in individuals who reported higher levels of physical activity.

Of note, although some reports suggested a dose–response relationship between increasing physical activity and improved outcomes, many reports demonstrated an improvement in prognosis with relatively modest levels of physical activity. For example, the NHS investigators prospectively examined relationships between physical activity and clinical outcomes in a cohort of 2,987 women diagnosed with stage I to IIIA breast cancer (24). Women who reported 9 to 14.9 MET hours of physical activity per week, equivalent to 3 to 5 hours per week of moderate pace walking, had a 50% lower risk of breast cancer mortality as compared to women who completed less than 3 MET hours per week of physical activity. A similar relationship between performance of relatively modest levels of physical activity after diagnosis and improved outcomes was reported in the Collaborative Women's Longevity Study (25), in which long-term breast cancer survivors who reported at least 2.8 MET hours per week of physical activity had significantly lower breast cancer mortality when compared to women with lower levels of activity. Taken together, the results are consistent with a modest increase in physical activity being associated with substantial improvement in clinical outcome for patients with early-stage breast cancer.

Physical Activity Interventions in Breast Cancer Survivors

Despite the observational data suggesting better outcomes in women who engage in modest levels of physical activity after cancer diagnosis, there are no randomized trials testing the impact of increased physical activity after diagnosis upon prognosis in women with early-stage breast cancer. Observational studies have demonstrated that a breast cancer diagnosis often is associated with a substantial decrease in physical activity (26), further underscoring the need for interventions designed to increase physical activity in breast cancer survivors.

Dozens of studies have tested the feasibility and potential benefits of physical activity interventions in breast cancer patients receiving adjuvant therapy and in the posttreatment setting (4). Studies have implemented both supervised and home-based intervention programs and have focused on a variety of exercise modalities including walking, cycling, yoga, strength training, and rowing. The American College of Sports Medicine recently published a comprehensive review of exercise intervention studies in cancer populations which included data from 54 randomized controlled trials of exercise in breast cancer survivors deemed to have high internal validity, based upon low rates of attrition, high rates of adherence, and standardization of the intervention (4). In both the adjuvant and posttreatment settings, there was consistent evidence to suggest that physical activity interventions were safe and led to increased aerobic fitness and strength. A modest level of evidence also suggested that individuals who participated in physical activity interventions experienced improvements in quality of life, anxiety, depression, fatigue, body image, body size, and body composition, although not all studies were consistent in these findings. Large-scale, randomized clinical trials are needed to determine whether increasing physical activity after breast cancer diagnosis will not only help women feel better, but also lead to improvements in prognosis.

DIETARY INTAKES AND BREAST CANCER OUTCOME

Studying the relationship between postdiagnosis dietary intakes and breast cancer prognosis represents an especially challenging area for observational studies, with methodologic issues related to the optimal timing of data collection, difficulty in accurately measuring the dietary exposure, and the modest range of intake for nutrients of interest in a general population (27).

The relationship between dietary fat intake and breast cancer outcome has been examined in more than a dozen observational studies (3). Although recent analyses suggest that commonly used instruments may have difficulty in accurately measuring this parameter, seven reports demonstrated a significant association between lower fat intakes and lower recurrence risk (3,19). These reports did not adjust for BMI or total energy intake, however, making interpretation problematic. Reports relating vegetable and related nutrient intake to breast cancer prognosis presents a similarly mixed picture with three of eight reports describing significant associations between higher intake and lower recurrence risk (3). Recently, two randomized clinical trials have provided a higher level of evidence on the question of the influence of nutrient intake on breast cancer outcomes.

Dietary Intervention Studies and Breast Cancer Outcomes

Two full-scale randomized clinical trials have evaluated lifestyle interventions targeting dietary change in the adjuvant breast cancer setting. The Women's Intervention Nutrition Study (WINS) (6) and Women's Healthy Eating and Living (WHEL) study (22) enrolled slightly different populations and studied different dietary patterns, but both aimed to reduce dietary fat intake. These trials are compared and contrasted below (Table 50-2).

The WINS was a randomized, prospective multicenter clinical trial evaluating the impact of a dietary intervention on disease-free survival (DFS) in women with early-stage breast cancer receiving conventional cancer management (6). The dietary intervention was designed to reduce fat intake with eight every-other-week visits during the intensive intervention period followed by every-3-month contacts during the maintenance period, implemented by centrally trained, registered dietitians using a previously developed low-fat eating plan. After 5.6 years' median follow-up, a sustained statistically significant reduction in dietary fat intake, in terms of both fat grams and percent calories from fat, was seen in intervention participants (Table 50-2). Although weight loss was not a specific intervention target, significantly lower body weight was also seen in the intervention group throughout. More relapse events occurred in the control (181 of 1,462, 12.4%) compared with the intervention group (96 of 975, 9.8%, HR 0.76, 95% CI 0.60–0.98, $p = .034$). Preliminary analyses from an additional 3 years of follow-up provided similar results (relapse-free survival HR 0.79, 95% CI 0.62–1.00), but the difference was no longer statistically significant (28). In exploratory analyses, substantially greater influence was seen in women with ER-negative, PR-negative breast cancer (overall survival HR 0.34, 95% CI 0.16–0.70) (28).

TABLE 50-2

Dietary Intervention Studies with Breast Cancer Outcomes

	WINS	*WHEL*
Eligibility		
Stage	I–III A	I–III A
Time from surgery	≤12 mo	≤48 mo
Age	48–79 yr	18–70 yr
Diet at baseline	≥20% calories from fat	Any
Dietary intervention	Individual sessions with dietitian	Telephone-based sessions
Number of patients	2,437 (3:2 randomization)	3,088 (1:1 randomization)
Intervention target		
Fat	↓ to 15% calories from fat	↓ to <20% calories from fat
Vegetable	Increase (no target)	Increase to 5 servings and 16 oz vegetable juice/day
Fruit	Increase (no target)	Increase to 3 servings/day
Follow-up interval	5 yr	7.3 yr
Change in dietary intakes (intervention vs. control)		
Fat	–33%	–13%
Vegetables	Not reported	+65%
Fruit	Not reported	+25%
Weight change (intervention vs. control)	–2.7 kg	None
End-point events (*n*)	277	518
Primary breast cancer outcome	HR 0.76 (95% CI 0.60–0.98, $p = .034$)	0.96 (95% CI 0.80–1.14, $p = .63$)

WINS, Women's Interventional Nutrition Study; WHEL, Women's Healthy Eating and Living Study.

The WHEL study was a multicenter, randomized prospective trial of a dietary intervention program in 3,088 women with early-stage breast cancer designed to determine whether a diet focused on increasing intakes of vegetables, fruit, and fiber intake and decreasing fat, would influence breast cancer recurrence risk and all-cause mortality (22). Intervention participants received a telephone counseling program involving 18 calls during the first year with a subsequent decrease in intensity. Significant changes were achieved in the nutrition targets: vegetables plus 65%, fruit plus 25%, fiber plus 30%, and energy intake from fat minus 13%. Over the 7.3-year mean follow-up, no difference emerged in invasive breast cancer events (HR 0.96, 95% CI 0.80–1.14, $p = .63$) or overall survival (HR 0.91, 95% CI 0.72–1.15; $p = .43$) (22).

Although both WINS and WHEL included dietary fat intake reduction as an objective and entered early-stage breast cancer patients, substantial differences between these trials exist. The WHEL intervention resulted in a substantial and sustained increase in vegetable, fruit, and fiber intake and a relatively short duration, moderate reduction in fat intake. The WINS intervention did not report increased vegetable, fruit, or fiber intake, but resulted in a substantial, sustained reduction in fat intake, which was associated with significant weight loss that may account for the apparent differences in influence on clinical outcome seen.

POTENTIAL MEDIATORS OF LIFESTYLE CHANGE

The biologic mechanisms underlying the relationship between lifestyle factors and cancer prognosis are not well understood. Current hypotheses suggest these effects may be mediated through metabolic and inflammatory pathways that have been linked to cancer risk and prognosis (29–34). Inflammatory and metabolic pathways are interconnected and dysregulation of this system contributes to the development of many common diseases, including cancer (35). Of the many mediators that have been purported to link lifestyle factors and cancer, evidence is strongest to support a significant role of insulin in this process (30,36). Hyperinsulinemia has been linked to poor outcomes in patients with early-stage breast cancer in several studies (Table 50-3). For example, Goodwin and colleagues demonstrated a twofold increase in the risk of cancer recurrence and a threefold risk of death in newly diagnosed breast cancer patients with the highest quartile of fasting insulin levels compared to the lowest (31).

Cross-sectional analyses in postmenopausal women without cancer suggest both low physical activity and high caloric intake are related to higher fasting insulin levels (37). A number of interventional studies in at-risk and breast cancer populations also demonstrate that modification of lifestyle factors can lead to favorable changes in fasting insulin levels. The Nutrition and Exercise for Women (NEW) trial evaluated the impact of weight loss and increased physical activity on levels of insulin and other biomarkers in 439 overweight postmenopausal women and demonstrated that weight loss induced a 26% decrease in levels of fasting insulin, whereas exercise without weight loss induced a much more modest change in insulin levels (38). In contrast, two small studies in overweight, inactive breast cancer survivors demonstrated a 20% to 30% decrease in insulin levels with exercise alone (39,40).

TABLE 50-3

Select Studies of Insulin (and Related Factors) and Breast Cancer Prognosis

	Study	*N*	*Factor Measured*	*Results*
Insulin	Goodwin (31)	512	Fasting insulin	Highest vs. lowest quartile: **Recurrence:** HR 2.0 (95% CI 1.2–3.3) **Death from Any Cause:** HR 3.1 (95% CI 1.7–5.7)
	HEAL (33)	527	Insulin resistance (Homeostatic Model Assessment [HOMA])	Higher HOMA scores vs. lower **Breast Cancer Death**: HR 1.12 (95% CI 1.05–1.20) **Death from Any Cause:** HR 1.09 (95% CI 1.02–1.51)
C-peptide	Pritchard (43)	667	Nonfasting c-peptide	Higher c-peptide levels associated with worse event free survival in adjusted analyses (p <.05)
	HEAL (32)	689	Fasting c-peptide	1 ng/mL increase in c-peptide: **Breast Cancer Death**: HR 1.35 (95% CI 1.02–1.87) **Death from Any Cause**: HR 1.31 (95% CI 1.06–1.63)
Metabolic/Insulin Resistance Syndrome	Emaus (34)	1,364	Components: • BMI • Cholesterol • BP	Risk of mortality for: **BMI ≥ 30 kg/m^2 vs. <30 kg/m^2** 1.47 (95% CI 1.08–1.99) **High vs. low cholesterol** 1.29 (95% CI 1.01–1.64) **High vs. low BP** 1.41 (95% CI 1.09–1.83)
	Pasanisi (44)	110	Metabolic Syndrome: • Hyperglycemia • Hypertension • Visceral adiposity • High triglycerides	In patients with vs. without metabolic syndrome: **Recurrence**: HR 3.0 (95% CI 1.2–7.1)

The evidence linking insulin to breast cancer outcomes has led to significant interest in the drug metformin, an oral biguanide used in the treatment of type 2 diabetes. Unlike most agents used for this purpose, metformin decreases systemic insulin levels by inhibiting hepatic gluconoegensis and thus suppressing insulin levels. A number of observational studies have shown an association between metformin use and decreased cancer incidence and mortality (41), and a report from MD Anderson demonstrated a higher pathological complete response rate to neoadjuvant therapy for locally advanced breast cancer in diabetic patients treated with metformin compared with diabetics treated with other agents (42). This work has led to the MA-32 trial (41), which will test the impact of adjuvant metformin on rates of invasive disease free survival in early breast cancer. The study randomized 3,582 individuals with stage Ic to III breast cancer to 5 years of metformin (850 mg bid) or placebo. Embedded correlatives will further elucidate the role of insulin and other metabolic mediators in breast cancer prognosis. Enrollment was completed in January 2012 and follow-up is ongoing.

CONCLUSIONS

As the evidence linking lifestyle factors and breast cancer outcomes mounts, there is a growing desire on the part of many patients to make lifestyle changes after breast cancer diagnosis. However, given the relative paucity of available randomized data, and that most medical oncologists lack expertise in this area, many breast cancer patients do not receive any guidance to help make these changes.

Observational evidence suggests that women who are overweight or obese at the time of breast cancer diagnosis, and possibly those who gain weight during and after cancer treatment, appear to have a worse prognosis as compared with leaner women. Similar evidence suggests that women who are inactive after breast cancer diagnosis also have a poor prognosis compared with women who engage in modest amounts of physical activity. Randomized data suggest that lowering fat intake, or modest weight loss, is associated with a modest decrease in breast cancer recurrence, whereas increasing fruit, vegetable, and fiber intake does not appear to have an impact on breast cancer outcomes. Randomized trials are needed to further explore the impact of lifestyle change after diagnosis on breast cancer outcomes, and to determine the most important lifestyle factors and target populations for intervention.

MANAGEMENT SUMMARY

- Advocating weight maintenance for women with a BMI less than 25, and moderate weight loss for overweight and obese women, are reasonable goals for most breast cancer patients.

- Specific recommendations for individual patients will depend on the goals of the treatment plan (weight maintenance vs. weight loss), as well as the presence of comorbid conditions that could influence diet or activity level.
- A diet emphasizing complex carbohydrates and limiting refined sugars and fats, combined with moderate-intensity physical activity, could be considered for most breast cancer patients.
- The U.S. surgeon general recommends 30 minutes of moderate exercise five times per week as a general health measure, and this level of physical activity may be associated with improved survival in breast cancer patients.
- Ongoing studies will evaluate the role of insulin-lowering strategies to improve prognosis in breast cancer patients.

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CHAPTER 51

Management of Menopausal Symptoms in Breast Cancer Survivors

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CHAPTER CONTENTS

INTRODUCTION

In the United States today, approximately 2.7 million women live as breast cancer survivors, a number that is increasing. This increase is particularly attributable to women diagnosed with early stage breast cancer, who have a life expectancy similar to age-matched controls. The issues facing cancer survivors are multiple and unique as the long-term side effects of cancer treatment and of aging play an increasingly prominent role in the routine care of these patients. Of special concern are the short and long-term effects of sex hormone deprivation such as vasomotor instability, osteoporosis, sexual dysfunction, arthralgias, and weight gain; currently there are several trials investigating ways to counteract these effects.

The average age of onset of natural menopause is 51 years. However, breast cancer therapy often leads to both an earlier onset of menopause and the exacerbation of existing menopausal symptoms. Hormone replacement therapy (HRT) is frequently used to treat these problems in the general population, but concerns about its potential to increase the risk of recurrence in breast cancer survivors have forced physicians to utilize alternative treatments.

While long-term HRT has beneficial effects on women's bones and menopausal symptoms, this is more than offset by an increased risk of venous thromboembolic disease, breast cancer, stroke, cognitive decline, and coronary heart disease. In addition, the routine use of HRT in women does not appear to increase quality of life. These results support that long-term combination therapy with estrogen and progesterone cannot be recommended to most women at this time.

This chapter reviews current issues surrounding the acute and late effects associated with hormone deprivation in breast cancer survivors, and summarizes the scientific and therapeutic discoveries to date to identify optimal non-estrogenic treatments for individual patients.

VASOMOTOR INSTABILITY

Pathophysiology and Epidemiology

Hot flashes affect about three-fourths of all postmenopausal women, being the most commonly described health problem among this age group. Vasomotor instability usually begins 1 to 2 years prior to menopause and often persists for 6 months to 5 years after menopause. It is characterized by the sudden onset of a sensation of intense warmth that typically begins in the chest and progresses to the neck and face, often accompanied by anxiety, palpitations, profuse sweating, and red blotching of the skin. Hot flash symptoms can affect a woman's ability to work, her social life, her sleep pattern, and her general perception of health and quality of life.

Changes in circulating estrogen levels can induce abnormalities of the central thermoregulatory centers, resulting in hot flashes. Perspiration and vasodilation, classic mechanisms of heat loss controlled by the hypothalamus, are activated during a hot flash. In normal homeostasis, these mechanisms are activated to maintain core body temperature in a regulated range termed the "thermoregulatory zone." Complex neuroendocrine pathways that involve norepinephrine, estrogen, testosterone, and endorphins appear to govern regulation in the thermoregulatory nucleus and are possible sites where dysfunction may occur. In women undergoing natural menopause there is an association of hot flash symptoms with maternal history of hot flashes and with cigarette smoking.

Hot flashes are the most common reason women seek estrogen replacement therapy and, while estrogen effectively relieves symptoms for 80% to 90% of women who initiate treatment, women with a history of breast, ovarian, or uterine cancer, venous thromboembolism, coronary artery disease, or a family history of breast cancer comprise large populations for whom estrogen therapy may be contraindicated. Results from the Women's Health Initiative (WHI) and the Million Women Study, in combination with other reports, suggest that long-term combined estrogen and progesterone therapy results in an increased risk of breast cancer, coronary heart disease, venous thromboembolism, and stroke. Although HRT with estrogen alone did not appear to increase the risk of breast cancer in the WHI study (1), the controversy surrounding its effects has been very influential in clinical practice and has led to a significant decrease in the use of HRT in the last decade (2). For these reasons, many women assume that hot flashes are an inevitable symptom of being a breast cancer survivor.

In breast cancer patients, vasomotor symptoms negatively impact sleep, quality of life, energy, as well as compliance with therapy and satisfaction with treatment decisions. The cause of vasomotor symptoms in breast cancer patients can be the result of abrupt estrogen loss due to surgery or chemotherapy, the use of adjuvant hormonal therapy, discontinuation of hormone replacement therapy, or from natural menopause. Tamoxifen, the most commonly prescribed pharmacologic treatment for breast cancer over the past decade, is associated with hot flashes in more than 50% of users (3,4). Tamoxifen-associated hot flashes increase over the first several months of treatment and then gradually resolve (3). Postmenopausal women with a history of significant hot flashes prior to tamoxifen and a history of prior estrogen therapy use are likely to experience more severe hot flashes with tamoxifen therapy (3,5). Compared to tamoxifen, adjuvant therapy with aromatase inhibitors (AIs) results in a lower incidence of hot flashes.

In premenopausal women with breast cancer, adjuvant chemotherapy is frequently associated with temporary or permanent amenorrhea, due to toxicity to the ovary. The incidence of chemotherapy-induced ovarian failure depends on the regimen used, the cumulative drug doses, and the age of the patient. The rapid changes in hormone concentrations associated with chemotherapy can lead to more severe symptoms than those of natural menopause.

Hormonal Therapies

Studies investigating the use of HRT for menopausal symptoms in breast cancer survivors have led to varying results. Although a few small pilot studies found the use of HRT after breast cancer safe, more recently, two randomized placebo-controlled studies of HRT—The HABITS study (6) and the LIBERATE study (7)—were closed early due to evidence of an increased breast cancer recurrence in the HRT group. The HABITS study of estrogen alone or in combination with progesterone versus placebo included 434 participants and closed at 2 years due to safety concerns, after a 3.5 relative hazard ratio for recurrence was seen in the HRT versus placebo group. In the LIBERATE study, 3,148 participants were randomized to tibolone (a synthetic compound with weak estrogenic, progestogenic, and androgenic actions) versus placebo; similar findings of increased breast cancer recurrence in the tibolone group were seen after a median follow-up of 3 years. In contrast to these findings, the Stockholm trial of 378 participants given estrogen with or without progestin versus placebo did not show a difference in recurrence after 4 years of follow-up (8). In this study the use of progesterone was minimized, which could explain the different results.

Some reports suggest that low-dose transdermal estrogen might be safer to use in this population and is very effective for symptom relief in the general population. In breast cancer survivors this therapy was not studied.

Current guidelines recommend that providers avoid the use of HRT for treatment of hot flashes in this population (9). If such therapy is used, it should be done over the shortest time period and with the lowest effective dose.

Progesterone alone, via oral megestrol acetate (20 mg/day) or the long-acting intramuscular depomedroxyprogesterone acetate (DMPA), was also demonstrated to be highly effective in the management of hot flashes in breast cancer survivors, with a 75% to 80% reduction in their severity and frequency (10,11). Although minimal side effects are described during the treatment period, some women experienced withdrawal bleeding 1 to 4 weeks after discontinuation of treatment with megestrol acetate; the effects of the progesterone on hot flash reductions appear to be long-lasting. In a randomized trial comparing a single intramuscular dose of medroxyprogesterone acetate to venlafaxine, medroxyprogesterone acetate was more effective and appeared to have fewer short-term toxicities (12). It should be noted, however, that there are no long-term prospective data to establish the safety of progesterone analogs agents for women with hormone-sensitive breast cancer.

Nonhormonal Therapies

Newer Antidepressants

It is difficult to evaluate the efficacy of pharmacologic therapy for hot flashes with anecdotal reports alone, because of placebo effects. Multiple placebo-controlled trials demonstrate a 20% to 35% reduction in hot flashes with 4 weeks of placebo treatment. The most studied and effective nonhormonal pharmacological agents in the treatment of hot flashes are the newer antidepressants (selective serotonin reuptake inhibitors [SSRIs] and selective norepinephrine reuptake inhibitors [SNRIs]), as well as the anticonvulsants gabapentin and pregabalin.

Venlafaxine is thought to inhibit serotonin reuptake at lower doses and to induce a more profound inhibition of norepinephrine reuptake at higher doses. A double-blind, placebo-controlled trial with 191 breast cancer survivors randomized subjects to placebo or to one of three target venlafaxine doses (37.5 mg, 75 mg, or 150 mg daily) (13). After 4 weeks of treatment, the placebo groups had a 27% reduction in symptoms, versus 40%, 61%, and 61% reductions in the three venlafaxine groups, respectively. The side effects observed with venlafaxine include dry mouth, decreased appetite, nausea, and constipation (the latter only at doses of 150 mg/day).

A comparison study between venlafaxine and DMPA injections (12) showed a decrease in hot flashes by 55% with venlafaxine and by 79% with DMPA. In a crossover study comparing target dose venlafaxine ER 75 mg daily with gabapentin at a target dose of 300 mg three times daily, both treatments were equally effective (reduction in hot flashes scores by 66%), but venlafaxine was preferred by the patients (14). From these studies, it appears that venlafaxine adequately balances the symptom relief with the side effects. When venlafaxine is started, it should be started at 37.5 mg/day. When the drug is to be stopped, it should be slowly weaned down.

Another SNRI, desvenlafaxine, was found to be more effective than placebo, in two RCTs of women without cancer, at a target dose of 100 mg daily, with a starting dose of 50 mg daily for 3 days (15,16).

SSRIs are also effective for the treatment of hot flashes. A double-blind, randomized, placebo-controlled, crossover clinical trial demonstrated that fluoxetine reduces the incidence of hot flashes, although the reduction does not appear to be as great as that observed with venlafaxine (13,17). No significant toxicity was observed. Two placebo-controlled, double-blinded randomized trials found that paroxetine decreased hot flashes significantly more than did a placebo (18–20). However, both paroxetine and fluoxetine are potent inhibitors of P450 (CYP) 2D6, an enzyme involved in the metabolism of tamoxifen to its active metabolite, endoxifen, thus raising concerns about the coadministration of these drugs with tamoxifen, as they may lower the mean endoxifen level. Endoxifen seems to also be the active metabolite in hot flashes, from studies showing that decreased CYP 2D6 activity leads to less prominent hot flashes after starting tamoxifen (and also worse breast cancer prognosis) and that patients without hot flashes on tamoxifen have an increase in breast cancer recurrence compared to those with hot flashes. Early studies supported that venlafaxine did not appear to inhibit CYP 2D6 to any appreciable degree; however, this remains a topic of investigation. Further information regarding tamoxifen metabolism can be found in Chapter 55.

Three randomized, placebo-controlled trials evaluating sertraline (50–100 mg/day) for the management of hot flashes failed to reveal any substantial benefit from this drug. Citalopram, a potent and specific SSRI, however, was shown to be effective against hot flashes in an RCT of 254 patients randomized to placebo, 10 mg, 20 mg, or 30 mg of citalopram daily (21). Hot flashes were reduced by 20%, 46%, 43%, and 50% respectively. Side effects were minimal. The recommended dose of citalopram is 10 to 20 mg daily. Escitalopram, a stereo-isomer of citalopram, was studied in 205 postmenopausal women and found to be more effective than placebo (47% vs. 33%) in decreasing the frequency of hot flashes (22). The dose used in this study was 10 mg/day. Increasing the does to 20 mg/day after 4 weeks was recommended in nonresponders.

Two randomized, placebo-controlled clinical trials of some of these newer antidepressants (23,24) have been interpreted to be negative studies (25). Nonetheless, neither of these trials had hot flash diary data from a baseline period prior to the initiation of the study agents, making it impossible to determine how much hot flash reduction occurred. An individual patient pooled analysis of all the randomized trials looking at newer antidepressants that had baseline data available (26) demonstrates that they significantly decrease hot flashes ($p < .0001$).

Anticonvulsants and Other Centrally Acting Agents

Four placebo-controlled trials and a pooled analysis have confirmed the ability of gabapentin, a gamma aminobutyric acid (GABA) analogue, to decrease hot flashes (27–31). Although one study suggested that gabapentin was as effective as estrogen therapy (29), this does not appear to be the case, as all data are considered together. The recommended starting gabapentin dose is 300 mg/day, titrating up to 900 mg/day. Side effects include lightheadedness and sleepiness early on, which generally resolve with continued treatment. Pregabalin also appears to be helpful for hot flash management, per a RCT of 75 mg twice a day versus 150 mg twice daily versus placebo (32). It is recommended at a starting dose is 50 mg/day, with a target dose of 75 mg twice a day.

Clonidine decreases hot flashes to a moderate degree but is associated with side effects that limit its utility. Methyldopa and belladonna alkaloids do not appear to be very useful for hot flashes due to modest efficacy and unpleasant side effects.

Complementary and Alternative Agents

Despite anecdotal reports, the benefits of herbal therapies in clinical trials have been disappointing to date. Herbal treatments, such as black cohosh (*Cimicifuga racemosa*), ginseng (*Panax Ginseng*), evening primrose oil (*Oenothera biennis*), wild yam (*Dioscorea villosa*), and a standardized blend of 12 Chinese herbs have been prospectively evaluated, with minimal activity observed.

A randomized, placebo-controlled, crossover trial in 120 women found that vitamin E therapy decreased the average hot flash frequency by one episode per day (33), whereas more significant improvements in the vitamin E group were seen in a crossover trial (34). The low cost and minimal side effects of vitamin E make a trial of this agent (800 IU qd) one approach for individuals with mild symptoms that do not interfere with sleep or daily function. Therapy with vitamin E may increase the risk of heart failure in patients with vascular disease and diabetes mellitus but does not appear to affect the risk of cancers.

Studies of phytoestrogens in the treatment of hot flashes are also inconclusive. The isoflavone group (soy, red clover) was found to be no better than placebo in a meta-analysis of 17 placebo-controlled trials (25). Similarly, the lignants (found in flaxseed, whole grains, miller, fruits, and vegetables) did not help in hot flash treatment more than placebo in a randomized trial of flaxseed versus placebo bars (35). Furthermore, the long-term safety of pharmacologic doses of soy (90–400 mg/day) in patients with a history of breast or uterine cancer is not established.

The effect of nonestrogenic agents on hot flashes is similar in women with or without a history of breast cancer, irrespective of their use of tamoxifen (36).

Nonpharmacologic Interventions

Mind–body interventions, such as acupuncture, relaxation-training/paced respiration, mindfulness-based stress reduction, cognitive behavioral therapy (CBT), and yoga all appear to be beneficial in small uncontrolled studies, but systematic reviews of some of these interventions have been inconclusive, given the small size of the studies and methodological flaws (37). Hypnosis has been suggested to be helpful via pilot trials and a small randomized trial of breast cancer survivors, published recently.

Although acupuncture appeared to be effective in alleviating hot flashes in uncontrolled studies, when compared to sham acupuncture, there was no significant reduction in symptoms. These findings were confirmed by a recent meta-analysis of 11 randomized trials (38), although some trials do still report positive results. There may be a form of acupuncture that does help hot flashes, but one has not been clearly identified, to date.

Another promising intervention in alleviating hot flashes in small studies is a stellate ganglion block; larger studies are underway to further investigate its effect. A review of RCTs on exercise for hot flashes was not able to demonstrate a benefit for this approach. For mild hot flashes, interventions such as using a fan, lowing room temperature, wearing loose-fitting clothing, consuming cold drinks, and avoiding alcohol and spices can be suggested.

Other comprehensive reviews of the pathogenesis and treatment of hot flashes in breast cancer survivors are available (39–41). Table 51-1 provides a summary of the most active available therapies for hot flashes.

TABLE 51-1

Hot Flash Treatment Options

Treatment Option	*Efficacy (%)*[a]	*Comment*
Estrogen	85%	Breast cancer concern
Progesterone[b]	85%	Breast cancer concern
Antidepressants (e.g., venlafaxine, paroxetine, desvenlafaxine, citalopram, and escitalopram)	50%–60%	Do not use paroxetine or fluoxetine with tamoxifen
Gabapentin	50%–60%	

[a]Percentage of reduction from baseline after about 4 weeks, noting that a placebo decreases them about 20% to 30%.
[b]Megestrol acetate 20 to 40 mg/d orally or medroxyprogesterone acetate 400 mg intramuscularly once.

OSTEOPOROSIS

Definition and Pathophysiology

Osteoporosis is a metabolic bone disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. Decreased body mass index (BMI) is an important known risk factor for low bone mineral density (BMD) and osteoporotic fractures. A BMD that is 2.5 standard deviations below the young adult female mean value is used to diagnose osteoporosis. At menopause, women enter a 10-year period of accelerated bone loss, responsible for a 20% to 30% loss of cancellous bone and a 5% to 10% loss of cortical bone. Estrogen and testosterone play important roles in the regulation of BMD and bone health. In postmenopausal women, the conversion of adrenal androgens to estrogen by the enzyme, aromatase, leads to continued low levels of circulating estrogen, which may play an important role in calcium homeostasis through its effects on renal and GI absorption of calcium. Osteoporotic fractures are an important health hazard; women have an estimated 1-year mortality risk of 21% after a hip fracture.

Characteristics in Breast Cancer Survivors

Women with premenopausal breast cancer have higher than average rates of bone loss and fracture, with nonmetastatic breast cancer patients having a risk of vertebral fractures nearly five times that of the general population. Premature ovarian failure due to chemotherapy, estrogen blocking therapies, or ovarian ablation therapy, as well as direct effects of chemotherapy on bone, inactivity, use of corticosteroids, and inadequate intake of calcium and vitamin D can all contribute to the increased osteoporosis risk in breast cancer survivors.

The effects of tamoxifen, a selective estrogen receptor modulator with both agonist and antagonist activity widely used as adjuvant endocrine therapy in hormone-receptor-positive breast cancer, on BMD differ depending on the menopausal status of the patient at the time of treatment. The first study to look at the bone effects of tamoxifen versus placebo was conducted by Love et al. in 1992, on 140 postmenopausal breast cancer survivors, over 2 years (42). The mean BMD at the lumbar spine increased by 0.61% per year in the tamoxifen group and decreased by 1% per year in the placebo group. Other studies in postmenopausal women have confirmed this observation (43,44) whereas in premenopausal women tamoxifen therapy is associated with varying levels of bone loss. In a chemoprevention study of tamoxifen versus placebo in 179 women at high risk for breast cancer, premenopausal women treated with tamoxifen experienced a 1.4% decrease in BMD per year over the 3-year study, while the BMD increased 1.2% per year in postmenopausal women in the tamoxifen group (42,45). In a population-based case-control study of women older than 50 who suffered a first osteoporotic fracture, the use of tamoxifen was associated with a lower risk of fractures compared to controls (46). Treatment with tamoxifen also reduces markers of bone turnover in postmenopausal women.

Aromatase inhibitors (AIs) play a central role in the management of postmenopausal breast cancer, being superior to tamoxifen for disease-free survival and time to recurrence. They almost completely eliminate endogenous estrogen production, affecting bone metabolism in breast cancer patients. This abrupt decline in serum estradiol and estrogen in both postmenopausal healthy women and postmenopausal patients with breast cancer may dramatically affect bone turnover and loss.

The effect of AIs on bone mineral densities (BMDs) and bone turnover was measured in studies of adjuvant AIs in breast cancer survivors. In the ATAC (Anastrozole, Tamoxifen, Alone or in Combination) trial, a subgroup of 197 postmenopausal women receiving anastrozole or tamoxifen and 46 control patients with breast cancer who did not receive hormone therapy, were included in a bone substudy (47). At five years, therapy with anastrozole was associated with bone loss at the lumbar spine (–6.08%) and total hip (–7.24%) whereas the tamoxifen-treated group experienced an increase in the BMD (+2.77% at the lumbar spine and +0.74 at the total hip). Most of the bone loss at the lumbar spine was seen in the first 2 years of therapy with anastrozole, whereas it continued uniformly at the hip. The control group showed an increase in the BMD at the lumbar spine (+1.35%) and a slight decrease at the hip (–2.81%). The 10-year safety data from the ATAC trial (48) reported more fractures in the anastrozole vs. tamoxifen group (14.5% vs. 11.3%, OR=1.33, CI 1.15–1.55) only during active treatment (difference was accounted for by fractures of the spine, not the hip), after which the number of fractures was similar in the two groups. The bone remodeling markers mirrored the changes in BMD, with AIs causing a significant increase in bone remodeling compared to the tamoxifen and control groups. Similar findings were reported in bone subgroup studies of exemestane (49) and letrozole (50) in the adjuvant breast cancer setting. It is unclear to what degree the decrease in BMD seen with AIs represents the effect on bones of this class of medication versus a reflection of the beneficial effect of tamoxifen. When tamoxifen is taken out of the picture, such as in the MAP-3 trial of exemestane versus placebo for breast cancer prevention (51), the incidence of fractures at 3 years was similar between the groups, although a significant decrease in BMD was noted in the exemestane group in the bone substudy (52). These findings might be a reflection of exemestane's weak androgenic activity, which was postulated to have favorable bone effects (53). However, a pharmacodynamics trial of biochemical bone markers and parathyroid hormone levels did not show a significant difference between the three AIs (anastrazole, exemestane, and letrozole) (54).

Importantly, in all of the adjuvant and chemoprevention AI trials, none of the participants with normal BMD at baseline had osteoporosis at follow-up, leading the investigators to conclude that, although treatment with AIs is associated with accelerated bone loss over the treatment period, patients with normal BMD at baseline do not appear to require bone density monitoring beyond that of healthy women. Patients with osteopenia at baseline should have BMD monitoring and bone-protection strategies, but the effect on bone loss need not influence the use of AIs for breast cancer treatment (47).

Screening

The American Society of Clinical Oncology recommends BMD screening for breast cancer survivors at high risk for osteoporosis (advanced age, estrogen deficiency, treatment with AIs, history of fracture, family history of osteoporosis, low BMI, inadequate physical activity, cigarette smoking, excessive alcohol consumption) and treatment with bisphosphonates for those diagnosed with osteoporosis (55). A recent cost-effectiveness analysis of different osteoporosis screening schedules and treatment strategies in breast cancer patients receiving AIs has supported this recommendation as being the most cost-effective for society, with a cost of less than $100, 000 per quality-adjusted life year gained (56). Given the fact that 80% of the fractures in the general population occur in women with normal BMD or osteopenia, the World Health Organization has developed a tool to assess the 10-year risk of a fracture based on clinical risk factors for fracture (http://www.sheffield.ac.uk/FRAX/). Based on this tool, therapy for osteoporosis is recommended for women with osteopenia and a 10-year risk of hip fracture 3% or higher or of major osteoporotic fracture greater than 20% (57).

Treatment

In the general population, estrogen administration reduces bone turnover and the rate of bone loss, and thereby increases bone mineral density substantially in postmenopausal women. It is associated with a reduced risk of vertebral and possibly hip fractures. However, as soon as estrogen therapy is discontinued, BMD begins to decline at a rate similar to that observed before initiation of estrogen therapy. For women with a history of breast cancer, the use of estrogen to prevent bone loss has classically been considered contraindicated.

Similar to what was noted above regarding tamoxifen's effect on bones, another selective estrogen receptor modulator, raloxifene, also reduces the risk of osteoporotic fractures in postmenopausal women (58). The effects of this agent in premenopausal women are currently unknown. The advantages and/or disadvantages of using raloxifene in patients who had previously been treated with tamoxifen have not been clarified. When it was previously thought that there was a potential disadvantage for using tamoxifen for longer than 5 years (no longer a viable thought), physicians had raised concerns regarding raloxifene use in this situation.

Four bisphosphonates (alendronate, risedronate, ibandronate, and zolendronate) are approved for both the treatment and prevention of osteoporosis. Bisphosphonates are pyrophosphate analogues that are avidly adsorbed to bone surfaces. They reduce bone turnover by specifically inhibiting osteoclastic bone reabsorption and have demonstrated therapeutic efficacy in the treatment of hypercalcemia of malignancy, lytic bone disease associated with multiple myeloma, and mixed lytic and blastic bone metastases associated with breast cancer.

Alendronate and risedronate, the most extensively studied bisphosphonates, reduce vertebral and hip fractures by 50% in women with osteoporosis, and prevent bone loss in perimenopausal and postmenopausal women without osteoporosis at baseline. Clinical trials suggest that these drugs prevent bone loss as effectively as the recommended dose of estrogen in standard hormone replacement therapy regimens. In addition, unlike estrogen, these drugs can be discontinued without causing rapidly accelerated bone loss. However, they can trigger erosive esophagitis. Newer, more potent bisphosphonates include zoledronate and ibandronate. The preclinical safety (toxicology) profile of zoledronate is, in general, similar to that of other bisphosphonates, but this compound appears to produce fewer and/or less severe adverse events. In addition, these intravenous second- and third-generation bisphosphonates can be given every 6 to 12 months to achieve appropriate effects on bone loss.

The ability of intravenous bisphosphonates to restore bone in patients with osteolytic lesions associated with breast cancer or multiple myeloma is established. An 11% increase in lumbar spine bone mineral density was noted in patients receiving zoledronic acid at 2 mg or 4 mg; with the 4 mg/month dose being more effective (59).

Oral clodronate has been evaluated in two British studies of early stage breast cancer (60,61). Among these patients, most of whom also received chemotherapy and/or hormonal therapy, oral clodronate taken for 2 years was efficacious in preventing bone loss. By 1 year, BMD had fallen by 2.2% in the placebo group and had risen by 0.2% in the clodronate group. In a second trial in premenopausal women receiving chemotherapy with CMF, the clodronate and placebo groups differed in lumbar spine BMD by 3% at 1 year and by 3.7% at 2 years ($p < .01$). Among patients who developed ovarian failure, the lumbar spine bone loss in the clodronate group was 5.9%, versus 9.5% in the placebo group ($p < .001$). In both groups, the treatment was well tolerated with no differences in adverse events.

The use of bisphosphonates for primary osteoporosis prevention has recently undergone evaluation in premenopausal women, as they initiate adjuvant systemic breast cancer treatment. Delmas et al. evaluated an unconventional cyclic regimen of risedronate in women who had entered early menopause secondary to chemotherapy and who had completed chemotherapy an average of 15 months before randomization (62). Greenspan et al. evaluated weekly oral risedronate in patients who had completed chemotherapy an average of 3 years before randomization, and who were receiving other medications known to affect bone metabolism, such as tamoxifen and aromatase inhibitors (63). In both studies, BMD remained stable or increased in the risedronate-treated groups. Similarly, risedronate given at the time of initiation of AIs therapy resulted in a reduction of bone loss over time compared to placebo (64).

In addition, premenopausal women were randomized before initiation of chemotherapy in several studies. Saarto et al. randomized women to 1,600 mg of clodronate or placebo. At 1 year, the women in the placebo group sustained 4% bone loss at the lumbar spine, while BMD declined by only 1% in the clodronate treated women (65). Clodronate, however, is not available in the United States and is associated with gastrointestinal side effects. A second study randomized 40 premenopausal Lebanese women to pamidronate, 60 mg every 3 months, or placebo prior to initiating chemotherapy (66). In the placebo arm, lumbar spine BMD declined by approximately 3.2% by 12 months, and by 4% in the group that became amenorrheic. This loss was

prevented with pamidronate. Similar results have also been reported with the use of zoledronate at a dose of 4 mg every 3 months (67). However, initiating bisphosphonate therapy in young women who are at low risk of fractures with the goal of preventing short-term bone loss that may result in future fractures may not be necessary, beneficial or cost-effective, and from this perspective, it remains unclear when to intervene.

The timing of treatment initiation with bisphosphonates has been evaluated in postmenopausal women initiating AIs therapy. Although some studies have shown that up-front use of bisphosphonates in patients treated with adjuvant AIs preserves the BMD and improves disease recurrence (68), recent meta-analyses did not confirm a decreased risk of fractures (69) nor did they show improvement in survival, recurrence or bone metastases in this population (70). As a result, the optimal timing for the initiation of bisphosphonate therapy in postmenopausal women on aromatase inhibitor therapy also remains unclear (71).

The duration of the treatment with bisphosphonates also remains controversial. In the general population, given the small but important potential risks of therapy with bisphosphonates (atypical femoral fractures, jaw osteonecrosis, and esophageal cancer) and the evidence that extension of bisphosphonate therapy beyond 3 to 5 years does not further decrease fracture risk, the FDA has added an "Important Limitation of Use" statement to the labeling of bisphosphonates. The statement indicates that the benefits and risks of this therapy should be reassessed periodically and therapy be discontinued, unless the patient remains at an increased risk for fractures.

Another osteoclast inhibitor, denosumab, was recently approved by the FDA for treating postmenopausal osteoporosis, osteopenia in women treated with AIs, and breast cancer with bone metastasis. Denosumab is a monoclonal antibody that inhibits the receptor activator of nuclear factor kappa-B ligand (RANKL), thus inhibiting the formation, function and survival of osteoclasts, resulting in its bone-protective effects.

In postmenopausal women, denosumab, at a dose of 60 mg SQ every 6 months, improves BMD by 9.2% at the lumbar spine and by 4% at the hip (vs. 0% and –2%, respectively, for a placebo), as shown in the FREEDOM trial of 7,868 women with osteoporosis (72). In addition, this study found that denosumab statistically significantly reduces the risk of new radiographic vertebral fracture, hip fracture, and non-vertebral fracture, compared to placebo. When compared with alendronate, denosumab was slightly, but statistically significantly, superior in improving the BMD in 1,189 postmenopausal women with a baseline BMD of –2.0 or less (73).

Denosumab has also been studied for patients receiving AIs for nonmetastatic breast cancer; 252 breast cancer survivors with osteopenia and treated with AIs were randomized to placebo versus denosumab (60 mg SQ every 6 months). Lumbar spine BMD increased by 5.5% at 12 months and 7.6% at 24 months for denosumab, compared to a placebo, regardless of the duration of AIs therapy (74).

Bisphosphonates and denosumab are also approved for use in decreasing bone-related events in patients with breast cancer metastatic to the bone.

Other pharmacologic agents used to prevent and treat bone loss include calcium and vitamin D supplements. This includes calcium (total daily dose 1,000–1,500 mg, including dietary intake) and vitamin D (800 IU or more daily), which have been shown to reduce hip and vertebral fractures by 43% and 32%, respectively. Salmon calcitonin is approved for the treatment of osteoporosis, but is less efficacious than the bisphosphonates with respect to improvement of BMD and the reduction of fracture rates.

TABLE 51-2

Management Options for Prevention and Treatment of Osteoporosis

Lifestyle recommendations	Weight-bearing exercise Maintenance of ideal body weight No smoking Moderation of alcohol
Dietary nutrients	Calcium (1,200–1,500 mg/d, including dietary intake) Vitamin D (800–1,000 IU/d)
Bone-modifying agents	Bisphosphonates: zolendronate, alendronate, risedronate, or clodronate RANKL-inhibitor: denosumab
Selective estrogen receptor modifiers (SERMs)	Raloxifene or tamoxifen
Thyroid-derived hormone	Calcitonin

Smoking cessation and weight-bearing physical activity should also be strongly recommended to all women for osteoporosis prevention.

Table 51-2 reviews common therapeutic options for preventing and/or treating osteoporosis.

SEXUAL DYSFUNCTION

Sexual dysfunction occurs in up to 60% of breast cancer survivors and may be due to the effects of surgery, radiation therapy, or chemotherapy. Many women are hesitant to discuss sexual dysfunction with their health care providers; however, when questioned, 96% of women report at least one problem (75,76). In one study of breast cancer survivors, 64% of women reported decreased libido, 38% reported dyspareunia, 44% anorgasmy, and 42% lubrication problems. Sexual dysfunction tends to worsen over the first several years of treatment, but improves with longer follow-up.

While breast-conserving surgery has shown benefits over mastectomy with regard to body image, most studies find no difference between lumpectomy and mastectomy in regard to sexual functioning. A prospective evaluation of women during the first year after mastectomy or lumpectomy and studies of survivors evaluated 4 to 8 years after treatment failed to show a difference in sexual function or quality of life between groups (77). Age may be a significant factor in a patient's self-image and thus lumpectomy may have a different effect than mastectomy on quality of life for younger women. In these studies, however, the relationship of self-image to sexual function is not entirely clear.

Women who have been treated with adjuvant chemotherapy are 5.7 times more likely to report vaginal dryness, 5.5 times more likely to report dyspareunia, 3 times more likely to report decreased libido, and 7.1 times more likely to

report difficulty achieving orgasm. Younger women appear to be at increased risk of sexual dysfunction after receiving chemotherapy and the chemotherapy-induced sexual dysfunction appears to diminish over time such that, at more than 10 years out from treatment, sexual functioning is similar, regardless of whether they had received prior chemotherapy.

Hormonal therapy with tamoxifen does not appear to cause sexual dysfunction, despite tamoxifen being associated with vaginal discharge. Ganz et al. surveyed 1,098 breast cancer survivors 1 to 5 years after primary breast cancer treatment (75). The women who had been treated with tamoxifen (n = 305), after controlling for adjuvant chemotherapy, did not report more sexual function troubles. Comparing women on tamoxifen to a group of noncancer controls, Mortimer et al. likewise found no differences in sexual desire, sexual arousal, or the ability to achieve orgasm (75,78). Treatment of breast cancer using the GnRH agonist zoladex in combination with tamoxifen was associated with increased sexual dysfunction, in comparison to patients treated with zoladex alone; the reason for this is not clear. Interestingly, in this same study, tamoxifen as a single agent did not produce sexual dysfunction.

Therapy with AIs contributes significantly to sexual dysfunction in breast cancer survivors. In a QOL analysis of the ATAC trial anastrozole caused more vaginal dryness (16.3% vs. 8.4%), dyspareunia (17.8% vs. 7.5%) and decreased libido (15.8% vs. 8.5%) compared to tamoxifen (79), although tamoxifen caused more vaginal discharge and vaginal bleeding (80). Similar findings were reported on the TEAM (Tamoxifen Exemestane Adjuvant Multicenter) trial. Compared to nonusers, women on current therapy with AIs have more decreased libido, vaginal dryness, and unsatisfactory sex drive. Although all these factors are important causes of sexual dysfunction, the most consistent predictor of sexual satisfaction in women with breast cancer is the quality of their relationships (81).

Treatment of sexual dysfunction requires comprehensive assessment and intervention. Ganz et al. found a significant decrease in sexual dysfunction in women randomized to undergo a comprehensive assessment of menopausal symptoms by a nurse practitioner who screened for symptoms of vaginal dryness. If symptoms of sexual dysfunction were identified, recommendations for vaginal lubricants were provided along with individualized counseling and referral as indicated (82). Other data also suggest that vaginal dryness may play a significant, if not central, role in sexual dysfunction after chemotherapy. Vaginal lubricants (Astroglide) and vaginal moisturizers (KY Jelly, Replens) can be used to treat symptoms of dryness or for lubrication, and may indirectly improve other sexual problems as well. A prospective study in breast cancer survivors reported that women using Replens had decreased vaginal dryness equal to that of women using a water-soluble lubricating placebo; however, a decrease in dyspareunia was significantly better with Replens than with the placebo lubricant (83).

Topical estrogen preparations appear to alleviate vaginal dryness more effectively than do nonestrogenic vaginal preparations. At least three formulations exist: Estring is an estrogen-impregnated ring that is inserted into the vagina, where it releases small amounts of estrogen over a 12-week period. Another is a vaginal estrogen tablet called Vagifem. Last, a small dose of Premarin vaginal cream can be helpful. Nonetheless, there is evidence of some absorption of virtually all vaginal estrogen products and newer data, showing that decreasing postmenopausal estrogen levels by AIs leads to improved breast cancer outcomes, makes clinicians concerned about the use of any vaginal estrogen products. The use of estrogenic vaginal preparations in women taking AIs doesn't make much sense, as the goal of AI therapy is to induce low estradiol levels. Given these concerns, nonhormonal vaginal preparations should be used as first line of therapy in breast cancer survivors, while the use of the hormonal agents should be short term and limited to women who are not receiving an AI and who have severe refractory symptoms.

Testosterone improves sexual desire and the frequency of sexual activity in women after surgical menopause or with sexual arousal disorders. A phase III randomized, placebo-controlled crossover clinical trial studied sexual desire in postmenopausal women with a history of cancer, who had no current evidence of disease, had reported a decrease in sexual desire, and had a sexual partner. Eligible women were randomly assigned to receive 2% testosterone in Vanicream, for a testosterone dose of 10 mg daily, or placebo Vanicream for 4 weeks and were then crossed over to the opposite treatment for an additional 4 weeks. Women who were on active testosterone cream had higher serum levels of bioavailable testosterone than women on placebo. However, the mean intrapatient libido change from baseline to weeks 4 and 8 was similar on both arms (84). The reason that this study was negative, while other similar studies have been positive, may be because all of the other positive studies involved women who were premenopausal or were receiving ongoing estrogen therapy, while the current study did not include women receiving concurrent estrogen therapy. Thus, it appears that testosterone, when used without concurrent estrogen, does not improve libido.

ARTHRALGIAS

Musculoskeletal symptoms commonly occur in postmenopausal women and are a frequent side effect of therapy with AIs, a standard of care for postmenopausal women with both early and late stage hormone-sensitive breast tumors. In large adjuvant trials involving AIs, the incidence of musculoskeletal disorders was 20% to 40%, and nearly 5% of patients discontinued therapy in the AI group because of toxic effects.

Recent studies have shown that AI arthralgias are more prevalent than originally reported from clinical trials. In a cross-sectional survey of 200 consecutive postmenopausal women receiving adjuvant AI therapy for early-stage hormone-sensitive breast cancer, 94 (47%) reported having AI-related joint pain and 88 (44%) reported AI-related joint stiffness. Being overweight (body mass index of 25–30 kg/m^2) and prior tamoxifen therapies were inversely associated with AI-related joint symptoms. Patients who received taxane chemotherapy were over four times more likely than other patients to have AI-related joint pain and stiffness (85). Not all studies, however, have noted an association with taxanes therapy. In clinical practice, 10% to 20% of women treated with AIs decide to discontinue this therapy due to arthralgias. AIs-associated arthralgias seem to improve within 6 months of therapy and some studies support that breast cancer survivors who experience arthralgias have a better prognosis. Women who reached menopause within 5 years of the start of AIs are more likely to experience AI-related musculoskeletal symptoms than whose menopause started more than 10 years from AI therapy (86).

The exact mechanism of AI-related arthralgia is unclear, but is thought to likely be related to estrogen deprivation.

It is postulated that estrogen has nociceptive protective effects and thus, a significant drop in the estrogen levels contributes to a decreased pain threshold. In addition, fluid buildup within the joints and tendons might contribute to the arthralgias seen with AI therapy and account for the increased incidence of carpal tunnel syndrome seen in these women.

No large prospective studies have defined an optimal treatment or prevention of AIs-related arthralgias. Nonsteroidal anti-inflammatories, acetaminophen, and opioids may have some efficacy for this condition in retrospective reports from the ATAC trial (87) and in small uncontrolled studies. A prospective, randomized, placebo-controlled study of vitamin D for AI-related arthralgias was reported in abstract form, with positive results (88). A large placebo-controlled study on vitamin D in arthralgias associated with AIs in underway (NCT00263185).

A prospective, randomized, placebo-controlled trial supported that testosterone could effectively treat AIs-associated arthralgias (89) which has led to the development of an Alliance cooperative group placebo-controlled trial. In addition, a Southwest Oncology Group placebo-controlled trial has been developed to look at an omega-3-fatty acid preparation for alleviating this problem.

In a randomized, sham-controlled, double-blind study of acupuncture in women with AI-associated arthralgias, the true acupuncture group had significant improvements in joint pain and stiffness, which was not seen in the sham-acupuncture group (90). Other strategies that might help alleviate the musculoskeletal side effects of the AIs include switching to another AI, taking a drug holiday or switching to tamoxifen, if clinically safe. The effects of switching between classes of AIs (steroidal vs. nonsteroidal group) has not been well studied.

WEIGHT GAIN

Weight gain is a common side effect for women who receive adjuvant chemotherapy. Gains in weight are typically around 2.5 to 6.2 kg, but can be up to 25 kg and may be influenced by menopausal status; nodal status; and the type, duration, and intensity of treatment. Although there is some variability in the literature, in one study, the mean change in weight of 100 women treated with chemotherapy was +3.68 kg ($p < .001$); 64% of patients gained more than 2 kg in weight, approximately one-third of patients gained more than 5 kg, and 6 patients gained more than 10 kg. The majority of these patients (85%) received steroids as antiemetics, but no effect of steroid dose was seen on the level of weight change (91). Weight gain appears to be greater among premenopausal women; those who are node-positive; those receiving higher dose, longer duration, multiagent regimens; and those who enter into menopause. Psychosocial research suggests that weight gain has a profoundly negative impact on the quality of life for patients with breast cancer.

Weight gain also leads to an increased risk of comorbid conditions such as cardiovascular disease, gallbladder disease, diabetes, and orthopedic complications and is associated with an increased mortality. In a prospective cohort of 4,000 breast cancer survivors, every 5 kg of weight gain after treatment was associated with a 12% increase in all-cause mortality, 13% increase in breast cancer–specific mortality, and a 19% increase in cardiovascular disease mortality (92) findings confirmed in other trials. However, other large studies did not show a correlation between posttreatment weigh gain and mortality (93).

Limited research conducted in this area does not support overeating as a major cause of weight gain among breast cancer patients. Mean body weight increases significantly during chemotherapy, primarily due to an increase in mean total body and mean fat mass and a decrease in fat free mass and leg lean body mass. Both chemotherapy and radiation were associated with development of sarcopenic obesity (gain of fat mass without gain of lean tissue mass). Adjuvant treatment with tamoxifen or AIs was not associated with weight gain (94). Weight gain in the presence of lean tissue loss or the absence of lean tissue gain supports the need for interventions focused on exercise, especially resistance training in the lower body, to prevent undesirable weight gain (95).

Premenopausal women starting adjuvant chemotherapy for breast cancer were randomized to a control group, or to receive monthly counseling by a dietitian aimed at weight maintenance. The median weight gains at 6 months after the start of chemotherapy were 2.0 kg in the dietitian counseling group versus 3.5 kg in the control group (statistically insignificant differences). The median changes in average caloric consumption were reductions of 120 versus 46 cal/day on weekdays and 196 versus 20 cal/day on weekends for the counseling and control groups, respectively. Routine prospective dietitian counseling aimed at weight maintenance thus appeared to produce small but statistically insignificant reductions in both caloric consumption and weight gain in this group of patients (96).

Caloric restriction, either alone or in conjunction with other interventions such as exercise and psychological support or counseling through Weight Watchers, has led to successful weight loss in this population. A recent study of home-based diet and exercise intervention in older overweight or obese, breast, prostate, and colorectal cancer survivors showed decreased weight and increased functional capacity (97). Similarly, a home-based exercise intervention during the first 4 cycles of chemotherapy in 78 women with breast cancer demonstrated that women who adhered to the exercise program maintained their body weight, while nonexercisers steadily gained weight ($p < .05$) (98). Finally, in a small randomized crossover study of a commercial-based exercise program (Curves), 6 months of the intervention resulted in moderate weight loss, but weight loss was not maintained postintervention (99).

However, it is not clear whether promoting weight loss impacts the disease outcomes (100). A large, multicenter trial (the ENERGY trial) of weight loss (through diet, physical exercise, behavioral strategies, cognitive restructuring social support, self-nurturing) in 2,500 breast cancer survivors is underway to further investigate this issue. Until more scientific evidence becomes available, women who are diagnosed with breast cancer should be advised to follow the general exercise recommendations of 30 minutes or more on most of the days of the week and follow a healthy diet, high in low-calorie density foods such as vegetable and fruits and low in fats and refined sugars and to maintain a healthy weight (100,101).

CONCLUSION

As the population of breast cancer survivors grows, it has become increasingly important to develop strategies to prevent and treat both short-term and long-term complications from breast cancer treatment. Advances in this area may improve the quality of life of the almost 3 million breast cancer survivors in the United States alone.

MANAGEMENT SUMMARY

- Nonhormonal means of treating hot flashes are available, including the use of antidepressants (e.g., venlafaxine, desvenlafaxine, citalopram, escitalopram, and paroxetine) and gabapentin.
- Paroxetine and fluoxetine should not be used in patients taking tamoxifen.
- Osteoporosis is a common problem in women with a history of breast cancer, primarily related to estrogen deprivation.
- Standard measures for preventing and treating osteoporosis should include adequate calcium and vitamin D intake and weight-bearing exercise.
- Bone-modifying agents should be used in patients with substantial osteopenia and osteoporosis.
- While bone-modifying agents can attenuate bone loss from chemotherapy-induced ovarian suppression or aromatase inhibitors, routine use of these in clinical practice for osteoporosis prevention is not yet recommended. Although some clinicians use these medications in selected patients, most would recommend routine surveillance with bone mineral density testing.
- While sexual dysfunction is common in women with breast cancer, testosterone, in the absence of estrogen, does not alleviate this problem.
- Vaginal dryness can be treated with nonestrogenic vaginal lubricants or local estrogen therapy, although there are some safety concerns regarding the latter except for patients on tamoxifen which remains effective even with the high estrogen levels in premenopausal women.
- Aromatase inhibitor-induced arthralgias are common, but there is no good established therapy for this problem.
- Weight gain is common after a diagnosis of breast cancer treatment and is managed by counseling the patient before the start of therapy, by decreasing caloric intake, and by increasing caloric output (i.e., exercise).

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CHAPTER 52

Long-Term and Late Effects of Primary Curative Intent Therapy: Neurocognitive, Cardiac, and Secondary Malignancies

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CHAPTER CONTENTS

The number of women living in the United States with a history of breast cancer has been rising and is estimated to be over 2.8 million (1). Every year, new treatments and refinements of existing treatments are incorporated into the armamentarium against breast cancer. Advances in therapy have led to decreases in breast cancer mortality, and are partly responsible for the large number of survivors. While efficacious, many treatments are associated with persistent difficulties that are especially impactful for those who are long-term disease-free survivors (2,3). Among the most feared and disabling are cognitive and cardiac dysfunction. Rarely, breast cancer treatment results in a new, second cancer. The ability to better characterize these treatment-related consequences, specifically the incidence, etiology, pathogenesis, and risk factors for development, will facilitate the design of effective preventive strategies and/or therapeutic interventions in the future. To this end, we review what is known about these long-term and late effects of breast cancer treatments, and where appropriate, discuss strategies for prevention and treatment.

NEUROCOGNITIVE EFFECTS OF BREAST CANCER TREATMENT

Etiology and Setting of Cognitive Dysfunction

Cognitive complaints are extremely common during adjuvant chemotherapy, and may be caused by anxiety, depression, supportive care medications (e.g., anxiolytics, steroids, and sedatives), or by the acute effects of cancer therapy such as fatigue. However, for the majority of women, these acute changes resolve in the months following the end of treatment (4). What is more concerning is the persistence of difficulties in cognitive functioning that affect work, self-management, and caring for others that have been identified for 20 years, as something called *chemobrain* (5). Chemobrain may be a misnomer, since the manifestations that include memory impairment and difficulty with attention and concentration are also seen in breast cancer patients who have not received chemotherapy. A more inclusive term to describe these manifestations is *cancer- or cancer-therapy-associated cognitive change* (6).

Across clinical studies of treatment associated cognitive dysfunction, the incidence varies greatly, ranging between 15% to 61% (7,8) and can be seen in association with chemotherapy and with endocrine therapy alone. Additionally, subtle cognitive impairment is present in many patients prior to treatment (9–11) and could reflect postsurgical systemic changes or psychological effects on the brain associated with the cancer diagnosis. In one study, 22% of patients with stages I to III invasive breast cancer scored "lower than expected" on cognitive testing prior to chemotherapy compared with the absence of such findings in patients with stage 0 breast cancer (12).

It has been difficult to accurately assess the scope of the problem due to heterogeneity in study design, including patient population and measurement instruments (13). Early studies were cross-sectional in design, and although comparison groups were available, it was difficult to assess causal attribution (14–16). Subsequent studies were designed to clarify the epidemiology of chemobrain, with assessments of neurocognitive function before and after treatment, at several timepoints, and using a concurrent control or comparison group. A recent meta-analysis of multiple posttreatment studies of breast cancer patients concluded that there were small, but significant differences in verbal abilities and visuospatial functioning in these survivors who had been treated with standard dose adjuvant chemotherapy (17).

The mechanism by which cancer treatment leads to cognitive dysfunction is not well understood. Additionally, there may be interplay of various mechanisms that collectively impair cognitive functioning. There are excellent reviews of this topic that the reader should consider that are beyond the scope of this chapter (18–20). However, in the text that follows, we highlight some of the findings from various studies that relate to cancer-associated cognitive dysfunction.

Risk Factors for Cognitive Dysfunction

There are a number of potential risk factors that interact with each other or work independently influencing cerebral function in the setting of early breast cancer treatment. Ganz and colleagues (21) have recently proposed a breast cancer specific model as part of their Mind Body Study (see Fig. 52-1). Below, we discuss how these factors may be influencing cognitive dysfunction in posttreatment breast cancer survivors.

Psychosocial Factors: Both the diagnosis and treatment of breast cancer result in psychological distress. The association of depression and deterioration in cognitive performance has been well described, and when severe is termed, *pseudodementia* (22). For the breast cancer patient, emotional factors can contribute to, but alone cannot explain the treatment-associated cognitive decline. In a prospective study of 41 women with breast cancer and without depression at baseline, who were followed prior to and during chemotherapy treatment, the objective cognitive decline seen was independent of emotional factors (7). However, the development of depression and anxiety did correlate with a self-reported decline in cognitive functioning, even when objective performance remained stable (7). In a report of the Cognitive Impairment in Therapy of Breast Cancer (COGITO) study (23), a validated battery of 12 cognitive tests, self-reports on cognition and emotional state, were assessed prior to and up to 1 year postchemotherapy treatment. In this study, depression and the personality trait negative affectivity predicted for self-reported cognitive impairment. However, there was no statistically significant association between self-reports and objective measures of cognitive changes (23). While asynchrony between self-report and formal neurocognitive testing has been observed in some studies, a recent report by Deprez et al. identified concordance between self-report, neurocognitive testing, and white matter tract changes in a prospective, observational study of women initiating chemotherapy (24). Similarly, in a long-term cross-sectional study comparing controls and breast cancer survivors who had been treated with chemotherapy (25), executive function self-report difficulties corresponded to decreased frontal activation on MRI as well as poorer performance on neurocognitive tests. These imaging studies, with examination of domain-specific cognitive complaints and relevant NP tests, suggest that it is possible to identify neurophysiological correlates of these subjective complaints (25,26).

Genetic Susceptibility: There has been considerable interest in establishing potential genetic vulnerability to the development of cognitive dysfunction after breast cancer treatments. Initial interest has focused on risk factors common for dementia in older adults. In a cross-sectional evaluation of long-term survivors of breast cancer and

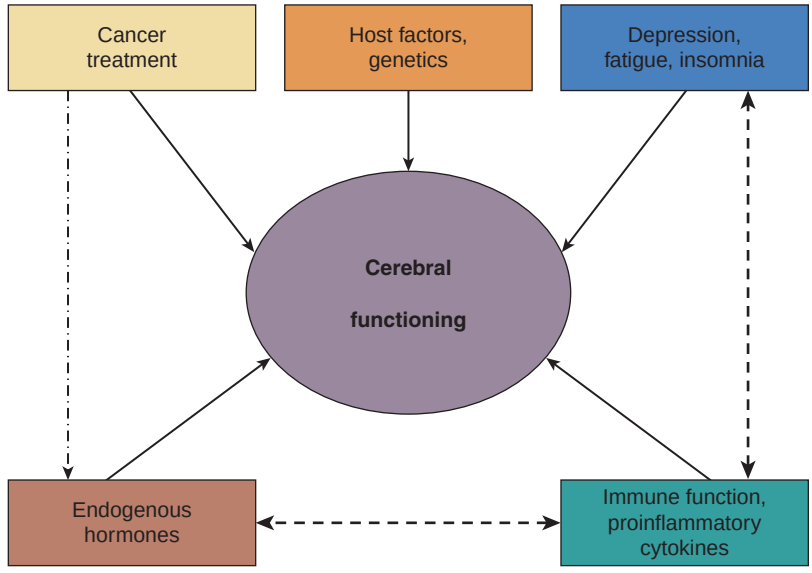

FIGURE 52-1 Risk factors for treatment-associated cognitive dysfunction.

lymphoma, Ahles et al. (27) found an association between poorer neuropsychological performance and the presence of the apolipoprotein (APOE) E4 allele. This was significant for visual memory and spatial domains, with a trend toward lower scores in the psychomotor domain, when E4 carriers were compared to noncarriers among the survivors.

In another study of breast cancer survivors, Small et al. (28) examined single-nucleotide polymorphisms (SNPs) in the catechol-*o*-methyl transferase (COMT) gene, which is involved in the metabolism of catecholamines through the methylation of dopamine, an important neurotransmitter. The valine version (val allele) of the gene is more active than the methionine (met allele), and individuals who are homozygous for the val allele are thought to metabolize dopamine more rapidly and thus have lower levels available than those with the met allele, potentially modulating the dopaminergic tone in the frontal cortex. In their study (28), breast cancer patients who had the *COMT*-val allele who received chemotherapy were found to have poorer neuropsychological performance on attention, verbal fluency, and motor speed in comparison to breast cancer patients who were *COMT*-met homozygotes.

In our work examining SNPs in the promoter region of several proinflammatory genes, we have found an association between cognitive complaints and the TNFα 308 G > A polymorphism (p = .055), and for a genetic risk index among polymorphisms in the *IL-1β* –511 C>T (rs16944), *IL6* -174 G>C (rs1800795), and *TNF* –308 G>A (rs1800629), p = .016) (28a). An additive genetic risk score was computed by summing the number of high expression alleles (0/1/2) across all three polymorphisms, reflecting the potential for interaction among multiple SNPs in leading the risk for a persistent elevation in proinflammatory cytokines as a result of cancer treatment. While this has been most extensively studied in the setting of post-treatment fatigue (29), uncontrolled systemic inflammation may also be affecting neurocognitive processes (see below).

Inflammatory Processes: A potential etiologic factor in cognitive decline is systemic inflammation. Proinflammatory cytokines have been found to be associated with cancer symptoms as well as age-related cognitive decline (30,31). Tumor necrosis factor alpha (TNFα), a cytokine involved in the inflammatory response, was elevated in a study of patient with Alzheimer's dementia (32). In addition to its role in inflammation, TNFα may play a regulatory role in mediating synaptic function in the brain (33). Thus, elevated circulating levels of TNFα from systemic inflammatory processes are implicated in the pathogenesis of Alzheimer's dementia and possibly other forms of cognitive dysfunction. In mice treated with doxorubicin, increased levels of TNFα in serum and brain tissue have been reported (34). Analysis of the first 93 patients of a prospective, longitudinal study of breast cancer patients who had been treated with surgery, radiation, and chemotherapy revealed increases in TNFα among those who reported cognitive dysfunction (21). In this study, patients were enrolled after chemotherapy, surgery, and radiation and monitored with neuropsychological tests and bloodwork including markers of inflammation. Of the inflammatory cytokines tested (IL-1ra, sTNF-RII, CRP, and IL-6), only sTNF-RII was elevated at baseline in those with memory complaints. Additionally, there was a statistically significant correlation between decrease in memory complaints and decline in levels of sTNF-RII (21). Another recent study in long-term breast cancer survivors (35) found an association between increased IL-6 and TNFα and decreased hippocampal volume, increased cognitive complaints, and poorer verbal memory test performance compared to a healthy control group. These emerging data suggest a potential inflammatory etiology for cognitive dysfunction in breast cancer patients and survivors.

Hormonal Effects and the Brain: Endocrine therapy has been implicated in therapy-associated cognitive decline among breast cancer patients. Additionally, endocrine effects of chemotherapy may play a role in cognitive impairment after treatment. In a prospective, longitudinal study of women with early-stage breast cancer, the ability to perform various neuropsychological "tasks" was assessed before and after treatment (36). Women who experienced chemotherapy-induced amenorrhea were more likely to show a decline from baseline in multiple tasks (36). Endogenous estrogen appears to play an important role in cognitive function, especially with respect to verbal memory. It has been shown that estrogen receptors are concentrated in the hippocampus, which is involved in cholinergic neurotransmission to areas of the brain involved with memory and learning. A second potential mechanism by which estrogen is neuroprotective lies in its ability to relieve oxidative stress by scavenging oxygen free radicals and reducing the formation of reactive oxygen species (37). A third mechanism by which estrogen affects cognition is via effects on telomeres. Telomeres are DNA protein structures that form caps on the ends of chromosomes, which results in genomic stability. During the process of aging, telomere length shortens. This increase in genomic instability may contribute to various age-related phenomena, including decline in cognitive ability (38). One study of 53 postmenopausal women on 1 year of hormone replacement therapy found that duration of endogenous estrogen exposure (length of reproductive years) was correlated with longer telomere length and decreased telomerase activity. Interestingly, duration of exogenous estrogen exposure did not show the same effects (39). However, in another study of 393 community-dwelling women aged 55 to 89 years who were not using replacement estrogen, there was no relationship of endogenous estrogen levels to higher performance tests of cognitive function, including the mini mental status examination (MMSE) (40).

The role of medications that alter estrogen levels in the body in cognition is unclear. The Women's Health Initiative Memory Study (WHIMS) assessed annual MMSE scores in 4,532 postmenopausal women enrolled in the larger WHI study who were over age 65 years and free of probable dementia at baseline (41,42). After a mean follow-up of 4.2 years, no significant improvement in global cognitive function was seen with combined estrogen–progestin therapy compared with placebo (41). In addition, more women in the combined hormone therapy group had clinically significant declines in MMSE scores compared with placebo (6.7% vs. 4.8%, respectively). A similar decline in cognitive ability was shown in women taking estrogen without progestin (43). This analysis was not able to assess the relationship of timing of estrogen replacement to cognitive decline, which is important in interpreting the significance of these data. Estrogen exposure may have differential effects depending on timing in relation to menopause. The critical window hypothesis posits that estrogen serves a neuroprotective role in perimenopause, but has neutral, and even detrimental effects later in the menopausal transition (44). One mechanistic explanation is that "healthy cells," such as those neurons in the younger female brain, derive benefit from estrogenic effects, whereas the age-damaged neurons of older women do not (45).

Evidence for Brain Abnormalities after Cancer Treatment

Neuroimaging has been utilized to define structural and functional correlates of cognitive function. Treatment-induced memory loss may be attributable to damage to the frontal lobes involved in executive function and the hippocampus, important for memory. Alterations in cerebral blood flow during neuropsychological testing have been observed in patients 5 to 10 years after adjuvant chemotherapy treatment (46). In this cross-sectional comparison study, the alteration was most marked in the inferior frontal gyrus, an area of the brain involved in memory processing, and was most marked in patients who had received both chemotherapy and tamoxifen. In a recent prospective, pretreatment study using MRI in patients with breast cancer treated with chemotherapy compared to breast cancer patients without chemotherapy and healthy controls, McDonald and colleagues (47) observed decreased gray matter density in the bilateral frontal, temporal, and cerebellar regions and right thalamus in both cancer groups that was most prominent after chemotherapy. These changes partially recovered, at 1 year posttreatment. Another prospective study demonstrated changes in white matter detected by magnetic resonance diffusion tensor imaging after chemotherapy treatment (24). White matter abnormalities were not seen at baseline in any group or in patients with breast cancer who did not receive chemotherapy. And in a more recent prospective pretreatment longitudinal study using functional MRI, with similar comparison groups, the investigators observed baseline frontal lobe hyperactivation during working memory tasks in cancer patients versus healthy controls (48). The cancer patients also exhibited a decline in frontal activation 1 month after completion of chemotherapy or at a similar interval for those patients who did not receive chemotherapy. One report of identical twins, one with breast cancer who received chemotherapy and the other without breast cancer, revealed marked differences in structural and functional MRI (49). The twin with breast cancer exhibited greater white matter volume, which is also seen in patients with Alzheimer's dementia. On functional MRI, she showed a greater spatial extent of brain activation than her untreated twin, a feature seen as a compensatory mechanism in patients with underlying brain dysfunction (49–51). Taken together, all of these studies provide increasing support for both structural and functional brain changes that are associated with chemotherapy treatment, along with evidence of both subjective and objective measures of impaired cognitive function in the patients who have been studied (26).

Strategies for Prevention and Treatment

Because the specific causal factors for cancer-related cognitive dysfunction are not well defined, preventive strategies have been difficult to develop. In addition, breast cancer adjuvant therapy has been shown to provide substantial survival benefit, and thus avoidance of therapy to prevent this side effect does not seem warranted at this time. Further, identification of at-risk populations has been difficult, although the earliest studies of chemotherapy-related cognitive problems were associated with the historic cytoxan, methotrexate, and 5-fluorouracil (CMF) regimen, which appears to have had long-lasting effects on cognitive function and brain structure (52–54). This regimen might be avoided given these problems, while uncertainty remains about the specificity of harms from regimens that are currently in common use in the adjuvant setting.

Thus, the few treatment approaches that have been developed focus on management of symptoms. Cognitive behavioral therapy has shown promise in smaller trials and is now being explored in larger-scale trials. In a pilot study of a brief cognitive behavioral intervention, improvements in cognitive function, quality of life, and standard neuropsychological test performance were observed (55). This intervention was further developed and evaluated in 40 patients with early-stage breast cancer. The study was randomized with a waitlist-control group. Postintervention, there were significant improvements in verbal memory and quality of life but not for cognitive complaints (56). A recent study examined a group-based cognitive intervention in 23 cancer survivors, compared to 9 waitlist-control cancer survivors and to 23 adults without a history of cancer. In comparison to the control groups, the intervention group demonstrated improvements in cognitive functioning, memory, and visuospatial function that were maintained over 3 months (57). Finally, a randomized waitlist-control trial, which included a computerized task, evaluated two different cognitive training interventions: speed of processing and memory training (58). Both interventions improved objective and perceived cognitive function, symptom distress, and quality of life. Interestingly, the speed of processing training resulted in transferred benefits on memory tests.

It is unclear whether medications have a role in the treatment of cognitive dysfunction. A randomized study was conducted to evaluate modafinil for the treatment of fatigue in patients posttreatment for breast cancer. Secondary analysis of the study to assess for modafinil effect on cognitive function was performed. Improvements in memory and attention skills were seen in the group treated with modafinil. These findings must be viewed with caution given that this study was designed to evaluate treatment of fatigue (59). While the aforementioned cognitive interventions hold promise, larger trials inclusive of a wider cancer population are necessary to establish effective treatment and prevention protocols for therapy-associated cognitive dysfunction.

Summary

As with many late effects of cancer treatment, it is sometimes difficult to assess how much of what is seen in long-term survivors is a direct effect of the cancer treatment or is a manifestation of normal age-related changes. This is certainly the case for cognitive dysfunction, which is common in the aging population. However, when one observes a midlife woman who was previously engaged in high-level intellectual activities who can no longer perform those tasks in the same way, and has great difficulty managing everyday activities, one must acknowledge the likely connection between treatment exposures and the outcomes. The perplexing problem for the clinician is the fact that this problem is apparent only in a handful of patients who receive the very same treatment regimens. Elucidating the mechanisms by which some women are susceptible to this complication of cancer treatment and others are not is now our main challenge. As with all aspects of cancer treatment, the patient or host meets the disease with a variety of personal risk factors and protective factors that will interact with the cancer treatment. Factors such as cognitive reserve may be critical in determining who will experience this problem. Research advances of the past decade and studies currently underway should provide greater precision in identifying vulnerability as well as developing preventive interventions. In the meantime, we should avoid exposing patients to treatments that are not evidence based or medically indicated, given the potential risk for this long-term effect of treatment.

CARDIAC EFFECTS OF BREAST CANCER TREATMENT

The cardiotoxicity of breast cancer therapy has a major impact given the large number of women treated with adjuvant therapy who have excellent long-term survival. This includes older women who may have preexisting subclinical cardiac disease at the time of treatment, as well as younger women who can expect long-term survival and could have accelerated or premature cardiac disease as they age.

Cardiotoxicity Associated with Specific Agents Used to Treat Breast Cancer

Anthracycline-Associated Cardiotoxicity

Mechanism: Cardiotoxicity is a known side effect of anthracycline chemotherapy, which is widely used in the treatment of breast cancer. The mechanisms of cardiac damage are multifactorial and include oxygen free radical production that preferentially damages cardiac myocyte mitochondria. In addition, anthracyclines intercalate into DNA, which affects intracellular signaling and may cause cell death and the disruption of sarcomere maintenance (60). Exposure to anthracyclines may also reduce the numbers of cardiac progenitor cells available to help repair damaged myocardium (61).

Risk Factors: It is well known that anthracycline-induced cardiotoxicity is partially related to dose. The toxicity is cumulative and more common when doses approach 450 mg/m^2 of doxorubicin. Von Hoff et al. reported the incidence of congestive heart failure (CHF) was 7% and 18% at doses of 550 mg/m^2 and 700 mg/m^2, respectively (62). However, a more recent analysis of patients enrolled in three studies of doxorubicin containing chemotherapy for breast or small cell lung carcinoma suggests that the incidence of CHF is actually higher than previously thought (63). This study estimated that doxorubicin-induced cardiotoxicity occurred in 5% of patients at a cumulative dose of 400 mg/m^2, 26% of patients at 550 mg/m^2, and 48% of patients at 700 mg/m^2 (63). Epirubicin is also commonly used in the treatment of breast cancer. In a retrospective analysis of over 1,000 anthracycline-naïve, metastatic breast cancer patients treated with epirubicin, the maximum dose of epirubicin associated with a 5% risk of congestive heart failure was calculated. Based on the patients' cardiac risk factors, including age, the maximum cumulative dose ranged from 300 mg/m^2 to 900 mg/m^2, underscoring the importance of taking individual patient characteristics into account when using cardiotoxic chemotherapy (64). In addition to cumulative dose, other risk factors for the development of anthracycline-induced cardiomyopathy include age, cardiovascular risk factors, prior radiation dose, and coexisting drug therapy.

Genetic polymorphisms may also play a role in susceptibility to anthracycline-induced cardiotoxicity. These genetic variants may affect the expression of proteins associated with the transport, metabolism, and mechanism of action of doxorubicin. Single-nucleotide polymorphisms (SNPs) in the carbonyl reductase (*CRB1* and *CRB3*) genes that encode drug-metabolizing enzymes that reduce doxorubicin to cardiotoxic alcohols may increase the risk of doxorubicin-induced cardiomyopathy. A recently reported case-control study examined the relationship between single-nucleotide polymorphisms in *CBR1 (CBR1* 1096G>A) and/or *CBR3* (*CBR3* V244M) and the dose-dependent risk of anthracycline-related cardiomyopathy in childhood cancer survivors. One hundred sixty-five cases of childhood cancer survivors were compared with 323 control subjects with no documented cardiomyopathy. The patients were prospectively genotyped at study entry. Homozygosity for the G allele in *CBR3* gene conferred an increase in risk for cardiomyopathy associated with low- to moderate-dose anthracyclines (65). This finding, however, was not replicated in candidate gene study of 2,977 single- nucleotide polymorphisms (SNPs) in 220 key drug biotransformation genes in a cohort of 156 children treated with anthracycline. There were 9 SNPs that were significantly associated with cardiac toxicity. *CBR3* polymorphisms were not among those 9 (66).

In addition to identifying susceptibility genes, there is an ongoing search for biomarkers that predict cardiomyopathy risk. In a small prospective study of patients treated with adjuvant chemotherapy and trastuzumab, cardiac biomarkers (Troponin and BNP), TVI (tissue velocity imaging), strain imaging, and cardiac magnetic resonance imaging were evaluated for ability to detect preclinical changes in LV systolic function before conventional changes in left ventricular ejection fraction (LVEF) appeared. Troponin I and BNP did not show an association with LVEF decline. TVI and strain imaging, however, were able to show preclinical cardiac function changes (67).

Time Course: Acute toxicities of anthracyclines are seen uncommonly and include cardiac arrhythmias, heart block, pericarditis, myocarditis, and left ventricular dysfunction. These toxicities are generally reversible and the relationship with the future development of chronic cardiotoxicity is unclear.

Chronic cardiotoxicity is a feared complication of anthracycline treatment especially when given in the adjuvant, curative setting. Typically patients present with heart failure symptoms from nonischemic dilated cardiomyopathy within 1 year after chemotherapy, but as late as 10 years after completion of chemotherapy. Very long-term cardiotoxicity has been difficult to assess and may be underreported in breast cancer survivors. It is particularly difficult to assess in a case-control study due to survival bias (i.e., those patients with the most severe cardiotoxicity may have already died as a result). In a prospective study of breast cancer patients treated as part of a SWOG (Southwest Oncology Group) protocol with adjuvant chemotherapy, both with and without an anthracycline, LVEF was measured at 5 to 8 and again at 10 to 13 years posttreatment. There was a significant difference in LVEF at 5 to 8 years in patients treated with an anthracycline (64.8% with anthracycline vs. 61.4% no anthracycline; p = .01) but not at 10 to 13 years posttreatment (68). Additional long-term prospective studies are needed with newer dose-dense regimens.

Because of the potential for anthracyclines to cause long-term, irreversible cardiomyopathy, there has been a search for effective adjuvant treatment regimens that maintain efficacy without the use of an anthracycline. Jones et al. showed that four cycles of TC (docetaxel plus cyclophosphamide) achieved superior disease-free and overall survival compared to four cycles of AC (adriamycin and cyclophosphamide) in 1,016 patients with early-stage breast cancer (69). There is an ongoing trial to evaluate whether the addition of an anthracycline- to a taxane-based regimen results in greater efficacy versus the taxane-based regime alone (ClinicalTrials.gov Identifier: NCT00493870).

Trastuzumab-Associated Cardiotoxicity

Mechanism: The incorporation of trastuzumab into the adjuvant treatment of HER2 positive breast cancer has had a dramatic impact on survival. However, trastuzumab-associated cardiac dysfunction is an important, but not well understood, adverse effect. It appears to be a result

TABLE 52-1

Cardiotoxicity of Doxorubicin versus Trastuzumab

Agent	*Type of Cardiac Dysfunction*
Doxorubicin	
• Cumulative dose dependent	CHF
• Irreversible>reversible	
• Acute	Arrhythmia, heart block, pericarditis, myocarditis (uncommon)
Trastuzumab	
• Not dose dependent	CHF
• Reversible>irreversible	
• Increased risk with anthracyclines	

of impaired HER2 signaling in the heart. The HER2 gene is involved in cardiac development during embryogeneses and after birth, with the growth, survival, and inhibition of apoptosis of cardiac myocytes (70). The cardiac effects of trastuzumab in many patients is reversible and amenable to rechallenge, which distinguishes it from the cardiomyopathy attributed to anthracycline use. Additionally, it does not appear to be dose related (see Table 52-1).

Risk Factors of Coadministration with Anthracyclines: In the BCIRG001 study that led to the widespread use of trastuzumab in the metastatic breast cancer setting, New York Heart Association class III or IV heart failure occurred in 16% of the group given an anthracycline, cyclophosphamide, and trastuzumab; 3% of the group given an anthracycline and cyclophosphamide alone; 2% of the group given paclitaxel and trastuzumab; and 1% of the group given paclitaxel alone. Most cases ultimately resolved. Of the 5 patients with persistent cardiac dysfunction, 3 were in the anthracycline, cyclophosphamide, and trastuzumab group (71). This finding describes the well observed phenomenon of synergistic cardiotoxicity with the use of anthracyclines and trastuzumab together.

Seven-year follow-up of cardiac safety in the NSABP B-31 trial has recently been published. In this study, 1,831 women with early-stage HER2-positive breast cancer were randomized to receive four cycles of adriamycin and cyclophosphamide, followed by paclitaxel with or with or without trastuzumab. At 7-year follow-up, 4.0% patients who received trastuzumab experienced a cardiac event (CE) versus 1.3% of patients who did not. A CE was defined as cardiac death or congestive heart failure manifested by dyspnea with normal activity or at rest and associated with an absolute decrease in LVEF of greater than 10 percentage points from baseline to a value less than 55% or a decrease of more than 5% to a value below the lower limit of normal. Risk factors for a CE included marginal left ventricular ejection fraction prior to trastuzumab (50% to 54%), baseline use of antihypertensive agents, and age 50 or older (72). In the Breast Cancer International Research Group (BCIRG) trial 006 comparing three different chemotherapy regimens—AC plus docetaxel (AC-T); AC plus docetaxel and trastuzumab (AC-TH); and docetaxel, carboplatin, and trastuzumab (TCH)—at a follow-up of 65 months, TCH had comparable efficacy to AC-TH (overall survival of 91% vs. 92%, respectively). Both TCH and ACTH had statistically significant improvements in DFS and OS, over the non-trastuzumab-treated group. However, the risk of grade 3 or 4 CHF was significantly lower among patients receiving TCH (0.4%) than among those receiving AC-TH (2%) (73).

The NCCTG N9831 Intergroup trial was a phase III study in which almost 2,000 patients with operable HER2 positive breast cancer treated with AC were randomized to receive (i) paclitaxel alone, (ii) paclitaxel followed by trastuzumab, or (iii) paclitaxel with concurrent trastuzumab. The 3-year cumulative incidence rates of cardiac events (symptomatic CHF or cardiac death) were 0.3%, 2.8%, and 3.3% in these three treatment arms, respectively. Of note, in this trial 5% of patients developed LVEF decreases precluding randomization to treatment after AC (74).

Multiple large, randomized trials of chemotherapy with trastuzumab show low rates of cardiac events that are easily overshadowed by improvements in patient survival. In a meta-analysis of over 11,000 patients in 8 randomized controlled trials of trastuzumab and chemotherapy, trastuzumab significantly increased the risk of congestive heart failure (relative risk [RR] 5.11, 90% confidence interval [CI] 3.00–8.72, $p < .00001$); and left ventricular ejection fraction decline (RR 1.83, 90% CI 1.36–2.47, $p = .0008$). However, the trastuzumab-containing regimens improved overall survival (HR for death 0.66, 95% CI 0.57–0.77, $p < .00001$), and disease-free survival (HR for relapse 0.60, 95% CI 0.50–0.71, $p < .00001$) (75). However, these trials have had stringent criteria for entry with regard to baseline cardiac function as well as criteria for monitoring and continuation of therapy. In an observational, community-based insurance database analysis, the risk of heart failure was higher in patients treated with anthracycline alone (hazard ratio [HR] 1.40, 95% CI 1.11–1.76), any chemotherapy (HR 1.49, 95% CI 1.25–1.77), versus no chemotherapy. This risk was increased in patients treated with trastuzumab alone (HR 4.12, 95% CI 2.30–7.42) and anthracycline plus trastuzumab (HR 7.19, 95% CI 5.00–10.35). One strength of this analysis was inclusion of real-world patients. However, increased reports of cardiotoxicity in the anthracycline- and trastuzumab-treated groups may partly be due to detection bias, as a result of more frequent monitoring and misclassification due to overcoding "heart failure" in these patients (76).

Monitoring for Treatment-Associated Cardiotoxicity

Ideally, close surveillance of cardiac function will reduce the incidence of irreversible heart failure. The most widely used surveillance method today is echocardiography. Left ventricular ejection fraction is measured to represent left ventricular systolic function. Echocardiography is widely available, but there is significant interoperator variability. Echocardiogram may also miss very small, subtle changes in cardiac function that may forewarn of later cardiotoxicity. Multiple gated acquisition (MUGA) scanning is comparable to echocardiography in terms of LVEF monitoring. It is a nuclear medicine scan, and assessments of LVEF may be more objective than echocardiography. However, MUGA does expose the patient to radiation. The Herceptin prescribing information recommends either echocardiogram or MUGA scan, prior to initiation, every 3 months during treatment, upon completion of treatment, and then every 6 months for 2 years postcompletion of therapy. If Herceptin is withheld due to cardiac dysfunction, repeat echocardiogram at 4 weeks is recommended (77).

There is no global agreement on the definition of cardiac dysfunction. The Cardiac Review and Evaluation Committee has sought to standardize the definition for cardiac

dysfunction in trastuzumab trials, diagnosed by echocardiography. The following criteria were proposed: (i) cardiomyopathy established by a decrease in LVEF that is global or more severe in the septum; (ii) symptoms of CHF; (iii) signs of CHF, including but not limited to third heart sound, tachycardia, or both; and (iv) a decline in LVEF of 5% or more to less than 55% with accompanying signs and symptoms of CHF or a decline in LVEF of 10% or more to less than 55% without signs or symptoms of HF (78). The doxorubicin hydrochloride prescribing information suggests that a 10% decline in LVEF to below the lower limit of normal or an absolute LVEF of 45%, or a 20% decline in LVEF at any level is indicative of deterioration in cardiac function (79). Both of these definitions do not capture subclinical cardiovascular damage occurring early in the course of treatment. There is an ongoing trial to evaluate long-term cardiac effects of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in patients treated as part of the NSABP B-31 trial, using MUGA, medication review, and quality of life 5 to 7 years postdiagnosis (ClinicalTrials.gov Identifier: NCT00004067).

Cardiotoxicity Associated with Newer HER2-Targeted Agents

When used in the adjuvant setting, trastuzumab is very effective in reducing breast cancer recurrence rates. However, patients who experience breast cancer recurrence eventually manifest resistance to trastuzumab over time. Therefore, several new agents targeting HER2 have been developed over the past several years and incorporated into clinical practice. Table 52-2 summarizes cardiotoxicity of adjuvant and neoadjuvant HER2-directed therapies.

Lapatinib: An oral, small molecule tyrosine kinase inhibitor that inhibits HER1 (EGFR) and HER2 is used in the treatment of metastatic HER2-positive breast cancer. The effect of lapatinib on cardiac function has been scrutinized, but to date it does not appear to be causally associated with cardiomyopathy. In a phase III study comparing paclitaxel with or without lapatinib as first-line treatment for metastatic breast cancer, six patients (2%) in each treatment group had a decrease in LVEF. None of these events was symptomatic and none required dose adjustment or resulted in treatment withdrawal or death. Forty-four percent of patients had prior exposure to anthracyclines in the adjuvant setting (80). The combination of lapatinib and trastuzumab versus trastuzumab was evaluated in heavily pretreated metastatic HER2-positive breast cancer; 3.4% of patients treated with the lapatinib with trastuzumab and 1.4% of patients treated with lapatinib alone experienced asymptomatic transient decreases in LVEF. Of patients with a decline in LVEF, for 5 of the 8 patients receiving combination therapy, and all 3 patients receiving monotherapy, the decline was reversible (81). In a pooled analysis of 3,689 patients treated with lapatinib across 44 prospective trials, there was a low incidence of cardiotoxicity. Only 60 patients experienced a cardiac event, of which most (83%) were asymptomatic. There were no cardiac deaths and development of cardiotoxicity did not correlate with anthracycline or trastuzumab pretreatment. Eighty-eight percent of the declines in LVEF were at least partly reversible regardless of continuation or discontinuation of lapatinib (82).

Since lapatinib is not associated with cardiomyopathy, like trastuzumab, large-scale trials have been undertaken to evaluate whether lapatinib can substitute for trastuzumab

TABLE 52-2

Cardiac Events in Adjuvant and Neoadjuvant Trials of HER2-Directed Therapies

STUDY	*Type of Cardiac Dysfunction*	*Incidence (%)*
BCIRG-006 (73)	Symptomatic HF	
AC + docetaxel		0.7
AC + docetaxel + trastuzumab		2
Trastuzumab + carboplatin + docetaxel		0.4
NSABP B-31 (72)	Symptomatic HF or cardiac death	
AC/paclitaxel		1.3
AC/paclitaxel plus trastuzumab		4.0
NCCTG9831 (112)	Symptomatic HF or cardiac death	
AC/paclitaxel		0.3
AC/paclitaxel + trastuzumab (concurrent)		3.3
AC/paclitaxel + trastuzumab (concurrent)		2.8
NEOALLTO (113)	LVEF decline, CHF, or "myocardial ischaemia"	
Lapatinib		0.6
Trastuzumab		1.3
Lapatinib + trastuzumab		2.6
NEOSPHERE (114)	LVEF decline over 10%	
Trastuzumab + docetaxel		0.9
Pertuzumab + trastuzumab + docetaxel		2.8
Pertuzumab + trastuzumab		0.9
Pertuzumab + docetaxel		1

in terms of efficacy. The COMPLETE (COMParison of Lapatinib Efficacy vs. Trastuzumab, each with a taxane, in first-line metastatic breast cancer) was one such study. It was closed early after an interim analysis in April 2012 revealed inferior progression free survival with lapatinib when compared with trastuzumab. PFS in the patients with centrally confirmed HER-positive cancer had HR 1.48 (95% CI 1.15–1.92, $p = .003$) (lapatinib + taxane to trastuzumab + taxane) (83). The ALTTO trial (Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation; ClinicalTrials.gov identifier: NCT00490139) is an ongoing, randomized, open label, multicenter, phase III study comparing the activity of lapatinib alone versus trastuzumab alone versus trastuzumab followed by lapatinib versus lapatinib concomitantly with trastuzumab in the adjuvant treatment of patients with HER2-positive breast cancer. In August 2011, the independent data monitoring committee review found that the lapatinib alone arm was unlikely to meet the prespecified criteria to demonstrate noninferiority to trastuzumab alone with respect to disease-free survival (DFS). Therefore, that study arm has been subsequently discontinued.

Pertuzumab: A monoclonal antibody that binds to the extracellular domain of HER2, similar to trastuzumab. However, it binds to a different epitope than trastuzumab. Pertuzumab prevents receptor homodimerization and heterodimerization within the HER-family and with IGF-1R. Pertuzumab inhibits HER family signaling and may also overcome trastuzumab resistance. In the CLEOPATRA study, 808 patients with metastatic HER2-positive breast cancer were randomized to receive trastuzumab plus docetaxel with or without pertuzumab. At a median follow-up of 19.3 months, patients who received pertuzumab demonstrated significantly improved PFS (12.4 months for control arm vs. 18.5 months pertuzumab arm, HR 0.62, 95% CI 0.51–0.75, $p < .001$). In this study, assessments of LVEF were performed at baseline, every 9 weeks during treatment, at treatment discontinuation, every 6 months in the first year after discontinuation, and annually thereafter for up to 3 years. Left ventricular systolic dysfunction was reported more frequently in the control group than in the pertuzumab group (8.3% vs. 4.4%). Grade 3 or higher left ventricular systolic dysfunction was also reported more frequently in the control group versus the pertuzumab group (2.8% vs. 1.2%). Of note, 89% of patients had not previously received trastuzumab (84). Therefore, more information on the cardiac safety of pertuzumab in trastuzumab pretreated patients will be available in the future.

Cardiotoxicity of Endocrine Therapies

Aromatase inhibitors (AIs) have emerged as an alternative to tamoxifen for use in adjuvant endocrine treatment. Among postmenopausal women with hormone-receptor-positive early-stage breast cancer, benefits in DFS have been demonstrated with AIs compared with tamoxifen without a corresponding clear benefit in overall survival. A possible explanation for this discrepancy may relate to the toxicity profile of AIs versus tamoxifen. In a meta-analysis of seven adjuvant endocrine therapy breast cancer trials, longer duration of aromatase inhibitor use was associated with a statistically significant increase in the odds of developing cardiovascular disease compared with tamoxifen alone or shorter duration of aromatase inhibitor use (OR 1.26, 95% CI 1.10–1.43, $p < .001$) (85,86). In the ATAC (anastrazole, tamoxifen alone or in combination) study among women with preexisting heart disease, the incidence of cardiovascular events was 17% with the AI, anastrazole, and 10% with tamoxifen (86). These data caution clinicians to consider individual cardiovascular risk in determining the best adjuvant endocrine treatment for early-stage breast cancer. One mechanism to potentially explain the decreased coronary risk seen in this study with tamoxifen may be its effects on lowering lipids. Tamoxifen decreases total cholesterol and low-density lipoprotein (LDL), without an effect on high-density lipoprotein (HDL). Triglycerides may increase while on tamoxifen. Women on AIs do not experience similar decreases in LDL. However, the changes in lipid profiles have no proven effect on cardiac outcomes. In the P-1 study, which randomized 13,387 women at higher than average risk of developing breast cancer to 5 years of tamoxifen or placebo, women treated with tamoxifen were no more or less likely to have an ischemic cardiovascular event (87).

Radiation-Associated Cardiotoxicity

Several studies have demonstrated an increase in coronary artery disease and/or nonfatal myocardial infarction associated with left-sided radiotherapy compared with right-sided radiotherapy or no radiotherapy. The incidence of heart disease was analyzed in 4,414 10-year survivors of breast cancer who were treated between 1970 and 1986. Those patients treated before 1980 had a greater incidence of heart disease than those treated after 1980 (88). This finding corroborates the notion that advanced radiation techniques have improved cardiovascular outcomes after breast irradiation. Also seen in this study was an increase in cardiovascular risk when chemotherapy was added to radiation. Smoking also conferred a more than additive risk of developing a second cancer when combined with radiation (88).

Strategies for Prevention of Treatment-Associated Cardiotoxicity

Cardioprotective Agents

Dexrazoxane: Several strategies to prevent and treat anthracycline-induced heart failure have been developed. Dexrazoxane is a cardioprotective agent that may have a role in preventing anthracycline-induced cardiomyopathy in high-risk patients. It is a cyclic derivative of EDTA that penetrates the cell membrane and is then converted intracellularly to a chelating agent that can interfere with the iron-mediated free radical generation which contributes to cardiomyopathy. In a meta-analysis of 10 randomized controlled trials enrolling over 1,600 patients, the use of dexrazoxane in addition to anthracycline containing chemotherapy, there was a significant decrease in the incidence of congestive heart failure with the use of dexrazoxane (RR 0.29, 95% CI 0.20–0.41, $p < .00001$). Additionally, no statistically significant difference in response rate between the dexrazoxane and control group was found (RR 0.89, 95% CI 0.78–1.02, $p = .08$) as had been suggested in earlier analyses (89,90). There was also no difference in progression free or overall survival in patients treated with or without dexrazoxane. In this meta-analysis, no definitive conclusions could be made regarding adverse effects of dexrazoxane (90). In the 2008 American Society of Clinical oncology guidelines issued on the use of cardioprotectants, the expert panel suggested that clinicians consider use of dexrazoxane for patients with metastatic breast cancer and other malignancies in patients who have received more than 300 mg/m^2 doxorubicin who may benefit from continued doxorubicin-containing therapy (91).

ACE Inhibitors and Beta Blockers: Both ACE inhibitors and beta blockers are important therapeutic agents for treating heart failure. These agents thus serve as ideal candidates for

treating anthracycline-induced cardiomyopathy. One study of 201 consecutive patients with anthracycline-induced cardiomyopathy and left ventricular ejection fraction 45% or less evaluated treatment with enalapril and carvedilol. Patients were more likely to respond to treatment and fully recover EF if cardiac therapy started earlier (i.e., closer to the end of chemotherapy) (92). In a single-institution study of patients receiving high-dose chemotherapy, those who developed increases in serum Troponin T were randomized to ACE inhibitor therapy or placebo. Patients who received ACE inhibitors were less likely to experience declines in ejection fraction (43% vs. 0%; $p < .001$). There were many patients who had not received anthracyclines as part of their chemotherapy regimen, so the broader applicability of this study to patients with anthracycline-induced cardiomyopathy is yet to be determined (93). Additionally, it is not known whether the use of these therapies as cardioprotective agents has any influence on breast cancer outcomes.

Exercise to Prevent Cardiotoxicity

Aerobic exercise forms an integral part of the cardiac rehabilitation programs used to treat patients with heart failure. Therefore, the use of exercise therapy for patients treated with doxorubicin has been evaluated. In several animal studies, exercise improved LVEF and diastolic function when instituted prior to and during doxorubicin treatment (94,95). However, studies in humans are necessary to assess whether these findings from animal studies are relevant to humans and, if so, whether exercise affects both acute and chronic cardiomyopathy.

Summary

The cardiac effects of breast cancer therapy have a major impact on quality of life and longevity of a subgroup of patients. Over the past several years we have identified patients at greatest risk of cardiotoxicity, based on baseline cardiac function. However, in the future the identification of genetic characteristics and biomarkers that indicate increased susceptibility to treatment-related cardiotoxicity will play a greater role in risk stratification of the individual patient. Currently, we are developing therapies that maintain efficacy while reducing risk of cardiac dysfunction.

SECONDARY MALIGNANCIES CAUSED BY BREAST CANCER TREATMENT

Breast cancer mortality has been declining over the past two to three decades, in part due to the advances in treatment. Now, with improved survival, the development of a second nonbreast malignancy, as a result of treatment, remains a major concern. While secondary malignancies are uncommon, they can be life threatening in an otherwise "cured" breast cancer survivor. In addition, there are concerns raised regarding the development of contralateral breast cancers.

Radiation-Associated Secondary Malignancies

Mechanism and Incidence: Radiation therapy can induce a secondary cancer via damage to DNA, which alters cellular programming to favor abnormal cell proliferation. Usually, there is a long latency period, from 5 to 20 years. In the first study to assess and quantify the long-term risk of all solid cancers after breast cancer radiotherapy in the United States using the Surveillance Epidemiology and End Results (SEER) databases, it was estimated that about 5% (95% CI 2.0–7.0) of contralateral breast cancers and 6% (3.0–8.0) of other solid cancers could be related to radiotherapy. For contralateral breast cancer, there was an estimated excess absolute risk of 2 cases per 10,000 person-years and for solid tumors 4 cases per 10,000 person-years. Of the solid tumors, most were located in areas receiving a higher dose of radiation such as the lung and esophagus (96).

These findings were substantiated in a second retrospective analysis of 647,672 patients across 15 primary solid cancer types who were analyzed for the development of a second cancer. Patients who were treated with and without radiation therapy were included in the analysis. Patients were excluded from the analysis if they did not survive to 5 years, given the latency period of secondary cancers. Among all patients, 60,271 (9%) developed a second solid cancer, of which 3,266 were estimated to be related to radiotherapy, corresponding to a risk of five excess cancers per 1,000 patients treated with radiotherapy by 15 years after diagnosis. In the specific subset of patients with breast cancer, there was a 5% increased risk in secondary cancer attributable to radiotherapy. Of note, the risk attributable to radiation decreased with patient age. The risk decreased with later year of treatment, suggesting that newer radiation techniques may be safer (97). These two analyses, while confirming that there is an increased risk of secondary cancer in breast cancer patients receiving radiation, also confirm that the absolute risk is low. In the breast cancer population, 10% of patients developed a second cancer of which only 0.5% were attributable to radiation. This indicates that other factors, both patient and treatment related, are involved.

Risk Factors for Radiation-Induced Secondary Malignancies

Genetic: A patient's genotype may confer an increased risk of developing radiogenic cancers. For example, *BRCA1, BRCA2*, and *ATM* are known to mediate cellular response to ionizing radiation, but it is unclear whether pathogenic mutations in these genes increase the risk of developing a radiogenic cancer. To date, a single susceptibility locus, in which allelic variants display a high-penetrance for radiogenic cancer, has not yet been identified. More likely, the development of a radiogenic cancer results from the coinheritance of multiple polymorphisms that increase risk in an additive fashion. Similar genetic factors that render a patient more susceptible to developing breast cancer in the first place may also contribute to developing a radiogenic cancer.

Age: Patient age was again identified as a risk for radiogenic cancers in the Women's Environmental, Cancer, and Radiation Epidemiology (WECARE) case-control study. Women with a second, asynchronous, contralateral breast cancer (cases) were compared with women with unilateral breast cancer (controls) matched by radiation treatment. Those women under the age of 40, who received higher doses of radiation, had an elevated risk of developing a second primary breast cancer (98).

Radiation-associated sarcomas (RAS) are rare secondary malignancies that deserve mention. The median latency period is approximately 10 years, ranging from 2 to 50 years. While there is some disagreement, one definition of RAS includes a "sarcoma within the path or adjacent to a radiation field, occurring at least 3 years post radiation" (99). The prognosis may be worse for RAS as opposed to sporadic soft-tissue sarcomas, adjusting for histologic type, size, age, margin status, and site (100).

Secondary Malignancies Associated with Specific Systemic Agents

Anthracycline-Induced Secondary Malignancies

Chemotherapy used in the adjuvant setting for early-stage breast cancer has improved overall survival. But, therapy-related myeloid neoplasms, such as treatment-related acute myelogenous leukemia (t-AML), are well described and deadly. Therapy-related AML constitutes 10% to 20% of all AML cases. Poor-risk cytogenetics and treatment resistance is often seen. Alkylating agents, such as cyclophosphamide, increase t-AML at approximately 5 years posttreatment. These leukemias are distinguished by certain morphologic and cytogenetic features. They are most often FAB subtype, M1 or M2, with abnormalities in chromosomes 5 and 7. In contrast, t-AML related to topoisomerase II inhibitors, such as doxorubicin and mitoxantrone, develops on average at 2 years posttreatment and is frequently associated with the 11q23 cytogenetic abnormality (101). Long-term survival after t-AML is worse compared with de novo AML (102). Common risk factors for both the development of breast cancer and t-AML may include genetic polymorphisms affecting DNA repair processes. Genetic factors influencing drug metabolism may also increase individual susceptibility to t-AML from chemotherapeutic agents. Additionally, older age, which in itself is linked with decreased DNA repair ability, is associated with t-AML. Using the SEER-Medicare database, 10,130 breast cancer patients who received adjuvant chemotherapy were compared with 54,585 who did not and observed for development of AML. All women in this study were older than 65 (median age 75.6). The absolute risk of developing AML at 10 years after any adjuvant chemotherapy for breast cancer was 1.8% versus 1.2% for women who had not received chemotherapy. These numbers may represent an underestimation of risk, since myelodysplastic syndrome (MDS) is not captured by claims in the database (103).

In a case-control study of women treated for breast cancer in France, there was a greater risk of AML/MDS with topoisomerase-II inhibitor–based chemotherapy than with other drug regimens (104). In this study, mitoxantrone treatment conferred a greater risk of MDS/AML than anthracycline treatment. Dose intensity may affect leukemia risk in patients treated with anthracyclines. An observational study of 9,796 patients treated with adjuvant chemotherapy regimens containing epirubicin demonstrated an 8-year cumulative probability of developing AML/MDS of 0.37% (95% CI 0.13–0.61) using standard doses (i.e., 720 mg/m^2 or less epirubicin and 6,300 mg/m^2 or less cyclophosphamide) compared with 4.97% (95% CI 2.06–7.87) for patients given higher doses of epirubicin and cyclophosphamide (105). In the randomized, prospective study comparing TC with AC, there were two cases of leukemia (myelofibrosis and myelodysplasia) in the 510 patients in the adriamycin group and none in docetaxel group. These numbers are small, but thought provoking (106).

Alkylating Agent–Induced Secondary Malignancies

In an analysis of six NSABP trials examining different schedules of adriamycin and cyclophophamide, the incidence of AML/MDS from 8,563 patients (representing 61,810 PYs of follow-up) was 0.50%. The cumulative incidence of AML/MDS at 5 years rose sharply according to the dose of cyclophosphamide given. For patients receiving the more intense regimens, the incidence was 1.01% (95% CI 0.63–1.62), compared with 0.21% (95% CI 0.11–0.41) for patients treated with standard AC (60 mg/m^2/600 mg/m^2 × 4). All of the protocols used standard dose adriamycin (60 mg/m^2), therefore dose intensity of adriamycin as a risk factor for AML/MDS could not be evaluated (107).

Granulocyte colony-stimulating factor (G-CSF) is commonly used with myelosuppressive chemotherapy to prevent neutropenia, specifically febrile neutropenia. While the NCCN guidelines recommend using G-CSF when the incidence of febrile neutropenia is 20% or greater, in clinical practice it is used more broadly. G-CSF activates signaling molecules, such as those in the Jak/STAT pathway, which are associated with hematologic malignancy. Therefore, there is a potential connection between t-AML and G-CSF. An evaluation of the incidence of secondary AML in breast cancer patients receiving chemotherapy with and without G-CSF was undertaken using the SEER-Medicare database. Of the 906 patients who were treated with G-CSF, 16 (1.77%) developed AML/MDS versus 48 (1.04%) of the 4,604 patients not treated with G-CSF, which corresponded to a HR of 2.14 (95% CI 1.12–4.08) (108). Dose and dose intensity was not available in the dataset, therefore the use of G-CSF may be a marker for increased dose. The population was over age 65 and may also represent a differential effect of either chemotherapy dose or G-CSF use in the elderly patient population. It is also important to note that in two large trials, one of dose-dense chemotherapy and the other using a SEER-Medicare database, there was no increase in t-AML observed with G-CSF use (103).

Radiation and chemotherapy together confer a greater risk of second cancers than either alone. A group of 5,790 patients with stages 0 to III breast cancer, treated with surgery and/or chemotherapy and/or radiation between 1990 and 2005, were analyzed for secondary malignancies using a community-based cancer center registry. There were 17 cases of MDS/AML, over an average 7.2 years' follow-up. Median survival of MDS/AML patients postdiagnosis was 9 months. No difference in MDS/AML was observed in the anthracycline compared to the nonanthracycline adjuvant chemotherapy treatment group. No cases of MDS/AML were observed in the surgery-only group. A threefold increase in risk was observed among patients treated with radiation alone and a sixfold increase in risk among patients treated with radiation and chemotherapy indicating a possible synergistic effect of radiation and chemotherapy. Ultimately, the authors concluded there was an elevated rate of MDS and AML was observed among breast cancer patients under 65, those treated with radiation, and those treated with radiation and chemotherapy compared to available population incidence data (109).

Endocrine Therapy–Induced Secondary Malignancies

The use of adjuvant endocrine therapy in women with early-stage breast cancer has improved overall survival in the 75% of patients with hormone-receptor- (ER- and/or PR-) positive disease. Tamoxifen, a selective estrogen receptor modulator, has been used for adjuvant treatment since the 1970s and remains the first-line adjuvant endocrine therapy in premenopausal women. Tamoxifen has also been shown to effectively prevent breast cancer in women at higher risk. It has agonist activity in several tissues of the body, including the endometrium. As a result, tamoxifen use is associated with an increased risk of endometrial cancer. The risks are small when compared with the benefits. But, the ability to identify risk factors will help tailor discussions of risk versus benefits to the individual patient.

In the P-1 trial, 13,387 women at higher than average risk of developing breast cancer were randomized to 5 years of tamoxifen or placebo. In this trial, tamoxifen reduced the risk of invasive breast cancer by 49% ($p < .0001$). However, the RR for endometrial carcinoma was increased among tamoxifen

users relative to nonusers (RR 2.53, 95% CI 1.35–4.97), primarily among women aged 50 or older. The absolute numbers were low—15 cases of uterine cancer with placebo versus 36 cases with tamoxifen. It is noteworthy that all 36 invasive endometrial cancers that occurred in the group receiving tamoxifen were FIGO stage I. There was no statistically significant increase in the incidence of endometrial cancer among women 49 and under (87). However, a case-control study using United Kingdom cancer registries demonstrated that tamoxifen use increased the risk of endometrial cancer in cases versus controls. Regardless of menopausal status, the elevated risk was present and continued for at least 5 years posttamoxifen discontinuation (110). Uterine sarcoma, a rare malignancy, is included in these reports of endometrial cancer. Across several NSABP trials (B-09, B-14, B-21, B-23, B-24, and P-1), uterine sarcomas comprised about 10% of uterine malignancies. The pooled results of these trials do suggest a slight increase in uterine sarcoma in tamoxifen-treated patients (111). See Chapter 43 for additional information.

CONCLUSIONS

For most women with breast cancer, the benefits of treatment outweigh the short- and long-term risks. However, an important minority suffer devastating consequences that affect longevity and/or quality of life. Researching the side effects of treatment, especially long-term side effects, must keep pace with the rapid development of new therapies. Observational data should serve as the foundation for prospective, longitudinal analysis of important treatment-related sequelae. With more information on these consequences, we can refine our risk–benefit assessments and target them to the individual patient.

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CHAPTER 53

Adjuvant Systemic Therapy Treatment Guidelines

C. Kent Osborne

CHAPTER CONTENTS

Adjuvant therapy decisions have become more complicated as breast cancers are further subdivided into groups that mandate different treatment approaches. Division of breast cancers into three groups, ER-positive, HER2-positive, and triple negative, while providing a general basis for treatment decisions, is insufficient to provide optimal therapy for a given patient. Multi-gene assays of the primary tumor in addition to other prognostic and predictive factors are often used to determine the molecular fingerprint of the tumor and, thus, to help guide patient therapy.

Because the rational for adjuvant systemic therapy is to eradicate distant micro-metastases that are present at diagnosis in many patients, the first step in decision-making requires an assessment of the likelihood that a given patient harbors occult distant metastases, which then translates into the risk for recurrence and death, using various validated prognostic factors. The second and equally important step is to estimate the benefit of treatment for that patient using validated predictive factors. It should be emphasized that the factors associated with risk for recurrence do not necessarily predict treatment benefit. For example, positive lymph nodes is a powerful prognostic factor and is associated with a higher risk for recurrence, but this does not necessarily mean that such tumors are responsive to chemotherapy. Considering the risk for recurrence and the estimated reduction in that risk, the third step is for the physician to have an honest discussion with the patient outlining the potential benefits relative to the side effects, toxicity, and cost of treatment, in the context of the patient's general health and preferences, to make a final decision.

Established prognostic markers include nodal status, pathological tumor size, histologic grade, markers of proliferation, ER status, and HER2 expression. Multi-gene assays such as the 21-gene recurrence score (Oncotype DX) and Mammaprint are widely used as prognostic factors in patients with ER-positive tumors based on results of retrospective studies. Prospective studies are underway to more fully evaluate their prognostic and predictive capabilities for response to chemotherapy. Retrospective studies suggest that the 21-gene recurrence score is predictive for chemotherapy benefit in both node-negative and node-positive, ER-positive patients with high scores predicting benefit of several chemotherapy regimens. Ki-67 (MIB1) is a proliferation marker used by some as both a prognostic and predictive marker although its widespread use is limited by the lack of standardization of the assay and its interpretation. An international consortium is working to standardize this potentially very valuable marker. Molecular classification of tumors into Lumina A and B, HER2-positive, basal-like, and claudin-low is still a research tool, but additional studies to evaluate its prognostic/predictive value are underway. For the most part, these assays all differentiate between the same tumor phenotypes. Well-differentiated, hormone receptor strongly positive, HER2-negative, slowly proliferating tumors respond well to endocrine therapy but less well, if at all, to chemotherapy, whereas more poorly differentiated tumors with low or absent ER, low or absent PR, rapid proliferation, and that are HER2-positive benefit from chemotherapy but respond less well, if at all (ER-negative), to endocrine therapy. In fact, studies suggest that immunohistochemical (IHC) assays for just four gene products, ER, PR, HER2, and Ki67, may be adequate to identify these phenotypes if they are done in a very standardized manner (1). This observation needs confirmation but is potentially important in reducing the cost of care and in extending this helpful test to patients in countries with fewer resources. Data are now emerging from DNA sequencing and other genomic, epigenomic, transcriptomic, proteomic, and metabolomic studies, suggesting that in the future breast cancer may be further broken down to even more subtypes with different prognoses and responses to therapy. At present, however, these studies are at the stage of cataloguing and characterizing these alterations, and none are clinically useful for adjuvant decision-making.

ADJUVANT ENDOCRINE THERAPY

Nearly all women with ER-positive invasive breast cancer should be considered for adjuvant endocrine therapy because of its favorable effects in reducing local and distant recurrence, mortality, and contralateral breast cancer, with relatively little toxicity. Even patients with tumors expressing low levels of ER (1% or more cells staining positive for ER) are candidates for endocrine therapy. This cutoff is similar

to that of the old ligand-binding assay where a cutoff of 4 or more fmoles per mg protein (lower limit of detection of the assay) predicted benefit from endocrine therapy. ER-negative but PR-positive tumors are rare with IHC, but patients with such tumors should probably receive endocrine therapy as the ER assay is likely to be falsely negative given that PR needs ER for its synthesis. ER- and PR-negative tumors do not benefit from adjuvant endocrine therapy, and it should not be given. For unclear reasons, the incidence of contralateral breast cancer is not reduced in these patients either.

All endocrine therapies block the effects of estrogen but in somewhat different ways. Tamoxifen binds to ER and prevents the binding of estrogen. Aromatase inhibitors (AIs) lower the level of estrogen available to bind ER in postmenopausal patients. They are ineffective in premenopausal patients with functioning ovaries. LHRH agonists block ovarian production of estrogen in premenopausal patients. Tamoxifen remains the treatment of choice for premenopausal women with ER-positive tumors and for many postmenopausal patients as well. Tamoxifen plus ovarian ablation or ovarian ablation alone is another option for premenopausal patients. Ovarian ablation plus an AI should not be used at the present time due to inferior results reported in one trial (2). The optimal duration of adjuvant endocrine therapy is in transition. Two large recent studies suggest that extending tamoxifen treatment to 10 years is superior to stopping at 5 (3,4). Five years may still be adequate for patients with very low-risk tumors because the anticipated additional benefit is very small and may be balanced by the additional toxicity. For many other patients, especially those remaining premenopausal, extending tamoxifen to 10 years is the new standard. Five years is still standard for breast cancer prevention and for ductal carcinoma in situ. Postmenopausal patients finishing 5 years of tamoxifen have the optional strategy of switching to an AI for 5 years rather than extending tamoxifen.

Aromatase inhibitors offer a slight advantage over tamoxifen in reducing recurrence and should be considered as part of the adjuvant endocrine therapy for many postmenopausal women. Randomized trials suggest that 5 years of an AI or the sequence of tamoxifen before or after an AI are acceptable strategies. Some studies suggest that 5 years of treatment with an AI, without a switch, should be considered in women at risk for early recurrence with higher-risk tumors characterized by high grade, lower ER and/or PR, HER2-positive, or higher rates of proliferation. Whether to extend initial AI therapy from 5 to 10 years is the subject of ongoing trials.

Because the recurrence benefits of an AI are not dramatically superior to tamoxifen and there is no definitive survival advantage for an AI, other factors should also be considered when making a treatment decision. Obesity is an adverse prognostic factor for outcome and some studies also suggest that obesity reduces the benefit from an AI. A history of venous thrombosis makes tamoxifen a poor choice for adjuvant endocrine therapy though it might be favored in women with a history of coronary artery disease or osteoporosis. Blood lipids and bone mineral density should be monitored in patients on an AI. Patients on tamoxifen should not be routinely monitored for endometrial cancer with ultrasound or endometrial biopsy in the absence vaginal bleeding or spotting. There are no clinical data to suggest the superiority of any of the three approved AIs: anastrozole, letrozole, or exemestane. Patients suffering joint/bone symptoms on anastrozole or letrozole sometimes have reduced symptoms upon switching to exemestane.

ADJUVANT CHEMOTHERAPY

Adjuvant chemotherapy is generally considered for healthy women with moderate to high-risk cancers. Chemotherapy is still the only option for patients with triple negative breast cancer. The use of chemotherapy has declined in the past 5 to 10 years with the recognition that many patients with ER-positive tumors, such as those with low grade, high ER and PR, negative HER2, and low proliferation, fail to benefit. Although several chemotherapy combinations provide options for patients, most include cyclophosphamide, an anthracycline, and a taxane together or in sequence. The dose-dense every 2-week regimen of doxorubicin plus cyclophosphamide for 4 treatments followed by paclitaxel for 4 treatments has been shown to be superior to the every 3-week regimen. The addition of paclitaxel provides the greatest benefit in patients with ER-negative tumors although some patients with ER-positive tumors with higher-risk features also benefit. Not all studies of dose-dense chemotherapy show positive results, but, because of the benefit of every 2-week AC followed by paclitaxel and its acceptable toxicity, this regimen has become standard for higher risk patients, particularly if they are ER-negative. Other regimens incorporating anthracyclines, cyclophosphamide, and a taxane are also acceptable and are used frequently. The docetaxel plus cyclophosphamide every 3-week for four treatments regimen, which was superior to doxorubicin plus cyclophosphamide in a large trial, is also used frequently in ER-positive patients who seem to benefit less from more intensive regimens. However, there are relatively little data comparing various regimens to demonstrate the clear superiority of one regimen over another. Older regimens using cyclophosphamide, methotrexate, and 5-flourouarcil are still used for some patients although they may be slightly inferior to newer regimens. The chemotherapy benefit in younger patients with ER-positive tumors is in part related to the ovarian ablation activity of the chemotherapy, which produces an endocrine therapy effect in addition to the cytotoxic effects.

CHEMO ENDOCRINE THERAPY

For women with ER-positive breast cancer, the addition of chemotherapy to endocrine therapy is an option. For Luminal A tumors with high ER and PR, negative HER2, grade 1, low rates of proliferation, and low 21-gene recurrence scores, the addition of chemotherapy provides little or no benefit. Although there are less data, while larger tumor size and lymph node positivity confer a higher risk for recurrence, still these tumors might not benefit from chemotherapy if they demonstrate the features noted above. Additional data on the predictive ability of the 21-gene recurrence score and Mammaprint will come from the TAILORx, RxPONDER, and MINDACT clinical trials that have or are nearing completion of the accrual phase.

In patients with ER-positive tumors who are considered candidates to also receive chemotherapy, endocrine therapy should be delayed until after the completion of chemotherapy. This recommendation is only based on studies of tamoxifen given concomitantly or sequentially with chemotherapy. Studies using an AI as the endocrine therapy together with chemotherapy are warranted because the effects of tamoxifen and estrogen deprivation on the biology of the cell are different.

ADJUVANT THERAPY FOR HER2-POSITIVE BREAST CANCER

Treatment of patients with HER2-positive tumors is also undergoing a transition. Neoadjuvant trials testing the hypothesis that multiple drugs targeting HER2 signaling are better than trastuzumab alone because they more completely block the HER2 pathway are strikingly positive (5,6).

Combinations of trastuzumab plus lapatinib or trastuzumab plus pertuzumab show a doubling of the pathologic complete response rate, suggesting that they will also be superior in the adjuvant setting for long-term DFS and OS. Adjuvant trials investigating this hypothesis are ongoing. Until completed, trastuzumab alone for one year remains the HER2-targeting agent to consider along with chemotherapy in patients with HER2-amplified tumors. The chemotherapy regimens to consider include combinations of cyclophosphamide, an anthracycline, and a taxane, or carboplatin plus docetaxel (TCH). Because of cardiac toxicity, trastuzumab should not be given together with doxorubicin but should be given concomitantly with a taxane. TCH is associated with slightly less cardiac toxicity than AC/paclitaxel plus trastuzumab. Patients on trastuzumab need to have serial monitoring of cardiac ejection fraction. For ER-positive, HER2-positive tumors, endocrine therapy should also be given after completion of chemotherapy and along with trastuzumab. There are no studies of trastuzumab plus endocrine therapy alone without chemotherapy. Furthermore, there are no large randomized trials of trastuzumab combined with a less intensive chemotherapy regimen such as paclitaxel alone. Patients with node-negative small tumors less than 1 cm were not included in the large randomized trials, but they do have higher than expected risks of recurrence, and treatment of such patients can be considered depending on other factors. Finally, small neoadjuvant studies of HER2-targeted therapy alone without chemotherapy suggest that there may be a subset of patients that does not need chemotherapy. However, this approach requires additional study and it should not be used outside of a clinical trial.

SUMMARY

Adjuvant systemic therapy has markedly improved the outcome of patients with early breast cancer and has contributed to the reduction in mortality rates observed in Western countries since 1990. Adjuvant therapy decision-making is complex and requires knowledge of the biology of breast cancer, the myriad breast cancer subtypes, prognostic and predictive factors, various treatment options, and patient characteristics and preferences. Several groups have provided evidence-based or expert opinion-derived guidelines to help in the decision-making process. Given the rapid changes occurring in this area, these guidelines may not always be up to date, but they can be very helpful to the clinician in determining optimal care for patients. Among them, the recommendations from the 2013 St. Gallen Consensus Conference and the National Comprehensive Cancer Network (NCCN) may be useful to clinicians (7,8). These recommendations should be viewed as guidelines and not mandates for management of individual patients. Although adjuvant therapy has improved patient outcomes, still many thousands of patients die each year from breast cancer. Participation in clinical trials provides optimal management for the patient while at the same time helping to further reduce mortality for patients in the future.

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SECTION VIII

Preoperative Systemic Therapy

CHAPTER 54

Preoperative Chemotherapy for Operable Breast Cancer

Aditya Bardia and José Baselga

CHAPTER CONTENTS

INTRODUCTION

Preoperative chemotherapy, also referred to as neoadjuvant chemotherapy or primary systemic therapy, today constitutes one of the standards of care in patients with newly diagnosed early stage breast cancer. This approach was initially introduced in the 1970s for the treatment of patients with locally advanced breast cancer (LABC) where it was found to result in high response rates, allow surgery for these initially unresectable tumors, and improve survival when compared to historical controls (1,2).

The success of preoperative chemotherapy for locally advanced disease together with emerging data on the benefits of adjuvant chemotherapy has led to the conduct of a number of studies in patients with operable breast cancer. These studies, some of which will be discussed in this chapter, have provided a number of important clinical insights regarding preoperative chemotherapy that are applicable to the management of patients with breast cancer. First, the majority of patients achieve a clinical response to induction chemotherapy, and the progression of disease during therapy, a legitimate concern, is rare. Second, preoperative chemotherapy results in surgical downstaging of tumors and allows breast conservation in women who, otherwise, would have needed a mastectomy. Furthermore, preoperative chemotherapy does not limit or interfere with posterior surgery and radiation therapy. Third, disease-free control and overall survival are similar between preoperative and postoperative (adjuvant) therapy. Fourth, the same chemotherapy agents and sequence of administration used in the adjuvant setting is also used in the preoperative space. As such, there are not preoperative or adjuvant-restricted chemotherapy regimens. Fifth, emerging data suggests that a good response to therapy resulting in absence of tumor at the time of surgery (pathological complete remission [pCR]) may be a surrogate marker of improved disease-free survival and overall survival. Finally, investigational agents are being increasingly studied in the preoperative setting even before the launch of large adjuvant studies as the number of patients required is smaller than in the adjuvant settings and follow up is shorter as a result of using the pCR rate, an early readout as a surrogate marker of improved disease-free survival and overall survival.

While preoperative chemotherapy is not for every patient and a large number of those patients with newly diagnosed breast cancer for whom chemotherapy is recommended will continue to be treated in the adjuvant setting, preoperative chemotherapy is a treatment approach to be considered and is likely to become a space for the rapid approval of active compounds in the early disease setting.

THE EVOLUTION OF PREOPERATIVE CHEMOTHERAPY

The first prospective preoperative study was launched in 1973 by investigators from the Milan Cancer Institute. The primary objective was to downstage the tumor and facilitate surgical resection. Women with stage III breast cancer received combination chemotherapy with adriamycin and vincristine for three cycles, followed by radiation therapy followed by additional chemotherapy. This preoperative approach was not only effective in downstaging the tumors

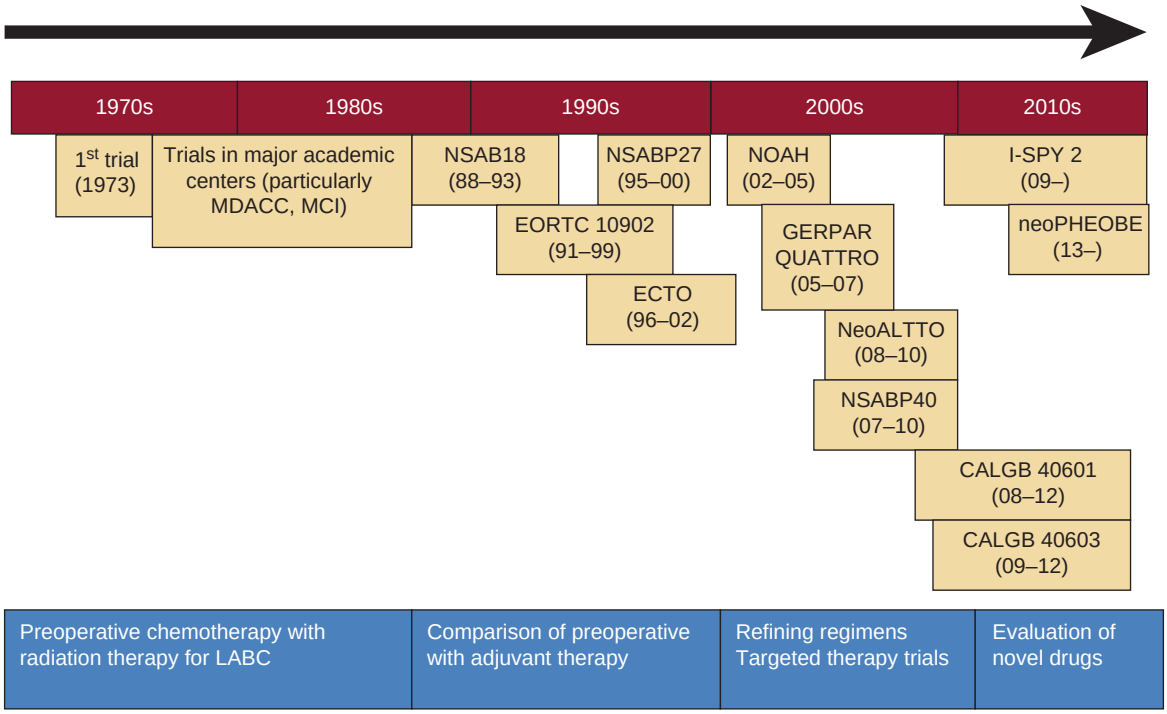

FIGURE 54-1 Evolution of preoperative chemotherapy over the past 30 years. MDACC, MD Anderson Cancer Center, USA; MCI, Milan Cancer Institute, Italy; LABC, locally advanced breast cancer.

but also improved survival (3,4). In the late 1970s and the 1980s, several preoperative trials assessed the benefit of chemotherapy in women with LABC, and, in addition to improving the rates of operability, most suggested a survival benefit as well (5,6). Based on these results and the lack of effective alternative strategies, the administration of preoperative chemotherapy with or without radiation therapy prior to surgery thus became the standard for initially inoperable, nonmetastatic breast cancer.

The success of preoperative chemotherapy in downstaging tumors and improving survival prompted further evaluation in operable tumors as well. Furthermore, there was a suggestion from preclinical models that chemotherapy before tumor removal may result in better outcomes than administration after surgery due to early eradication of micrometastasis (7,8). Consequently, in the late 1980s and the 1990s, a new series of clinical trials were launched in the United States and Europe that compared preoperative and adjuvant therapies. The National Surgical Adjuvant Breast and Bowel Project (NSABP) conducted a large phase III study (NSABP B-18), in which 1,523 women with operable breast cancer were randomly assigned to pre- or postoperative doxorubicin and cyclophosphamide (adriamycin cyclophosphamide [AC]; 60/600 mg/mg^2 for four cycles) (9). Preoperative chemotherapy was associated with a higher rate of breast conservation surgery (68% vs. 60%; p = .001) as compared to adjuvant therapy. However, there was no difference in the Disease Free Survival (DFS, 55% vs. 58%) or Overall Survival (OS, 72% vs. 72%) observed between the preoperative and adjuvant groups. Among those patients who received preoperative therapy, achieving pCR was associated with significant improvement in DFS (HR = 0.47; p <.0001) and OS (HR = 0.32; p <.0001) compared with those who had residual tumor at the time of surgery. Similar results were observed in other randomized trials comparing preoperative and adjuvant regimens (10–12).

Although any of these trials showed superiority in DFS or OS, the demonstration of equivalence between preoperative and adjuvant chemotherapy set the stage for the development in the preoperative setting of a number of treatment regimens that were developed in parallel with new adjuvant approaches. Today, similar guiding principles apply for the choice of agents, sequencing, and duration of therapy between the preoperative and adjuvant setting. In addition, new targeted agents are today being tested preoperatively. Figure 54-1 outlines the evolution of preoperative chemotherapy over the past 30 years.

CURRENT PREOPERATIVE REGIMENS AND PRACTICE

A number of conditions have to be met in order to consider the administration of preoperative therapy. First, appropriate tumor tissue in the diagnostic specimen should be available for histological diagnosis, including assessment of hormone receptor (HR) and Human epidermal receptor-2 (HER2) status. Ideally, enough tumor tissue for additional studies, such as gene-signature profile, should also be available. Second, it is helpful to place clips to mark the tumor location as it aids the radiologist, surgeon, and pathologist in providing post-treatment assessment. Third, biopsy of clinically palpable axillary lymph nodes, and sentinel lymph node biopsy in the absence of palpable lymph nodes, may be considered before initiating preoperative therapy. The management of sentinel lymph node (SLN) is detailed in Chapter 56. The determination of pathological involvement of axillary lymph nodes has prognostic significance and could influence the radiation therapy decision after surgery. Finally, preoperative chemotherapy requires a fully integrated, strong multidisciplinary team.

The commonly used preoperative regimens are summarized in Table 54-1. The salient features are reviewed below.

TABLE 54-1

Commonly Used Neoadjuvant Chemotherapy Therapy Regimens

Regimen	*Dose and Frequency*
AC-T[a]	Adriamycin/doxorubicin 60 mg/m^2 Cyclophosphamide 600 mg/m^2 every 3 weeks for four cycles, followed by Paclitaxel 80 mg/m^2[b]
ddAC-T[a]	Adriamycin/doxorubicin 60 mg/m^2 Cyclophosphamide 600 mg/m^2 every 2 weeks for four cycles with pegfilgrastim, followed by Paclitaxel 80 mg/m^2[b]
TC[a]	Docetaxel 75 mg/m^2 Cyclophosphamide 600 mg/m^2 every 3 weeks for six cycles
TAC	Docetaxel 75 mg/m^2 Doxorubicin 50 mg/m^2 Cyclophosphamide 500 mg/m^2 every 3 weeks for six cycles with pegfilgrastim
FAC	5-Fluorouracil 500 mg/m^2 (days 1, 8 or days 1, 4) Doxorubicin 50 mg/m^2 Cyclophosphamide 500 mg/m^2 every 3 weeks for six cycles
FEC-D	5-Fluorouracil 500 mg/m^2 Epirubicin 100 mg/m^2 Cyclophosphamide 500 mg/m^2 every 3 weeks for three cycles, followed by Docetaxel 100 mg/m^2 day 1 every 3 weeks for three cycles
CMF	Cyclophosphamide 100 mg/m^2 PO (days 1–14) Methotrexate 40 mg/m^2 IV (days 1, 8) 5-Fluorouracil 600 mg/m^2 IV (days 1, 8) every 4 weeks for six cycles

[a]Preferred regimen.
[b]Can also be given as paclitaxel 175 mg/m^2 every 2 weeks with pegfilgrastim or every 3 weeks.

Choice of Drugs

A standard preoperative chemotherapy regimen should ideally include an anthracycline such as doxorubicin or epirubicin. Doxorubicin is usually given as 50 to 60 mg/m^2 every 2 to 3 weeks, and epirubicin as 90 to 100 mg/m^2 every 3 weeks. A baseline evaluation of heart function (ejection fraction) should be obtained before initiating anthracyclines.

The addition of taxanes to anthracycline-containing regimens should also be strongly considered as it improves efficacy and clinical outcomes. This was well demonstrated in the NSABP-27 trial, wherein 2,400 patients were randomly assigned to receive either (a) preoperative AC alone (every 3 weeks for four cycles) followed by surgery or (b) preoperative AC followed by docetaxel (100 mg/m^2 every 3 weeks for four cycles) followed by surgery or (c) preoperative AC followed by surgery followed by adjuvant docetaxel (13). Preoperative AC-docetaxel significantly improved pCR rate as compared to AC alone (26.1% vs. 13.7%; p <.001). Like the NSABP B-18, the pCR was a significant predictor of DFS (HR = 0.49; p <.0001) and OS (HR = 0.36; p <.0001) regardless of treatment. Multiple other preoperative trials have demonstrated the advantage of adding docetaxel (14–16), and paclitaxel (17,18) in the preoperative setting.

If there is a contraindication to use of anthracyclines, a non-anthracycline regimen preferably with a taxane, such as TC, should be considered based on extrapolation from the adjuvant studies (19). The TC regimen involves the administration of docetaxel 75 mg/m^2 with cyclophosphamide 600 mg/m^2 every 3 weeks for a total of four cycles. This should be given in conjunction with appropriate antiemetic prophylaxis and growth factor support.

Schedule

Weekly paclitaxel seems to be superior to every-3-week paclitaxel, similar to that observed in the adjuvant setting. For example, in a preoperative trial led by investigators at MDACC, 258 patients were randomly assigned to receive a) weekly paclitaxel (either 80 mg/m^2 for 12 weeks to those with clinically node-positive disease or 150 mg/m^2 3 weeks on and 1 week off for 12 weeks to those with clinically node-positive disease) or b) every-3-week paclitaxel (225 mg/m^2 every 3 weeks for four cycles). Both the pCR rates (28.2% vs. 15.7%; p = .02) and breast conservation rate (47% vs. 38%; p = .05) were higher in those who received weekly paclitaxel than those who received every-3-week paclitaxel (20).

Conceptually, the same regimen and schedule used for adjuvant therapy could be used for preoperative therapy. Thus, as in the adjuvant setting, the administration of chemotherapy cycles every 2 weeks instead of every 3 weeks, an approach that is being referred to as *dose-dense chemotherapy,* might be superior to a conventional dose regimen, though strong data from randomized clinical trials is lacking. Trials comparing dose-dense regimens to conventional regimens have had differences in the dose and regimen between the groups, making it difficult to draw clear conclusions. For example, in the AGO-1 trial (21), eligible patients (n = 668) were randomly assigned to receive either a) dose-dense epirubin (150 mg/m^2 every 2 weeks for three cycles) followed by paclitaxel (225 mg/m^2 every 2 weeks for three cycles) or b) a conventional dose of epirubicin (90 mg/m^2 every 3 weeks for four cycles) and paclitaxel (175 mg/m^2 every 3 weeks for four cycles); the dose-dense sequential schedule was associated with higher pCR (18% vs. 10%; p = .008) as well as improvement in DFS (HR = 0.71; p = .011), and OS (HR = 0.83; p = .041) as compared to the conventional combination schedule. However, it is unclear whether the superiority of the dose-dense regimen was due to the dose-dense schedule or the addition of taxanes.

Nevertheless, in the U.S., dose-dense AC (followed by paclitaxel) is commonly used in clinical practice. This involves the administration of Adriamycin 60 mg/m^2 every 2 weeks along with cyclophosphamide 600 mg/m^2 every 2 weeks for a total of four cycles. This should be given in conjunction with appropriate antiemetic prophylaxis and growth factor support.

Sequence

The sequential administration of taxane following anthracyclines appears to be better than combination therapy. In the German Preoperative Adriamycin Docetaxel Trial (GeparDUO) trial, women (n = 913) were randomized to either a) a combination of doxorubicin and docetaxel (AD; 50/75 mg/m^2 every 2 weeks for four cycles) or b) AC (60/600 mg/m^2 every 3 weeks for four cycles) followed by docetaxel (100 mg/m^2 every 3 weeks for four cycles) (16). As compared to the AD

group, the AC-D group had better clinical responses (75.2% vs. 85%; p <.001), radiographic responses (68.6% vs. 78.6%; p <.001), breast conservation surgery rate (58.1% vs. 63.4%; p = .05), and pCR rate (7% vs. 14.3%; p <.001). The Hoosier Oncology Group trial also demonstrated the superiority of the sequential adriamycin-docetaxel regimen over the combination regimen (22).

Duration

There is a consensus of opinion based on currently available data that preoperative chemotherapy should be administered for at least six cycles, as in the adjuvant setting (2). The continuation of the same regimen beyond the standard number of cycles is not recommended, and sequential use of cross-resistant therapy is preferred over a longer duration of the same regimen (14,15). A German meta-analysis has suggested that duration of chemotherapy might be more important for HR+ tumors, and dose intensity more important for triple-negative breast cancers (TNBCs) (23), but this approach has not been validated in prospective studies.

In general, it is recommended that the full preoperative regimen should be administered before surgery, particularly if breast conservation surgery is desired. Sometimes preoperative therapy is used as a "bridge" until the mastectomy and reconstruction can be scheduled, and, in such settings, a sandwich technique (i.e., delivering part of chemotherapy before surgery and the remainder after surgery) can be used. The survival outcomes are similar as demonstrated by the NSABP-27 trial (13).

After preoperative chemotherapy, definitive breast surgery should be performed. The American Joint Committee on Cancer Staging manual uses "y" to indicate pathologic staging after preoperative therapy. After surgery, radiation and/or biologic therapy as appropriate (i.e., trastuzumab in HER2-positive disease, hormonal therapy for HR+ disease) should be pursued. The presence of residual disease after completion of preoperative therapy can be a therapeutic challenge, particularly for TNBCs. While the presence of residual disease is associated with worse outcomes as compared to pCR, there is no data that demonstrates additional postoperative chemotherapy improves outcomes. This is an area of active research and several clinical trials are investigating the role of additional therapies in this setting (NCT01401959, NCT0087750, NCT00925652, NCT01772472).

ADDITIONAL CHEMOTHERAPY AGENTS

In addition to the standard anthracyclines and taxanes discussed above, other chemotherapeutic agents have been studied in the preoperative setting. While they have shown clinical activity, they are not considered to be standard of care at this time.

Platinum

Gene-expression profiling of breast cancer has demonstrated that triple-negative breast cancer shares molecular features with basal-like BRCA-1 tumors, which are very sensitive to DNA cross-linking agents such as cisplatin (24). This has led to a renewed interest in the role of platinum agents in breast cancer.

Various small preoperative trials have investigated the role of platinums in TNBC. In a small phase II trial, women with triple-negative breast cancer (n = 28) were treated with preoperative cisplatin (75 mg/m^2 every 3 weeks for four cycles), and a pCR rate of 22% was observed (25). Other authors have reported a higher pCR rate (as high as 67%) with platinum and taxane combinations (26,27), albeit still lower than the >80% pCR rate reported for BRCA tumors (28). Randomized trials comparing platinum-containing chemotherapy to nonplatinum-based chemotherapy, such as CALGB 40603, are ongoing and will help identify predictive biomarkers of platinum response.

Capecitabine

While capecitabine can improve response rates and survival among women with locally advanced or metastatic disease, in the preoperative setting the addition of capecitabine to an anthracycline and taxane-based regimen has not been associated with any significant benefit and leads to higher toxicity. For example, in the NSABP trial B40, 1,206 women with primary operable HER2-negative breast cancer were randomly assigned to receive preoperative therapy consisting of either (a) docetaxel (100 mg/m^2), (b) docetaxel (75 mg/m^2) with capecitabine (825 mg/m^2 days 1 to 14), or (c) docetaxel (75 mg/m^2 plus gemcitabine 1000 mg/m^2), every 21 days for four cycles, with each regimen followed by AC for four cycles (29). The addition of capecitabine or gemcitabine to docetaxel therapy, as compared with docetaxel therapy alone, did not significantly increase the rate of pathological complete response (29.7% and 31.8%, respectively, vs. 32.7%; p = .69), but both capecitabine or gemcitabine-containing regimens were associated with increased adverse effects, particularly hand-foot syndrome, mucositis, and neutropenia. Similar results were observed in the German GeparQuattro preoperative trial in which women with large or locally advanced tumors (n = 1,509) were randomized to receive four cycles of 5-fluorouracil, epirubicin, and cyclophosphamide (FEC), followed by either (a) docetaxel (100 mg/m^2), (b) docetaxel (75 mg/m^2) plus capecitabine (1,800 mg/m^2), or (c) docetaxel (75 mg/m^2) followed by capecitabine (1,800 mg/m^2), every 21 days for four cycles. There was no significant difference in pCR rates (22.3%, 19.5%, and 22.3%, respectively; p = .298), or breast conservation rates (70.1%, 68.4%, and 65.3%, respectively; p = .781) between the groups, but increases in adverse effects were noted (30). Thus, addition of capecitabine to an anthracycline and taxane-based preoperative regimen is not routinely recommended.

Ixabepilone

Ixabepilone has demonstrated efficacy in metastatic breast cancer including taxane-resistant tumors. In the preoperative setting, the single agent ixabepilone has been reported to have a pCR rate close to 20%, comparable to taxanes, and is particularly associated with a higher pCR rate among ER-negative tumors. In a phase II preoperative study designed to evaluate genomic predictors of ixabepilone response, ER, microtubule-associated protein *tau*, and a 10-gene penalized logistic regression (PLR) model were reported to be predictive of ixabepilone sensitivity (31). If confirmed in additional randomized trials, ixabepilone might serve as an alternative to taxanes for certain breast cancers.

Eribulin

Eribulin, a mitotic inhibitor similar to the taxanes, has significant activity among women with heavily pretreated metastatic breast cancer and was FDA approved for this purpose in 2010. While eribulin is not approved for use in the preoperative setting, clinical trials are ongoing. These include comparison of eribulin versus weekly paclitaxel after AC (NSABP FB-9, NCT01705691) or FEC (NCT01593020) and eribulin in combination with cyclophosphamide as a potential alternate to TC (NCT01527487). Similar to ixabepilone, eribulin might serve as an alternative to taxanes for certain breast cancers.

INCORPORATION OF BIOLOGICAL AGENTS IN PREOPERATIVE CHEMOTHERAPY

Anti-HER2 Agents

The study of new anticancer agents, mostly chemotherapy, in the preoperative setting has usually lagged behind their development in the adjuvant setting. However, with the demonstration of similar outcomes in both the preoperative and adjuvant setting and the early readout of clinical benefit provided by clinical and pathological responses, there has been a progressive shift in studying new agents earlier in the preoperative setting. This trend is well exemplified in the case of anti-HER2 therapies. After the pivotal study with the anti-HER monoclonal antibody trastuzumab showed improved outcomes in the metastatic setting, a number of studies both in the adjuvant and preoperative setting were launched almost simultaneously. These early studies with anti-HER2 agents in the preoperative setting were exploratory, hypothesis testing, and mostly supportive of the large registration phase III adjuvant studies. These studies were found to have comparable outcomes to those of the larger adjuvant studies, and, as a result, second-generation anti-HER2 studies with newer anti-HER2 therapies and combinations have been initiated and already reported ahead of their adjuvant counterparts. If the results of these second-generation anti-HER2 studies are confirmed in the adjuvant studies, it is conceivable that some of these newer agents could be approved for use based on the outcomes of preoperative studies.

The first generation of anti-HER2 therapies in the preoperative setting were based on the addition of trastuzumab to anthracycline and taxane-based chemotherapy (32–36). In summary, all these studies observed a higher pCR when therapy with trastuzumab was added to a number of chemotherapy regimens when compared to chemotherapy alone (Table 54-2). Among them, the NOAH study was a phase III study that showed that in patients with HER2-positive locally advanced or inflammatory breast cancer, addition of 1 year of trastuzumab (starting as preoperative and continuing as adjuvant therapy) to preoperative chemotherapy improved overall response rates, almost doubled rates of pathological complete response, and reduced risk of relapse, progression, or death compared to patients who did not receive trastuzumab. The benefit of trastuzumab was observed in all subgroups tested, including women with inflammatory disease (27% of HER2-positive patients) who benefitted substantially from trastuzumab. The important point to consider about NOAH is that it showed a good correlation between a higher rate of pCR and improved survival, suggesting that in HER2-positive tumors, pCR may be a correlate of survival. In addition, this study led to approval of preoperative trastuzumab in a number of countries, including those of the European Union. In support of the findings that pCR is correlated with improved overall outcomes, in the TECHNO trial that studied preoperative trastuzumab in combination with anthracyclines and taxanes (33) followed by up to 1 year of trastuzumab, the 3-year disease-free survival (DFS) was 88% in patients with pCR compared to 73% in patients without pCR ($p = .01$).

The next generation of preoperative studies in patients with HER2-positive breast cancer has explored the combination of two anti-HER2 agents given together. This approach was based on preclinical studies (36–37), as well as emerging clinical data in patients with advanced disease. In clinical trials of patients with metastatic disease that had progressed on trastuzumab, the combination of trastuzumab and the tyrosine kinase inhibitor lapatinib was superior to lapatinib alone (38). Likewise, the addition of pertuzumab (an antibody that prevents dimerization of HER2 with the closely related HER3 receptor) to trastuzumab was found to be superior to trastuzumab alone (39). In the case of pertuzumab, a phase III study in the first-line metastatic setting in patients with HER2-positive breast cancer has demonstrated that the combination of trastuzumab and pertuzumab with chemotherapy is superior to trastuzumab alone with chemotherapy and has resulted in its recent approval for therapy (40).

A number of studies have shown the superiority of the combination of trastuzumab and lapatinib when compared to either trastuzumab or lapatinib alone. In the NeoALTTO study, patients with HER2-positive primary breast cancer with tumors greater than 2 cm in diameter were randomly assigned to lapatinib, trastuzumab, or lapatinib plus trastuzumab therapies (41). Anti-HER2 therapy alone was given for the first 6 weeks; weekly paclitaxel was then added to the regimen for a further 12 weeks, before definitive surgery was undertaken. After surgery, patients received adjuvant chemotherapy followed by the same targeted therapy as in the preoperative phase for 52 weeks. The pCR rate was significantly higher in the group given lapatinib and trastuzumab (78 of 152 patients [51.3%; 95% CI, 43.1–59.5]) than in the group given trastuzumab alone (44 of 149 patients [29.5%; 95% CI, 22.4–37.5]; difference 21.1%; 95% CI, 9.1–34.2; $p = .0001$). No significant differences in pCR existed between the lapatinib (38 of 154 patients [24.7%; 95% CI, 18.1–32.3]) and the trastuzumab (difference –4.8%; 95% CI, –17.6 to 8.2; $p = .34$) groups. The recently reported NSABP-B41 study compared lapatinib versus trastuzumab in combination with weekly paclitaxel following AC, as well as combining weekly lapatinib and trastuzumab with weekly paclitaxel following AC on pathologic complete response (pCR) rates (42). Unlike the NeoALTTO study, following surgery, all patients received trastuzumab to complete 52 weeks of HER2-targeted therapy. At the time of initial presentation, pCR assessments were available for 519 patients. The pCR percentages in the HR-positive subset were 46.7%, 48% ($p = .85$), and 55.6% ($p = .18$), respectively, and were 65.5%, 60.6% ($p = .57$), and 73% ($p = .37$) in the HR-negative cohort. The corresponding pCR breast and nodes percentages were 49.1%, 47.4% ($p = .74$), and 60.4% ($p = .04$). Finally, the smaller CHER-LOB study also showed the superiority of dual HER2 blockade with trastuzumab and lapatinib (43).

The combination of trastuzumab and pertuzumab has also been shown to be superior to trastuzumab alone. In the Neosphere study, a randomized phase II study, a total of 417 treatment-naive women with HER2-positive breast cancer were randomized to receive 4 preoperative cycles of trastuzumab plus docetaxel or pertuzumab and trastuzumab plus docetaxel or pertuzumab and trastuzumab or pertuzumab plus docetaxel (44). The primary endpoint was, like in NeoALTTO, pCR in the breast. Patients given pertuzumab and trastuzumab plus docetaxel had a significantly improved pCR rate (49 of 107 patients; 45.8% [95% CI, 36.1–55.7]) compared to those given trastuzumab plus docetaxel (31 of 107; 29.0% [95% CI, 20.6–38.5]; $p = .0141$). And 23 of 96 (24.0% [95% CI, 15.8–33.7]) women given pertuzumab plus docetaxel had a pCR. In this study, the one group that received pertuzumab and trastuzumab without chemotherapy also had a substantial pCR rate (18 of 107 (16.8% [95% CI, 10.3–25.3]), raising the hope that a subgroup of patients with early HER2-positive breast cancer may not need chemotherapy. The molecular features of these tumors that are sensitive to anti-HER2 therapy without chemotherapy are yet to be identified, and it is anticipated that this will be an area of intense research over the next few years.

TABLE 54-2

Neoadjuvant Clinical Trials Evaluating Combinations of Dual Anti-HER2 Therapies

Study	*Regimen*	*Sample Size*	*Results*
NeoALLTO	A) Trastuzumab with paclitaxel weekly*12 B) Lapatinib with paclitaxel weekly*12 C) Trastuzumab and lapatinib with paclitaxel weekly*12	455	pCR 29.5% in Group A vs. 24.7% in Group B vs. 51.3 in Group C p = .32 B vs. A p = .0001 C vs. A
NSABP-41 (NCT00486668)	A) Doxorubicin plus cyclophosphamide (AC)*4 followed by weekly paclitaxel with trastuzumab B) Doxorubicin plus cyclophosphamide (AC)*4 followed by weekly paclitaxel with lapatinib C) Doxorubicin plus cyclophosphamide (AC)*4 followed by weekly paclitaxel with trastuzumab and lapatinib	522 (reported on 519)	pCR (breast and nodes) 49.1% in Group A vs. 47.4% in Group B vs. 60.4% in Group C p = .74 B vs. A p = .04 C vs. A
TBCRC 006	Trastuzumab and lapatinib*12 (ER+ patients also received letrozole)		pCR Overall: 28% ER+ = 21% ER– = 42%
CHERLOB (81)	A) Paclitaxel weekly*12, followed by 5-fluorouracil, epirubicin, cyclophosphamide (FEC) q3weeks*4 with trastuzumab B) Paclitaxel weekly*12, followed by 5-fluorouracil, epirubicin, cyclophosphamide (FEC) q3weeks*4 with lapatinib C) Paclitaxel weekly*12, followed by 5-fluorouracil, epirubicin, cyclophosphamide (FEC) q3weeks*4 with trastuzumab and lapatinib	121	pCR 28% in Group A vs. 32% in Group B vs. 48% in Group C p <.05 for C vs. A p <.05 C vs. B
Neosphere (97)	A) Trastuzumab with docetaxel q3weeks*4 B) Pertuzumab with docetaxel q3weeks*4 C) Trastuzumab and pertuzumab with docetaxel q3weeks*4 D) Trastuzumab and pertuzumab q3weeks*4	417	pCR 29% in Group A vs. 24% in Group B vs. 45.8% in Group C vs. 16.8% in Group D p = .01 C vs. A p = .03 C vs. B p = .01 D vs. A
TRYPHEANA (98)	A) Pertuzumab and trastuzumab*6 with FEC*3 and then docetaxel*3 B) Pertuzumab and trastuzumab*3 with FEC*3 C) Pertuzumab, trastuzumab, docetaxel, and carboplatin*6	225	pCR rates ranging from 45% to 66% with no significant difference between the groups
CALGB 40601 (NCT00770809)	A) Paclitaxel weekly with trastuzumab*4 B) Paclitaxel weekly with trastuzumab and lapatinib*4	400 (planned)	Clinical trial ongoing

pCR, pathological complete remission; ER, estrogen receptor.

These second-generation anti-HER2 preoperative studies were initiated concurrently or prior to their companion registration adjuvant trials, and, at this time, the results of the much larger adjuvant studies of lapatinib plus trastuzumab (ALTTO; NCT00490139) and pertuzumab plus trastuzumab (Aphinity; NCT01358877) have not yet been reported. If these adjuvant studies are positive and confirm the findings from the preoperative studies mentioned here, it would strongly support that pCR in the preoperative setting is a surrogate marker of disease-free survival and overall survival in HER2-positive breast cancer.

Finally, the role of endocrine therapy in combination with anti-HER2 therapy needs to be addressed in patients with HER2-positive and HR-positive tumors for a number of reasons. First, as mentioned above, the pCR rate in patients with HR-positive tumors is lower than in patients with HR-negative tumors. For example, the pCR rates of the chemotherapy- and endocrine-free trastuzumab and pertuzumab group of the NeoSphere trial were 5.9% and 27.3% in patients with HR-positive and HR-negative tumors, respectively. This data clearly indicates that the different responses according to HR status is an intrinsic characteristic of tumors and not just due to the known differential effect of chemotherapy in HR-positive and HR-negative disease. Second, a recently reported pilot study known as TBCRC006 suggests that combined endocrine and HER2 therapy is highly effective in the preoperative setting (45). In this study, 66 patients with primary HER2-positive breast cancer were treated with trastuzumab and lapatinib without chemotherapy for 12 weeks in the neoadjuvant setting. Patients with estrogen receptor (ER)-positive disease also received endocrine therapy. Of note, the study population had particularly poor prognostic features with 52% of patients aged 50 or below at diagnosis, and 62% of patients with stage III disease (i.e., >5.0 cm). The study reported an overall pCR rate of 27% without chemotherapy (HR+ = 21%; HR– = 36%). The high pCR rate in patients with HR-positive disease treated with dual HER2 blockade in combination with endocrine therapy in the TBCRC006 trial was 3.5-fold higher than the pCR rate in the NeoSphere chemotherapy- and endocrine-free group (21.0% vs. 5.9%) and more similar to the pCR rates of HR-negative tumors treated with trastuzumab/pertuzumab alone (36.0% in TBCRC006 and 27.3% in NeoSphere) or the pCR rates of HR-positive tumors treated with trastuzumab/pertuzumab and docetaxel (26.0%). Because pCR after endocrine therapy alone or dual HER2 blockade alone is an infrequent event in HER2-positive/HR-positive disease, the 21.0% pCR rate after dual HER2 blockade and endocrine therapy should be interpreted as a confirmation of the cross-talk between HER2 and the estrogen receptor as was elegantly shown by the same authors and others in preclinical models.

Anti-Angiogenic Agents

The role of the antivascular endothelial growth factor antibody bevacizumab has been studied in two large preoperative trials. The GeparQuinto study randomized 1,948 patients to conventional preoperative chemotherapy with epirubicin and cyclophosphamide with or without concomitant bevacizumab (46). Overall, the improvement of pCR was modest with a pCR rate of 14.9% with epirubicin and cyclophosphamide followed by docetaxel and 18.4% with epirubicin and cyclophosphamide followed by docetaxel plus bevacizumab (odds ratio with addition of bevacizumab, 1.29; 95% CI, 1.02–1.65; p = .04); however, the corresponding rates of pathological complete response were 27.9% and 39.3% among 663 patients with triple-negative tumors (p = .003) while patients with hormone-receptor–positive tumors benefitted less. Another large study, NSABP B40, randomized 1,206 patients to receive a series of anthracycline and taxane-based chemotherapy combinations with and without bevacizumab (29). The addition of bevacizumab significantly increased the rate of pathological complete response in the breast, from 28.2% to 34.5% (p = .02). When the rate of pathological complete response was examined according to hormone-receptor status, the effect of bevacizumab was more pronounced in the hormone-receptor–positive subset (15.1% without bevacizumab vs. 23.2% with bevacizumab; p = .007), with a weaker effect in the hormone-receptor–negative subset (47.1% without bevacizumab vs. 51.5% with bevacizumab; p = .34). There was an increase in the rate of pathological complete response in the breast and nodes with bevacizumab therapy, but the difference in the overall cohort was not significant (23.0% without bevacizumab vs. 27.6% with bevacizumab; p = .08).

The results of these two studies have to be analyzed in the context of the recently reported bevacizumab adjuvant phase III study BEATRICE that failed to show that bevacizumab improved disease-free survival in the postoperative setting (47). BEATRICE randomized 2,500 patients with TNBC to receive ≥4 cycles of chemotherapy alone or with the addition of bevacizumab for 1 year. The 3-year disease-free survival rate was 82.7% in the control group and 83.7% in the bevacizumab group (HR = 0.87; 95% CI, 0.72–1.07; p = .18).

Taken together, there are two positive preoperative studies and a large adjuvant negative study with the same anti-angiogenic agent. From the patient care viewpoint, the results of the adjuvant study prevail, and the use of bevacizumab in this setting should not be considered outside clinical trials. However, it is important to try to interpret the underlying reasons for the discrepancy. One potential explanation is that with bevacizumab, as with other anti-angiogenic agents, there is an initial response followed by the rapid development of resistance due to the activation of additional angiogenic pathways. This rapid development of acquired resistance has been well documented in experimental models (48) and may also explain the increased response rate observed in the trials in the metastatic setting that does not correlate with improved disease-free survival. The implication of this hypothesis is that several anti-angiogenic pathways would need to be inhibited at the same time in order to achieve a durable clinical benefit. The other potential explanation is that the results from the preoperative studies were not robust enough in addition to the lack of consistency between the two studies of the subgroups of patients that derived clinical benefit. For example, in GeparQuinto, the benefit was seen in the TNBC tumors, whereas in the NASBP study, the benefit was almost restricted to the HR-positive subgroup. Furthermore, as will be discussed in the next section, we do not know yet what magnitude in the improvement of pCR correlates with true clinical benefit.

SIGNIFICANCE OF PATHOLOGICAL COMPLETE REMISSION

One of the limitations of adjuvant chemotherapy clinical trials is that it does take a long time to be able to document the presence of clinical benefit. In contrast, preoperative trials may allow for an earlier readout of clinical benefit by documenting responses to therapy in the tumors. While monitoring clinical response has been proven to be challenging for a variety of reasons (49), the documentation of the absence of invasive tumor at the time of surgery, also known as pathological complete remission (pCR), is a powerful indicator of the benefit of preoperative chemotherapy and

is associated with improved clinical outcomes. A potential concern, however, is that the definition of pCR has not been consistent among the clinical trials. For example, some trials have considered pCR to be the absence of both invasive and DCIS (ductal carcinoma in situ), while others have considered pCR as the absence of invasive cancer in the surgical specimen. Because the presence of residual ductal carcinoma in situ (DCIS) after preoperative therapy does not impact DFS or OS, pCR may not require the absence of DCIS. Also, some trials have considered pCR to be the absence of cancer in both the breast and lymph nodes, while others have considered pCR as the absence of cancer in the breast only. Because the presence of residual tumors in lymph nodes after preoperative therapy could impact DFS or OS, absence of cancer in both the breast and lymph nodes should be required for pCR. In March 2013, the FDA released a regulatory guideline defining pCR as "the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of preoperative systemic therapy (i.e., ypT0ypN0 in the current AJCC staging system)."

Overall, pCR has been shown to be a strong predictor of improved disease-free and overall survival. We recently conducted a systematic review of published preoperative chemotherapy studies and found that pCR after preoperative chemotherapy was associated with significantly improved survival across the various breast cancer subtypes (50). While HR-positive tumors were less likely to achieve pCR compared to triple-negative tumors, when present, pCR was associated with significantly improved outcomes. Another large meta-analysis based on the pooling of individual patient data (n = 12,993) from 12 preoperative randomized controlled trials recently reported similar results (51). The authors of the working group of investigators, collectively known as the Collaborative Trials in Neoadjuvant Breast Cancer (CTNeoBC), reported that pCR was a strong predictor of improved DFS (HR = 0.48; p = <0.001) and OS (HR = 0.36; p = <0.001). The positive association between pCR and outcomes was seen for all the three breast cancer subtypes: HR-positive (HR = 0.49; p <.001), HER2-positive (HR = 0.39; p <.001), and TNBC (HR = 0.24; p <.001). For HR-positive tumors, the association was stronger for grade 3 tumors (HR = 0.27; p <.001) than grade 1 or 2 tumors (HR = 0.63; p = .07). In the meta-analyses, the magnitude of pCR improvement that predicts long-term clinical benefit could not be established.

ROLE IN IDENTIFICATION OF PREDICTIVE BIOMARKERS

Besides quick and efficient assessment of therapeutic efficacy using pCR as an endpoint, the preoperative setting also provides an ideal opportunity to identify predictive biomarkers of response and assess pharmacodynamic effects of individual agents.

A randomized two-group study design, similar to the NeoALLTO study design (41), could be used to achieve these objectives and is outlined in Figure 54-2. In such a preoperative trial, eligible women with biopsy-proven invasive breast cancer (T2 or higher) are randomized to receive the novel targeted therapy (experimental group) or standard targeted therapy such as trastuzumab (control group). A short lead-in phase with mandatory biopsy is built in to facilitate pharmacodynamic evaluation of the targeted therapy. After this "biological window," patients continue on the same targeted therapy plus standard chemotherapy, such as weekly paclitaxel for 12 weeks, up to definitive surgery. The primary endpoint of the trial is a difference in the rate of pCR. Such a study design has the potential to answer multiple questions rather quickly. For example, midtreatment research biopsies could be built in to identify early prediction of drug efficacy similar to those used for early response to preoperative endocrine therapies (52). Noninvasive functional imaging modalities such as PET (positron emission tomography)

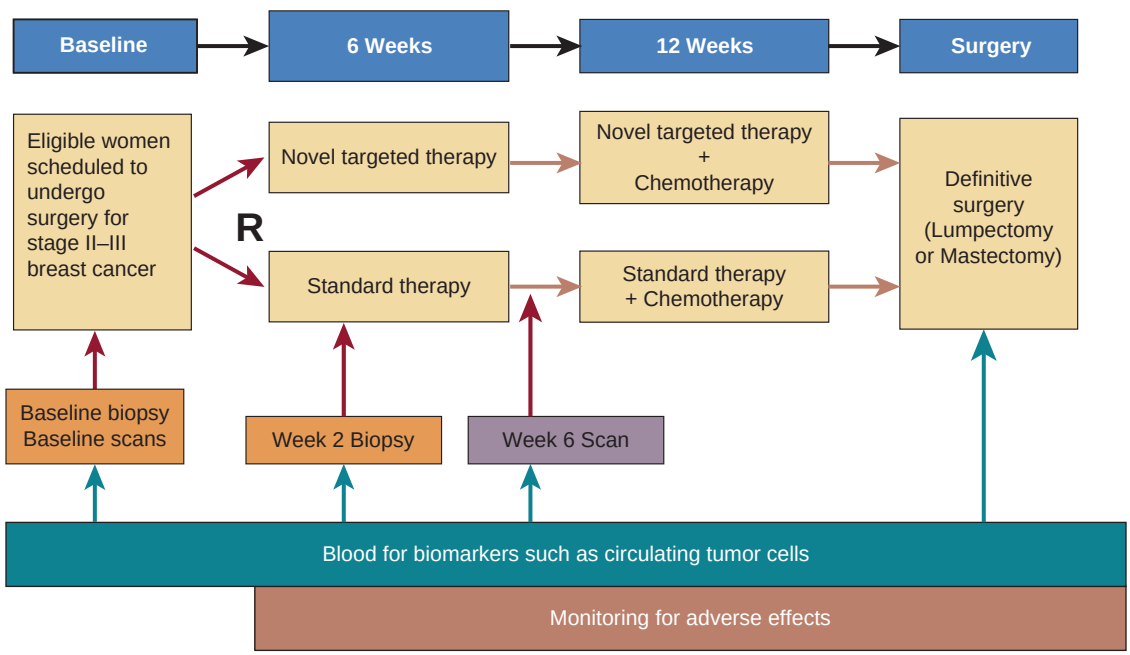

FIGURE 54-2 Schema of a clinical trial evaluating a novel preoperative therapy. MDACC, MD Anderson Cancer Center, USA; MCI, Milan Cancer Institute, Italy; LABC, locally advanced breast cancer.

scans could be incorporated to identify potential pharmacodynamic effects and early prediction of response. Similarly, blood can be collected to check for serum biomarkers such as circulating tumor cells. Besides estimating pCR, the surgical specimen could be analyzed for changes in various biomarkers such as downstream effectors and activators of compensatory pathways. Thus, such a preoperative study design provides an ideal setting for biomarker identification and evaluation of efficacy.

ROLE IN ACCELERATED APPROVAL OF NOVEL DRUGS

The traditional drug model of taking drugs from phase I to phase II to phase III studies is slow, inefficient, and expensive. It takes an average of 10 years from phase I to FDA approval (53). The unselected patient population requires large-scale trials to see any treatment benefit. Furthermore, the early testing of new agents is usually done in heavily pretreated patients with metastatic cancer. This is not optimal as these tumors may have already evolved into high-resistance clones. Testing in the adjuvant setting takes a long time to document the presence of clinical benefits and is an inefficient model for drug development.

Preoperative trials could be potentially used for drug approval purposes. In this regard, in 2012, the FDA stated that they would be willing to consider randomized trials of preoperative breast-cancer treatment for an accelerated-approval submission (54). A randomized trial in this setting, if adequately powered, could both support accelerated approval of a drug on the basis of substantial improvement in the pathological complete response rate and, with further follow-up, provide data on potential improvements in disease-free and overall survival to establish clinical benefit. Demonstration, with mature data, of a clinically and statistically significant improvement in disease-free or overall survival would still be needed to fulfill the requirements for regular approval. The advantages in the setting of preoperative studies would be many. First of all, preoperative studies are faster, require far fewer patients, and are less costly than large adjuvant studies. The current data available with chemotherapy in TNBC and with anti-HER2 agents in HER2-positive disease strongly support that pCR is a good correlate of disease-free and overall survival. However, an important aspect of this approach would be the amount of safety data required because, unlike in the advanced disease setting, these are patients with curable disease, and there is concern about potential long-term toxicities.

SUMMARY AND FUTURE DIRECTIONS

Preoperative chemotherapy requires careful patient selection and a multidisciplinary care set up. Clear indicators for preoperative chemotherapy are locally advanced and inflammatory breast cancer (Table 54-3). This treatment modality also needs to be considered in the case of large operable tumors that would require a mastectomy. In the case of smaller tumors, outside of a clinical trial, this option has no clear benefit to adjuvant chemotherapy and both approaches may be used interchangeably for tumors small enough to be candidates for breast conserving surgery upfront. On the other hand, clear indicators not to pursue preoperative chemotherapy are multicentric tumors that would require a mastectomy regardless of the benefit of chemotherapy and those small tumors with limited tissue for full anatomic and molecular characterization.

TABLE 54-3

Recommendations for Neoadjuvant Chemotherapy for Breast Cancer

Recommendation	*Indication*
Absolute recommendation	1. Locally advanced breast cancer 2. Inflammatory breast cancer
Relative recommendation	1. T2–T3 tumors with goal of breast conservation therapy 2. Alternative to adjuvant therapy
Not recommended	1. Small (T1N0), HR+/HER-2 negative, grade 1–2 tumor 2. Multicentric tumor

Preoperative chemotherapy requires a fully integrated multidisciplinary team that includes an oncologist, a breast surgeon, a radiation oncologist, a pathologist, and a radiologist who should coordinate care, monitor therapy, and coordinate the different sequential therapies. Only in a setting with a seasoned multidisciplinary team should this approach be contemplated. A standard preoperative chemotherapy regimen should ideally include an anthracycline and taxane. The continuation of the same regimen beyond the standard number of cycles is not recommended, and sequential use of cross-resistant therapy is preferred over a longer duration of the same regimen. Anti-HER2–based therapy should be strongly considered for patients with HER2-positive breast cancer.

In the future, preoperative trials testing targeted therapy combinations with or without chemotherapy could change the landscape of localized breast cancer management. A number of preoperative trials investigating novel drugs such as PI3K inhibitors (NeoPHOEBE, NCT01816594), PARP inhibitors (NeoPARP, NCT01204125), multikinase inhibitors such as sunitinib, pazopanib (NCT00849472, NCT00887575), and IAP (Inhibitor of Apoptosis Protein) antagonists such as LCL161 (NCT01617668) are ongoing. The results of these trials will help establish the role of targeted therapy regimen combinations with less chemotherapy or no chemotherapy, representing a paradigm shift in the management of breast cancer.

MANAGEMENT SUMMARY

- Preoperative chemotherapy, also referred to as neoadjuvant chemotherapy or primary systemic therapy, is the administration of chemotherapy before surgery.
- Preoperative chemotherapy is the preferred therapeutic modality for locally advanced (T3 or T4) and inflammatory breast cancer. Preoperative chemotherapy can be used to downstage tumors and facilitate breast conservation in women who would have otherwise needed a mastectomy.
- A standard preoperative chemotherapy regimen should include a taxane. In addition, anthracyclines should be considered. For HER2-positive tumors, incorporation of anti-HER2–directed therapy, such as trastuzumab, is strongly recommended.

- Patients receiving preoperative chemotherapy should be followed at regular intervals for monitoring response. Even among patients who have a complete clinical response to preoperative chemotherapy, definitive breast surgery after chemotherapy is recommended as there could be microscopic residual disease. The absence of any residual invasive tumor in the surgical specimen is referred to as pathological complete remission (pCR) and is associated with good prognosis.
- Preoperative clinical trials are increasingly being used to evaluate novel therapies. In the coming years, preoperative targeted therapy combinations with or without chemotherapy will be preferentially used to manage localized breast cancer.

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CHAPTER 55

Preoperative Endocrine Therapy for Operable Breast Cancer

Ian E. Smith

CHAPTER CONTENTS

INTRODUCTION

Preoperative estrogen therapy was first described more than 50 years ago for postmenopausal women with large and sometimes locally advanced breast cancers (1). In the modern era of breast cancer management, its use has been overshadowed until recently by preoperative chemotherapy. Today, however, the potential of neoadjuvant endocrine therapy is being increasingly exploited, not simply to downstage large cancers to allow less extensive surgery but also as a scientific tool, using molecular markers to predict outcomes both in adjuvant trials and for the individual patient. This chapter will address both the clinical and research potential of the preoperative endocrine approach to operable breast cancer.

PREOPERATIVE TAMOXIFEN

From the 1980s onward, tamoxifen was evaluated before, or as an alternative to, surgery in a series of small studies usually involving elderly women. Most of these studies reported response rates of over 50% (2–4). In one of the larger trials, carried out by the Cancer Research Campaign in the UK, tamoxifen alone was compared with surgery and tamoxifen in 381 women aged 70 or over. In the initial analysis after 34 months follow-up, there were no significant differences in survival or quality of life between the two approaches (5). A significantly higher local regional relapse rate was, however, seen in the tamoxifen alone group (23% vs. 8%), and, in a subsequent later analysis, both overall mortality and breast cancer mortality were worse with tamoxifen alone (hazard ratio of 1.29 and 1.68, respectively) although these differences took over 3 years to emerge (6).

In contrast, a similarly designed Italian multicenter trial involving 474 patients over 70 years of age did not show any difference in overall survival or breast cancer survival with a median follow-up of 18 months, but there was a significantly higher incidence of locoregional recurrences in the tamoxifen alone group (p = .0001) (7).

These pioneering trials in elderly patients urged caution in using preoperative endocrine therapy instead of surgery but nevertheless showed the approach to be a reasonable one for patients unfit for surgery.

THE MODERN ERA: PREOPERATIVE AROMATASE INHIBITORS VERSUS TAMOXIFEN

Over the last decade, the aromatase inhibitors (AIs) anastrozole, letrozole, and exemestane have established themselves as having modestly superior long-term outcomes to

tamoxifen as adjuvant therapy for early breast cancer in a series of adjuvant trials described elsewhere in this book.

These results have been largely mirrored by smaller neoadjuvant trials with short-term clinical and biological endpoints. The first of these, a very small trial comparing vorazole (a now discontinued nonsteroidal third-generation inhibitor) with tamoxifen, unsurprisingly showed no significant difference in outcome (8), but it was one the first to compare the effects of treatment on molecular markers within the tumor (see below).

Letrozole versus Tamoxifen

There has been one multinational double-blind randomized trial (PO24) comparing preoperative letrozole 2.5 mg with tamoxifen for 4 months prior to surgery (9). This involved 337 postmenopausal women with estrogen receptor (ER) or progesterone receptor (PgR)-positive cancers, defined by at least 10% nuclear staining. All patients would have otherwise required mastectomy at entry to the trial or were considered inoperable (14%). The overall clinical response rate, the primary endpoint, was significantly higher for letrozole than for tamoxifen (55% vs. 36%; $p = .001$). The median time to response was 66 days for letrozole and 70 days for tamoxifen. Progressive disease during treatment was seen with 12% of patients treated with letrozole and 17% with tamoxifen. Letrozole was also more effective than tamoxifen when the response rate was determined by ultrasound (35% vs. 25%; $p = .0042$) and by mammography (34% vs. 16%; $p = .001$).

The main secondary endpoint of the trial was breast conservation, and significantly more breast-conserving surgery was achieved with letrozole than with tamoxifen (45% vs. 35%; $p = .022$). Pathological complete remission (pCR) in the primary breast lesion was seen in only 2 patients treated with letrozole and 3 with tamoxifen. Only 2 of these 5 patients with pCRs had no involved nodes at surgery.

In a further analysis of the same study, ER and PgR expression were re-assessed in a central laboratory, and 12% of patients were found to have tumors that were both ER and PgR-negative (10). In patients whose tumors were confirmed ER or PgR-positive, the response rate to letrozole was 60% compared with 41% for tamoxifen ($p = .004$), and 48% versus 36%, respectively, underwent successful breast-conserving surgery ($p = .036$).

In this analysis ER and PgR were quantified using the Allred scoring system in which an intensity score (range, 1–3) is added to a frequency score (range, 1–5) (11). Letrozole response rates were numerically superior to tamoxifen for all ER Allred scores from 3 to 8; furthermore, responses to letrozole were seen in all Allred scores between 3 and 8, whereas responses were only seen in tamoxifen for scores between 6 and 8. Based on this, the authors suggested that letrozole might be more effective than tamoxifen in patients whose tumors show relatively low ER expression, but it is important to note that the numbers were small in each of these Allred groupings and no definite conclusions should be drawn.

Anastrozole versus Tamoxifen

There have been 2 multinational double-blind trials comparing preoperative anastrozole 1 mg daily with tamoxifen 20 mg daily for 12 weeks prior to surgery in postmenopausal women with ER-positive breast cancer.

The IMPACT (IMmediate Preoperative Anastrozole, tamoxifen or Combined with Tamoxifen) trial compared anastrozole with tamoxifen or with both in combination given for only 12 weeks (in contrast to 16 weeks for PO24 above) (12); the trial was designed to be the preoperative equivalent of the adjuvant ATAC trial described elsewhere. The main clinical aim was to compare the efficacies of these treatments in terms of response and in downstaging to avoid mastectomy. An important further aim, however, was to determine whether short-term surrogate endpoints of response could be identified to predict for long-term outcome in the adjuvant ATAC trial; these included clinical changes after 12 weeks or biological changes in proliferation assessed by the proliferation marker Ki-67 after 2 and 12 weeks. For this reason, postmenopausal patients with smaller breast cancers not necessarily requiring mastectomy were also included, in contrast to the preoperative letrozole trial described above. This trial involved 330 patients with confirmed invasive histology and ER positivity on core needle biopsy. Median age was 73 years, median tumor size was 4 cm for each of the three groups, and tumors were confirmed in a central reference laboratory as ER-positive in 98% of cases. Objective clinical response rates by caliper measurement for anastrozole, tamoxifen, and the combination were 37%, 36%, and 39%, respectively, on an intent-to-treat basis, and none of these differences was significant. Ultrasound response rates were 24%, 20%, and 28%, respectively; again, none of these differences was significant. Progressive disease during treatment occurred in only 9%, 5%, and 5% of patients respectively.

A subgroup of 124 patients was assessed by the surgeon as requiring mastectomy at baseline. In these, 46%, 22%, and 26% were deemed to have achieved tumor regression sufficient to allow breast-conserving surgery after treatment with anastrozole, tamoxifen, and combination therapy, respectively. The improvement with anastrozole compared with tamoxifen was statistically significant with an odds ratio (OR) of 2.94 ($p = .03$).

There was no significant difference between the tamoxifen and combination groups.

An important secondary endpoint in the IMPACT trial was the reduction in proliferation as measured by Ki-67 staining after preoperative treatment. This was significantly reduced by all three treatments after 2 and 12 weeks, anastrozole by 76% and 82%, tamoxifen by 60% and 64%, and the combination by 65% and 64% (13). Change after 2 weeks correlated with the change after 12 weeks. The decrease with anastrozole was significantly greater than that with tamoxifen, as assessed by geometric mean ratios of the changes in Ki-67 after 2 weeks' treatment ($p = .04$) and again after 12 weeks' ($p = .001$), but there were no significant differences between tamoxifen and the combination. The changes in Ki-67 after only 2 weeks of treatment therefore predicted for long-term differences in relapse-free survival in the adjuvant ATAC trial, suggesting that change in proliferation as measured by Ki-67 might be a short-term surrogate for predicting differences in long-term outcome between different endocrine therapies in adjuvant trials.

This possibility is reinforced in an earlier and much smaller preoperative trial comparing vorozole with tamoxifen, which found a similar but nonsignificant trend in favor of an aromatase inhibitor, with mean drops in Ki-67 of 58% and 43% for vorozole and tamoxifen, respectively, after 2 weeks' treatment (20).

A statistically significant correlation was found between Ki-67 reduction after 2 weeks and response in the IMPACT trial, but this was not seen with Ki-67 reduction at 12 weeks: A weakly significant relationship was seen between the percentage of tumor shrinkage and change in Ki-67 (13).

In the second preoperative anastrozole trial, PROACT (PReOperative Anastrozole Compared with Tamoxifen), also multicenter and double-blind, 451 postmenopausal women with operable or locally advanced but potentially operable

(T2-4b) hormone receptor–positive breast cancers were randomized to anastrozole 1 mg or tamoxifen 20 mg for 12 weeks prior to surgery (14). As in the IMPACT trial, patients with small breast cancers appropriate for breast-conserving surgery were eligible for entry. In contrast to other trials, concomitant chemotherapy was also allowed and was given to 29% of patients on anastrozole and 32% on tamoxifen. Mean age was 67 in both groups, and mean ultrasound tumor diameter was 3.6 cm. Overall ultrasound response, the primary endpoint, was 40% for anastrozole and 35% for tamoxifen (p = .29). Clinical response by caliper measurement was 50% and 46%, respectively (p = .37). Chemotherapy was clearly confounding here, and in the 314 patients treated with endocrine therapy alone without chemotherapy, ultrasound and clinical response rates for anastrozole and tamoxifen, respectively, were 36% versus 27% (p = .07) and 50% versus 40% (p = .08).

In the 262 patients treated with endocrine therapy alone without chemotherapy who would have required mastectomy or had locally advanced disease at baseline, surgical improvement (inoperable to mastectomy or mastectomy to breast-conserving surgery) was deemed feasible in 47% after anastrozole compared with 38% after tamoxifen (p = .15) and actually occurred in 43% versus 31% (p = .04).

Combined IMPACT and PROACT Results

A common population of 535 patients treated with anastrozole or tamoxifen alone was derived from the combined results of the IMPACT and PROACT trials, with respective caliper-measured response rates of 45% for anastrozole and 36% for tamoxifen (p = .052) (15). Of these, 344 were deemed to require mastectomy or had inoperable cancer at baseline, representing a comparable group to the PO24 letrozole trial (21), and in this subgroup the clinical response rate was significantly higher for anastrozole than for tamoxifen (47% vs. 35%; OR 1.65; p = .026). In this group, improvement in feasible surgery was 47% and 35% (OR 1.67; p = .021) and in actual surgery 43% and 31% (OR 1.70; p = .019), respectively.

Exemestane versus Tamoxifen

Preoperative exemestane has also been shown to be active in achieving clinical responses and downstaging to avoid mastectomy (16), but so far only one small randomized trial, comparing preoperative exemestane with tamoxifen, has been reported. Seventy-three postmenopausal women with hormone receptor–positive status were randomized to receive exemestane 25 mg or tamoxifen 20 mg daily for 3 months before surgery (17). Clinical objective response rates were reported as 89% for exemestane compared with 57% for tamoxifen (p = .05), including complete clinical remission rates of 14% and 11%, respectively (ns). Ultrasound response rates were 70% and 41% (ns), and breast conservation rates 39% versus 11%, respectively (p = .05). Two pathological complete remissions were found with exemestane and one with tamoxifen.

The authors reported without details that responses were more likely with higher levels of estrogen-receptor expression.

AIs versus Tamoxifen in HER2-Positive Breast Cancers

In the PO24 trial, preoperative letrozole was markedly superior to tamoxifen in the small subgroup of 36 patients with HER2-positive cancers (88% vs. 21%; p = .004) (10), and a similar marked numerical difference was seen for anastrozole over tamoxifen for the 34 patients with centrally confirmed HER2-positive cancer in the IMPACT trial (58% vs. 22%; p = .09) (10,12). These differences were not, however, supported by subsequent results from the equivalent large adjuvant trials BIG 1-98 and ATAC (see Chapter 43), neither of which showed an increased benefit for AIs over tamoxifen compared with cancers not overexpressing HER2. These results therefore emphasize the potential pitfalls of extrapolating clinical preoperative data as a surrogate marker for long-term outcomes. A possible explanation for this discrepancy emerged with molecular marker studies from the IMPACT trial, described later in this chapter.

Response to Preoperative AIs and Body Mass Index (BMI)

There are some data suggesting that a high body mass index (BMI) may be associated with inferior outcome after adjuvant anastozole. In a recent Japanese study involving 109 patients treated with preoperative exemestane, a low BMI was paradoxically associated with a lower objective response rate (ORRs were 21.7% in low BMI, 56.0% in intermediate BMI, and 60.6% in high BMI, respectively; p = .01) (18). In a multivariate analysis, a low BMI was an independent negative predictor of clinical response. The authors do not postulate an explanation for these paradoxical results.

Conclusions from Neoadjuvant Trials Comparing AIs with Tamoxifen

Although these trials were relatively small compared with large adjuvant trials, the balance of evidence from them shows that the AIs are more effective clinically than tamoxifen in achieving objective responses and in downstaging to avoid mastectomy or to convert inoperable to operable cancers. AIs should therefore be considered the first-line preoperative endocrine therapy of choice for postmenopausal patients with ER-positive breast cancers.

AROMATASE INHIBITORS VERSUS OTHER ENDOCRINE AGENTS

Anastrozole versus Fulvestrant

A French trial, UNICANCER CARMINA 02, randomized 116 postmenopausal women with T2–T4, N0–N3, ER-positive, HER2-negative breast cancers to preoperative anastrozole 1 mg daily or fulvestrant 500 mg on Day 1, 15, and 29 and then 4 weekly, for 4 to 6 months. Clinical response rates at 4 months were 54% for anastrozole and 44% for fulvestrant and at 6 months 53% and 35% (a smaller number were treated to 6 months), respectively. These differences were not significant (19).

IS THERE A BEST PREOPERATIVE AROMATASE INHIBITOR?

The preoperative efficacy of the 3 currently used aromatase inhibitors have been compared in the Z1031 trial, a randomized phase 2 study in which 377 postmenopausal women with stage 2–3 ER-rich (Allred score 6–8) breast cancer were randomized to receive preoperative exemestane, letrozole, or anastrozole, with the aim of choosing which should go ahead for further investigation. Clinical response, the primary endpoint, was achieved in 63% (n = 78) patients on exemestane, 75% on letrozole (n = 95), and 69% (n = 85) on anastrozole (20). Letrozole and anastrozole went forward for further biomarker study on the basis of achieving the

highest scores. This analysis included comparison of the change in Ki-67 after treatment compared with baseline, but no significant differences emerged between the three treatments: The geometric mean percentage change in Ki-67 for anastrozole was 78% (standard error of the mean [SEM], 4%), for exemestane, 81.2% (SEM, 3.5%), and for letrozole, 87.1%. The authors concluded that large adjuvant trials comparing these agents were therefore unlikely to find significant differences in outcome (see below). Surgical outcomes were markedly improved in all 3 groups with overall 83% of those initially marginal for breast conservation and 51% of those initially deemed candidates for mastectomy only achieving breast conservation after preoperative treatment. No significant differences in surgical outcome were detected between the 3 aromatase inhibitors. Clinical response and surgical outcomes were similar for Luminal A and Luminal B tumors.

AROMATASE INHIBITORS IN COMBINATION WITH OTHER AGENTS

Letrozole and the mTOR Inhibitor Everolimus

There are good experimental data to show that cross-talk between the ER and the phosphoinositide-3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathways is a mechanism of resistance to endocrine therapy. Preclinical models have shown that blockade of both pathways can enhance antitumor activity (21). A phase 2 randomized trial of 4 months of letrozole in combination with everolimus (RAD001), an oral mTOR inhibitor, in a dose of 10 mg/day, versus letrozole alone was carried out in 270 postmenopausal women with operable ER-positive breast cancer. Response rate by clinical palpation, the primary endpoint, was significantly higher at the preplanned, one-sided 0.1 level in the everolimus group than with letrozole alone (68.1% vs. 59.1%; $p = .062$). An antiproliferative response, as defined by a reduction in Ki-67 expression to natural logarithm of percentage positive Ki-67 of less than 1 at day 15, occurred in 52 (57%) of 91 patients in the everolimus group compared with 25 (30%) of 82 patients in the placebo group ($p = .01$) (22). Marked downregulation of phospho-S6, a downstream intermediary of mTOR, occurred only in the everolimus group.

These positive results, particularly with respect to differences in Ki-67 suppression, prompted a subsequent phase 3 trial (BOLERO 1), which confirmed the clinical superiority of the everolimus combination; this trial is described in detail elsewhere in this book.

Anastrozole and Gefitinib

Preclinical evidence suggests that concurrent blockade of both estrogen-receptor and EGFR-signaling pathways might enhance response to endocrine therapy (23). Gefitinib is an orally active EGF tyrosine kinase inhibitor shown to suppress the growth of MCF7 cells otherwise resistant to estrogen withdrawal (24). This hypothesis was tested in a preoperative endocrine therapy trial in which 206 postmenopausal women with hormone receptor–positive early breast cancer received anastrozole daily for 16 weeks and were randomized in a 2:5:5 ratio to receive in addition gefitinib 250 mg daily orally for 16 weeks versus placebo orally for 2 weeks and then gefitinib for 14 weeks versus placebo for 16 weeks (25). The trial was designed to see whether tumors that did not show significant Ki-67 suppression after 2 weeks (and by implication were relatively resistant to endocrine therapy) could have this resistance reversed by the addition of gefitinib. There was no significant difference in the mean change in Ki-67 with anastrozole and gefitinib versus anastrozole alone between baseline and 16 weeks, baseline and 2 weeks, or between 2 and 16 weeks. Forty-eight percent achieved clinical response with anastrozole and gefitinib versus 61% on anastrozole alone, and this nonsignificant trend in favor of anastrozole alone was reflected in the Ki-67 change at 16 weeks with reductions of 77.4% and 83.6%, respectively. In the PgR-positive subgroup, there was a significant difference in favor of anastrozole alone versus the combination (72% vs. 48%; $p = .03$), and this was consistent with the Ki-67 changes in this subgroup. This trial, using biological as well as clinical endpoints, therefore failed to demonstrate a benefit from the addition of gefitinib to anastrozole and, indeed, suggested the possibility of an adverse interaction. It demonstrates, however, the potential of preoperative studies to investigate therapies that might overcome endocrine resistance using Ki-67 as an endpoint.

Letrozole and Zoledronic Acid

In a German trial (FEMZONE), 168 postmenopausal patients with ER-positive early breast cancer were randomized to 6 months' treatment with neoadjuvant letrozole alone or in combination with zoledronate 4 mg every 4 weeks. Clinical overall response rates at 6 months were 54.5% compared with 69.2% (externally assessed). This numerical trend in favor of letrozole with zoledronic acid was, however, not statistically significant. Overall there was no difference in the number of patients requiring mastectomy after neoadjuvant treatment (15.6 vs. 15.2%, respectively) (26).

PREOPERATIVE ENDOCRINE THERAPY IN PREMENOPAUSAL WOMEN

In contrast to postmenopausal women, data are very limited on preoperative endocrine therapy in premenopausal women.

Recently, however, a Japanese group has reported on the primary analysis of the STAGE (Study of Tamoxifen or Arimidex combined with Goserelin Acetate to Compare Efficacy and Safety) trial to compare the efficacy of anastrozole with goserelin versus tamoxifen with goserelin for 24 weeks preoperatively in 197 premenopausal women with ER-positive and HER2-negative early breast cancer. The clinical complete or partial response rate in the anastrozole group (70.4%) was significantly higher than in the tamoxifen group (50.5%) ($p = .04$) (27). Overall response was also higher for the anastrozole group when response was measured by ultrasound, MRI, or CT. Tumor responses increased gradually throughout the 24-week treatment period for both treatment groups.

The mean Ki-67 index at baseline and again at week 24 was 21.9% and 2.9% for the anastrozole group compared with 21.6% and 8% for the tamoxifen group. The difference in Ki-67 at 24 weeks was significantly greater in favor of anastrozole (estimated ratio of reduction 0.35 $p < .0001$).

This significantly improved clinical response rate for anastrozole and goserelin versus tamoxifen and goserelin reflects results in postmenopausal patients with preoperative letrozole versus tamoxifen (9) but not anastrozole in the IMPACT study (12), as described above. The significantly greater Ki-67 suppression with anastrozole reflects similar findings in the postmenopausal preoperative IMPACT trial described above (13).

These results are encouraging and indeed are better in terms of response rate than for the postmenopausal preoperative endocrine therapy trials. They do not, however, reflect my own albeit limited experience with preoperative endocrine therapy in premenopausal women,

where objective clinical responses have been uncommon. Likewise, the significantly improved short-term benefit with anastrozole and goserelin in terms of both response and Ki-67 suppression is not so far reflected in the ABCSG-12 adjuvant trial, which has so far failed to show any significant difference in long-term outcomes between anastrozole and goserelin versus tamoxifen and goserelin (28). Nevertheless, these data should serve as a stimulus for further preoperative endocrine therapy trials in premenopausal women in downstaging to avoid mastectomy where chemotherapy is contraindicated for whatever reason and in the planning of subsequent adjuvant trials (see below).

Current dogma based on the SWOG INT-0100 study is that premenopausal women should not be given adjuvant tamoxifen concurrently with chemotherapy (29). A retrospective preoperative endocrine therapy analysis challenges this belief, however. A group of 119 premenopausal women with locally advanced breast cancer treated with preoperative letrozole plus GnRH analogue (GnRH-a) administered concurrently with preoperative chemotherapy was compared with a matched group of 95 controls given only preoperative chemotherapy (and adjuvant endocrine therapy); the pCR rate was 5.0% in those given GnRH-a compared with only 1.1% in the control group. Likewise, significantly greater Ki-67 suppression was observed in patients receiving combined chemo endocrine therapy compared with controls ($p = .003$). Five-year disease-free survival (DFS) was 78 versus 41% in the study and in the control group, respectively (adjusted HR 0.46; 95% CI, 0.27–0.79; $p = .0047$) (30). These data argue for further clinical studies in this field to challenge current dogma.

PREOPERATIVE ENDOCRINE THERAPY VERSUS NONE

Many years ago, it was shown that noncurative surgery in a murine model was associated with serum growth factor stimulation of residual metastases that could be blocked by tamoxifen (and by chemotherapy) (31). More recently, it has also been shown that short-term preoperative endocrine therapy in the clinic for 2 weeks prior to surgery significantly reduces tumor cell proliferation in women with estrogen receptor–positive early breast cancer (32). There is therefore some experimental background to argue that preoperative endocrine therapy might improve long-term outlooks.

Curiously, only one clinical trial appears to have reported so far on this important issue. An Indian group randomized 976 eligible pre- and postmenopausal women with operable breast cancer to receive or not receive a single intramuscular injection of depot-hydroxyprogesterone 500 mg 5 to 14 days before surgery. There was no overall difference in the primary endpoint, disease free survival (73.9 vs. 70.2%) or overall survival (80.2 vs. 78.4%), but, in a pre-planned analysis of 471 women with node-positive disease, the progesterone-treated group had a significant improvement in 5 year DFS (65.3% vs. 54.7%; HR 0.72; $p = .02$) and OS (75.7% vs. 66.8%; HR 0.70; $p = .4$). In a post-hoc analysis, the effects of preoperative progesterone did not differ significantly according to menopausal status or estrogen receptor status. The authors considered their finding to be hypothesis-generating (33).

There are important caveats to this trial including why a benefit would also be seen in women with ER-negative tumors, and an uncertainty about the underlying mechanism of action of progesterone. Nevertheless, further trials are now clearly indicated in this important area, given the potential for improved long-term outcome with no increase in resources.

The question is being addressed in the much larger UK POETIC trial (Perioperative Endocrine Therapy-Individualizing Care) in which 4,000 postmenopausal women with ER-positive breast cancer have been randomized to 2 weeks preoperative and a further 2 weeks perioperative aromatase inhibitor therapy or not (Fig. 55-1). Accrual completes early in 2013. The primary endpoint is relapse-free survival (RFS), but the POETIC trial is also assessing whether Ki-67 and other molecular markers 2 weeks after the start of treatment will provide more accurate prognostic information than pre-treatment values (see below).

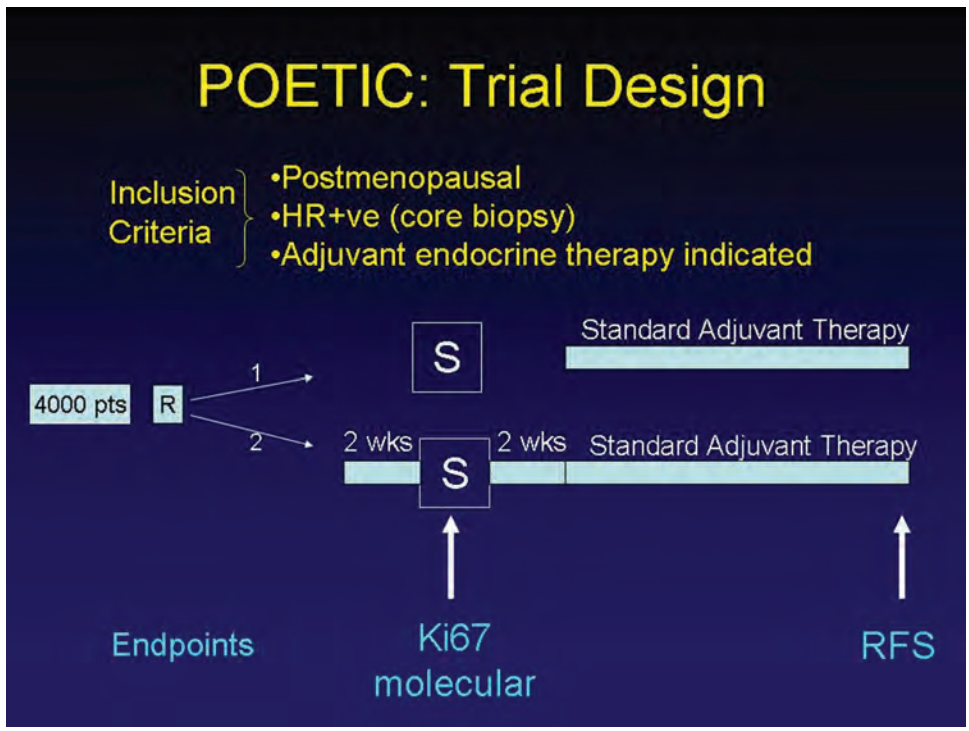

FIGURE 55-1 Schema for POETIC trial.

THE OPTIMAL DURATION OF PREOPERATIVE ENDOCRINE THERAPY

The main preoperative endocrine therapy trials described above have used treatment for 3 to 4 months prior to surgery. Yet the clinical response rate to anastrozole given for 12 weeks in our IMPACT trial was 37% (12,25) but was 61% in a subsequent trial by the same investigators where treatment was extended to 16 weeks (25), raising the possibility that longer duration might be more effective.

In a series of 182 consecutive postmenopausal patients with ER-rich breast cancers treated in Edinburgh with preoperative letrozole for 3 months or longer (63 of these continued letrozole beyond 3 months), the median reduction in clinical volume in the first 3 months was 52%, but similar reductions in median clinical volume were seen between 3 and 6 months (50%), 6 to 12 months (37%), and even between 12 and 24 months (33%) (34). The overall clinical response rate at 3 months was 69.8% of the original 182 patients, increasing to 83.5% with prolonged letrozole treatment. At 3 months, the number of women originally requiring mastectomy who became suitable for breast-conserving surgery was 60%, but this rose to 72% with more prolonged therapy. In this study, the median time to treatment failure had not been reached by 3 years.

A multicenter, prospective, longitudinal phase IV study involving 139 eligible postmenopausal patients with early breast cancer requiring mastectomy tried to establish the optimal duration of preoperative letrozole that would allow breast-conservation surgery (BCS). At study closure, 69% of patients were eligible for BCS. The median time to achieve a tumor response sufficient to allow BCS with neoadjuvant letrozole was 7.5 months (95% CI, 6.3–8.5 months) (35).

In the Japanese preoperative endocrine therapy study involving premenopausal patients described above, clinical responses for both the anastrozole plus goserelin and the tamoxifen plus goserelin groups continued to rise from 62.2% and 47.5%, respectively, at week 16 to 75.5% and 56.6%, respectively, at week 24 (27). In a small German study, 16 of 29 postmenopausal women with ER-positive breast cancer and clinical stage T2 or greater achieved a complete or partial response to preoperative letrozole after 4 months (55%), and 3 more subsequently achieved a partial or complete response between 4 and 8 months (final total 72%). Although all patients were initially candidates for mastectomy, 22 of 29 (76%) eventually managed conservative surgery (36).

In a phase 2 multicenter, open-label study addressing the same question, 70 postmenopausal patients over 65 years of age with a median age of 79 were given preoperative letrozole. In this study, 43 of 56 evaluable patients (77%) achieved an objective response with a median time to maximum response of 4.2 months (95% CI, 4.0–4.5), although 20 (37.1%) patients took 6 to 12 months to achieve a maximal response (37).

Finally, in a recent Italian study, so far presented only in abstract, 120 postmenopausal women were given neoadjuvant letrozole for 4, 8, or 12 months with overall clinical response rates of 50%, 85%, and 95%, respectively. These results are surprisingly high, as were the pathCR rates of 2.5%, 5%, and 17.5%, respectively (38), but they reinforce the point that longer treatment beyond 4 months is often more effective.

The optimal duration of preoperative endocrine therapy very likely varies for individual patients, but relapses within less than 12 months appear rare (34), and a pragmatic policy is to continue preoperative endocrine therapy in responding patients initially requiring mastectomy until downstaging is sufficient to allow conservative surgery.

PREOPERATIVE ENDOCRINE THERAPY VERSUS CHEMOTHERAPY

A Russian trial directly compared preoperative chemotherapy (doxorubicin 60 mg/m^2 and paclitaxel 200 mg/m^2 every 3 weeks in four courses) against AI endocrine therapy (exemestane or anastrozole for 3 months) in 239 postmenopausal women with hormone receptor–positive cancer (39). The primary endpoint, overall clinical response rate, was similar for each treatment (63% for chemotherapy, 67% for exemestane, and 62% for anastrozole). Rates of breast-conserving surgery were higher in the endocrine therapy group (33% vs. 24%; p = .058). The authors concluded that neoadjuvant endocrine therapy, with its low toxicity, was a reasonable alternative to chemotherapy in this elderly population.

In a more recent GEICAM Group trial, preoperative endocrine therapy with exemestane 25 mg daily for 24 weeks (combined with goserelin in premenopausal patients) was compared with chemotherapy (epirubicin 90 mg/m^2 plus cyclophosphamide 600 mg/m^2 for 4 cycles [cy] followed by docetaxel 100 mg/m^2 for 4 cy [EC-T]) in 95 postmenopausal patients defined as having immunophenotypical Luminal B breast cancer (ER+/PR+/HER2-/cytokeratin 8/18+ assessed in a central laboratory), operable stage T2 or 3. Adjuvant treatment was individualized. Clinical response rate, the primary endpoint, was 66% for chemotherapy and 48% for endocrine therapy (p = .07). Three patients on chemotherapy and none on endocrine therapy achieved a pCR (p = ns). Mastectomy rates were similar in both groups, at 49% and 35%, respectively (p = .18). An unplanned analysis based on Ki-67 levels showed similar clinical response rates in both groups in patients with low Ki-67 (<10%) (63% and 58%, respectively; p = .7), but patients with higher Ki-67 had a better response to chemotherapy (67% vs. 42%; p = .07). The authors concluded that a luminal immunophenotype was insufficient to identify patients who would not benefit from neoadjuvant chemotherapy (40).

These trials make the important point that for many postmenopausal patients preoperative endocrine therapy may have as high a chance of achieving a response as chemotherapy, but in the current era, when increasing emphasis is being placed on molecular markers including gene expression assays to select appropriate adjuvant therapies, the value of further direct comparative "one size fits all" trials of this type is doubtful.

HISTOLOGICAL EFFECTS OF PREOPERATIVE ENDOCRINE THERAPY

Pathological complete remissions (pCR) are increasingly used as an endpoint to predict long-term outcome following preoperative chemotherapy, but these are rare with preoperative endocrine therapy (9,12,17,41) and, as such, are of no prognostic or predictive value. Interestingly, and in contrast to chemotherapy, preoperative aromatase inhibitors have been reported as producing the histological feature of central scarring with a statistically significant correlation between central scarring and clinical tumor volume reduction (p = .034) (42). This observation requires validation; if confirmed, central scarring could be explored as a predictive endpoint for long-term outcomes.

PREOPERATIVE ENDOCRINE THERAPY TRIALS TO PREDICT LONG-TERM OUTCOMES IN ADJUVANT ENDOCRINE THERAPY TRIALS

Preoperative trials involve much smaller patient numbers than large adjuvant trials and have short-term primary endpoints (e.g., response rate versus disease-free survival). They therefore produce results much faster and at a fraction of the cost. It is attractive therefore to question whether they might predict for long-term outcomes in adjuvant trials, and, if so, they could therefore act as substitutes for such trials.

Some preoperative endocrine therapy trials have shown an excellent correlation between clinical response and subsequent long-term outcome in an adjuvant trial; examples described above include the PO24 trial, in which a superior response rate to letrozole correctly predicted long-term benefit for adjuvant letrozole over tamoxifen in the BIG 1-98 trial, and the preoperative everolimus trial, in which the marginally superior response rate of combined letrozole and everolimus over letrozole alone correctly predicted the improved results for the combination in the treatment of advanced disease shown in the BOLERO 2 (Breast Cancer Trials of Oral Everolimus-2) trial described elsewhere in this book. Others did not, however: The comparative clinical response rates in the IMPACT trial failed to predict the long-term gain for adjuvant anastrozole over tamoxifen or the combination shown in the equivalent ATAC trial, and, as already described, the very marked gain for a preoperative AI over tamoxifen in patients with ER-positive, HER2-positive cancers shown in both PO24 and IMPACT was not reflected in subsequent adjuvant trials.

In contrast, the proliferation biomarker Ki-67 seems a more secure endpoint for extrapolating results from preoperative to subsequent adjuvant trials. In the IMPACT trial, Ki-67 after 2 weeks and 12 weeks of treatment, in contrast to clinical response rate, correctly predicted for the superiority of anastrozole over tamoxifen or the combination found in the 9,000-patient adjuvant ATAC trial. Likewise, differences in Ki-67 after preoperative letrozole versus tamoxifen treatment in the PO24 trial correctly predicted the outcome of the equivalent 8,000-patient adjuvant BIG 1-98 trial, and, in the preoperative combination letrozole/everolimus trial, Ki-67 after treatment was a more powerful discriminator of benefit for the combination than clinical response, in predicting subsequent benefit for the combination in advanced disease. In the Z1031 trial described above comparing preoperative anastrozole, letrozole, and exemestane, the absence of a significant difference in the *change* in Ki-67 after treatment between the 3 groups led the authors to predict a similar difference in treatment outcomes in currently running comparative adjuvant trials. Time will tell.

Quality assurance is an important issue here, and guidelines for standardization of Ki-67 measurement have recently been proposed (43).

Serial Ki-67 Measurements

Ki-67 measurements after treatment may also help to explain the major lack of correlation between preoperative clinical response rates and long-term outcomes in ER-positive, HER2-positive cancers described above. In the IMPACT trial, Ki-67 levels 2 weeks after therapy were very similar to those after 12 weeks, except in around 15% of patients, where Ki-67 levels rose significantly, suggesting the rapid emergence of acquired resistance (44). HER2-positive cancers predominated in this group, supporting experimental evidence that the emergence of cross-talk between overexpressed HER2 and ER may be an important mechanism of acquired resistance to endocrine therapy.

It is possible that a similar approach using serial posttreatment Ki-67 levels could determine the emergence of acquired resistance in individual cancers that could be amenable to other combination therapies, including topical everolimus. Indeed, this approach has already been used in a trial described above aimed at determining whether gefitinib might overcome resistance to preoperative endocrine therapy (25).

PREOPERATIVE ENDOCRINE THERAPY TO PREDICT LONG-TERM OUTCOME IN THE INDIVIDUAL PATIENT

One of the most important challenges in the treatment of early ER-positive breast cancer is to determine which patients will do well with endocrine therapy alone without the need for additional chemotherapy. A similar issue is emerging in selecting those patients who might benefit from the m-TOR inhibitor everolimus in addition to endocrine therapy.

It is well established that the proliferation biomarker Ki-67 in the cancer at baseline is of prognostic significance in ER-positive breast cancer, but its predictive role for treatment outcome is less certain (45). Preoperative endocrine therapy has the potential to predict long-term benefit in the individual patient by measuring posttreatment levels of Ki-67 and other molecular markers, by incorporating both the innate biology of the tumor (prognostic) and the treatment sensitivity (predictive) (Fig. 55-2).

Many studies have shown that endocrine therapy can have a profound effect on proliferation in ER-positive cancers, and a few have suggested that early changes in Ki-67 following endocrine therapy correlate positively with clinical response (46–49). Long-term follow-up in the IMPACT trial described above showed that tumor Ki-67 2 weeks after starting preoperative endocrine therapy significantly predicted relapse-free survival (p = .004), the highest tertile of Ki-67 expression carrying an excellent prognosis

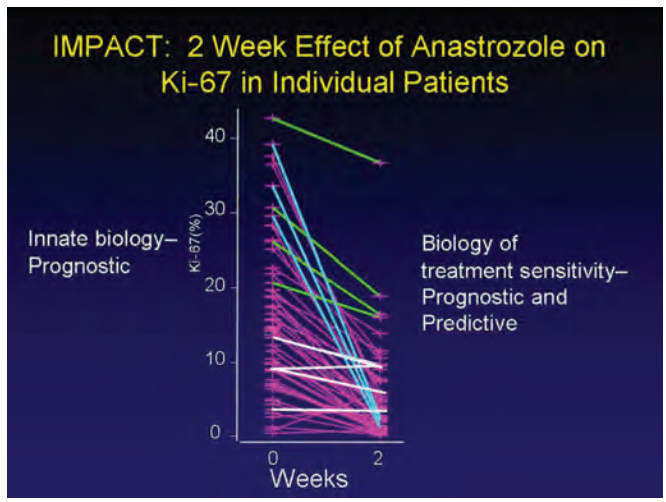

FIGURE 55-2 Change in tumor percentage of Ki-67 in individual patients after 2 weeks' treatment with anastrazole. Data from IMPACT trial (see text for details).

and the lowest tertile a poor one (32). The predictive significance of 2-week Ki-67 was sustained in a multivariate analysis. In contrast, baseline Ki-67 was only just significant in univariate analysis and dropped out in multivariate analysis, confirming the greater predictive significance of posttreatment levels (Fig. 55-3).

These findings, if validated, could provide the basis for predicting which patients might require additional chemotherapy (or indeed an m-TOR inhibitor) following 2 weeks' preoperative treatment with an aromatase inhibitor. This is now being investigated further in the 4,000-patient UK POETIC trial described above. In addition to the primary aim of determining whether short-term preoperative endocrine therapy might improve long-term outcomes, an additional and equally important aim is to determine the accuracy with which posttreatment Ki-67 in the individual tumor 2 weeks after starting an aromatase inhibitor predicts for long-term RFS compared with pretreatment Ki-67. This will establish whether preoperative endocrine therapy can indeed be used as standard practice to predict outcome and determine which patients will have a very good outcome with endocrine therapy and will not require additional adjuvant therapies, including chemotherapy. A key feature of the POETIC trial is that all patients with a measurable breast cancer 1.5 cm or larger on ultrasound were eligible (the majority of breast cancer patients), not just the minority patients with large breast cancers as in the traditional neoadjuvant model.

A similar approach has been developed using a preoperative endocrine prognostic index (PEPI) to determine which postmenopausal patients with ER-positive breast cancers have an extremely low risk of relapse and are therefore unlikely to benefit from adjuvant chemotherapy (50). Tumors from 158 women with confirmed ER+ stage 2 and 3 breast cancers in the P024 neoadjuvant endocrine therapy trial (comparing 4 months preoperative letrozole with tamoxifen) were analyzed for posttreatment ER status, Ki-67 proliferation, histological grade, pathological tumor size, node status, and treatment response. A PEPI for RFS was developed from these data with a median follow-up of 61 months. Patients with confirmed baseline ER-positive clinical stage 2 and 3 tumors that were downstaged to stage 1 or 0 at surgery had 100% RFS (compared with higher stages, $p < .001$). Multivariable testing of posttreatment tumor characteristics revealed that pathological tumor size, node status, Ki-67 level, and ER status were independently associated with both RFS and breast cancer–specific survival (BCSS). These results were validated in an independent study of 203 postmenopausal women in the IMPACT trial described above where the PEPI model again predicted RFS ($p = .002$).

The disadvantage of the original PEPI approach is that it requires around 4 months' treatment and surgical excision of the primary tumor, greatly limiting its potential for early prediction of treatment outcomes. The same group have therefore carried out a phase 2 trial in which 245 postmenopausal patients with stage 2 or 3 ER+ve (Allred score 6–8) cancers are treated with short duration (2–4 weeks) preoperative aromatase inhibitor followed by rebiopsy, similar to the POETIC trial described above. Patients whose tumors had a persisting Ki-67 of >10% were triaged to neoadjuvant chemotherapy or immediate surgery, while those with Ki-67 less than or equal to 10% continued on the aromatase inhibitor for 16 to 18 weeks and then had surgery. In this latter group, the PEPI was then calculated to determine whether adjuvant chemotherapy should be offered or not (50). Only 2 out of 35 patients triaged to neoadjuvant chemotherapy have so far had tumors achieving a pCR (6%). Pathological CR rates are low anyway in patients with ER-positive, HER2-negative tumors treated with chemotherapy, but these results nevertheless suggest that for some cancers neither endocrine therapy nor chemotherapy might be adequate and that new therapies up front may be required in this group. Whatever the interpretation, this approach further emphasizes the potential of preoperative endocrine therapy with short-term posttreatment molecular markers to determine optimal long-term adjuvant treatment in the individual patient.

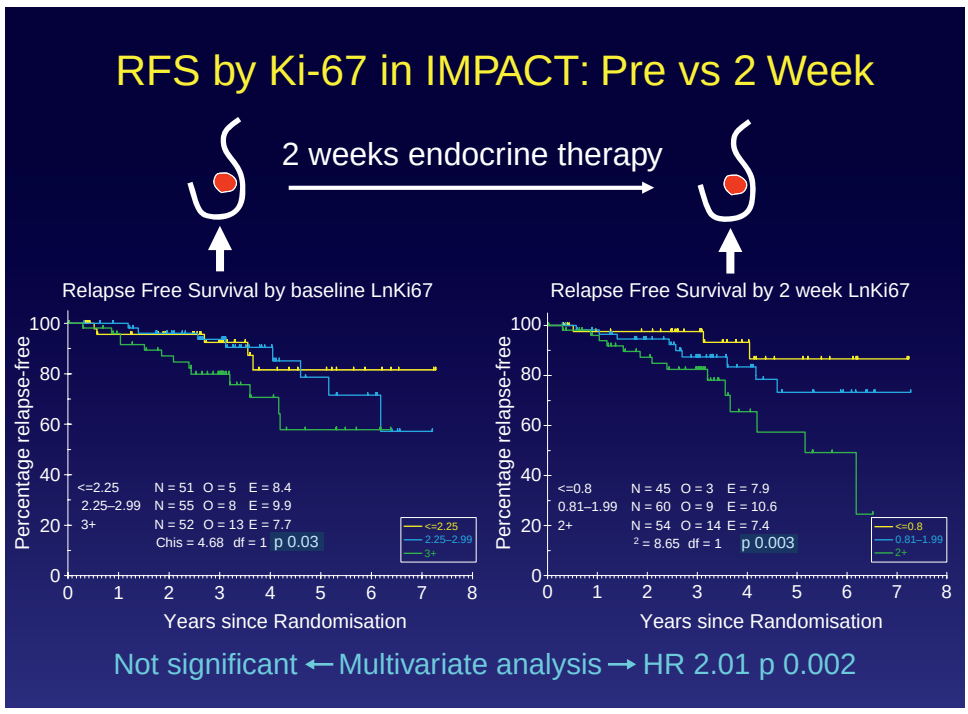

FIGURE 55-3 Relapse-free survival by log Ki-67 tertiles. **(A)** Before treatment, left panel. **(B)** After 2 weeks of anastrazole, right panel. (From Dowsett M, Smith IE, Ebbs SR, et al.; IMPACT Trialists Group. Prognostic value of Ki67 expression after short-term presurgical endocrine therapy for primary breast cancer. *J Natl Cancer Inst* 2007;99(2):167–170.)

MANAGEMENT SUMMARY

- Preoperative tamoxifen instead of surgery is a reasonable short-term approach in patients unfit for surgery, but it is associated with a higher risk of local relapse and perhaps impaired long-term overall survival.
- Preoperative aromatase inhibitors are more effective than tamoxifen at downstaging large ER-positive breast cancers in postmenopausal women and allow conservative surgery in up to 50% of patients.
- No individual preoperative aromatase inhibitor has been shown to be clinically superior to the others.
- The optimal duration of preoperative endocrine therapy to achieve conservative surgery varies considerably between patients but can be more than 6 months. A pragmatic policy is to continue treatment in responding patients until downstaging is sufficient to avoid mastectomy.
- Preoperative endocrine therapy cannot yet be considered standard in premenopausal women but is an important area for further study.

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CHAPTER 56

Pathologic Assessment of Treatment Response after Neoadjuvant Therapy

Sunati Sahoo and Susan Carole Lester

CHAPTER CONTENTS

INTRODUCTION

Neoadjuvant therapy (NAT) reveals the response of cancers to therapy *in vivo* and, thus, generates a wealth of information for individual patients as well as for clinical trials. Pathologic downstaging after treatment is a strong predictor of disease-free and overall survival. In addition, pre- and post-therapy tumor samples are an essential resource underpinning research to understand the biologic mechanisms of how and why tumors respond. Clinical and radiologic examinations are helpful to evaluate changes in tumors during treatment, but these modalities frequently overestimate or underestimate the amount of residual carcinoma present. For example, extensive but paucicellular carcinomas may not be palpable or detectable by imaging. In contrast, densely fibrotic tumor beds often mimic residual carcinoma. Only careful pathologic examination can determine the type and extent of residual tumor and provide detailed information about treatment-related changes. However, without coordination and communication this information can be lost. In a recent review of a NAT trial for which there were no consensus guidelines for processing and reporting the specimens, only 45% of pathology reports for patients without a pathologic complete response (pCR) included an evaluation of treatment-related changes in the breast and fewer than 10% utilized a specific method to classify the degree of response (1). In addition, less than one-third of reports commented on nodal-related treatment changes. Thus, careful presurgical planning and close communication among surgeons, radiologists, medical oncologists, and pathologists are necessary to maximize the amount of pathologic information obtained from specimens after NAT.

PATHOLOGIC EVALUATION PRIOR TO TREATMENT

Breast Core Needle Biopsy

For patients who achieve a pCR, the diagnostic core needle biopsy may be the only sample of their carcinoma. Therefore, a definitive diagnosis of invasive carcinoma must be established and it is essential that all marker studies (in general, estrogen receptor [ER], progesterone receptor [PgR], and HER2) be completed before treatment. If very limited tumor is available for evaluation (e.g., < 0.5 cm) and marker studies are negative, repeat biopsies may be considered to obtain a more representative sample.

The type of breast cancer most likely to respond to chemotherapy is negative for hormone receptors, is poorly differentiated, and has a high proliferative rate. Typical pCR rates range from 30% to 40% (2). If the carcinoma also overexpresses HER2, HER2 targeted therapy often results in even higher rates of pCR. The type of breast cancer least likely to respond to therapy is well differentiated, expresses hormone receptors, and has a low proliferative rate. Lobular

carcinomas are frequently of this type. Fewer than 10% of these cancers undergo a pCR after chemotherapy (2). For these cancers, pCR is not a good predictor of prognosis, as many patients with extensive residual cancer experience long-term survival with endocrine therapy.

Additional predictors of a pCR are extensive tumor necrosis and a dense lymphocytic infiltrate (3,4). Immunohistochemical markers for identification of carcinomas more likely to be of basal type as defined by gene expression profiling (basal cytokeratins or epidermal growth factor receptor) have not been shown to predict response (5).

It is essential that a clip or clips be placed at the time of core needle biopsy to mark the site of the carcinoma prior to treatment, as this may be the only method to identify the tumor bed in many cases after treatment. If the tumor bed cannot be identified with certainty, a pCR cannot be confirmed.

Lymph Node Evaluation

The method of evaluating lymph nodes prior to treatment will impact the ability to identify node-negative and node-positive patient groups, to evaluate response in the lymph nodes, and to utilize some of the systems for classifying response to NAT.

Clinical Evaluation

Determination of nodal status by palpation alone is not accurate in many cases. In one study, 85% of patients with locally advanced breast cancer determined to be clinically node negative were found to be node positive after sentinel lymph node biopsy (6). Therefore, pretreatment nodal staging based on clinical examination alone will preclude accurate classification after treatment of cancers that never metastasized from cancers with metastases that have completely responded to treatment. This could confound efforts into investigating the biologic basis of tumor response to therapy.

Fine-Needle Aspiration (FNA) or Core Needle Biopsy of Nodes

Palpable nodes can be sampled using either FNA or core needle biopsy. If no nodes are palpable, ultrasound is a useful method to identify and biopsy suspicious nodes. Needle biopsy can confirm node positivity and also allows the evaluation of response to therapy, thus maximizing the amount of information gained from NAT.

Sentinel Lymph Node Biopsy (SLNB)

If the results of FNA or core needle biopsy do not reveal metastatic carcinoma, SLNB may be used to document node negativity before treatment. A negative SLNB prior to treatment may be more predictive of the status of the remaining nodes than SLNB after treatment due to the observation that metastases may not all respond to treatment to the same extent.

Excising a positive lymph node prior to treatment precludes the ability to evaluate response in the metastasis and also precludes documentation of a pCR in the nodes. Therefore, needle biopsies that do not completely remove the metastasis are advantageous when NAT is planned.

PATHOLOGIC EVALUATION AFTER TREATMENT

Gross Evaluation of the Breast Specimen (Partial or Total Mastectomy)

If a clinically palpable tumor mass is present after treatment (usually associated with a minimal to moderate response), the pathologist should be able to identify the mass by gross examination. However, carcinomas typically become softer and more compressible after treatment, and thus are more difficult to palpate. The reasons for the change in palpability most likely relate to loss of cellularity and the composition of the desmoplastic stroma. In addition, a decrease in blood flow is frequently detected by MRI and could contribute to a change in the firmness of the carcinoma. If the carcinoma is no longer palpable or visible on follow-up imaging studies after treatment, then the prior tumor area (tumor bed) will likely be difficult to identify. In those cases, it is preferable to have the specimen radiographed before slicing to identify a clip, calcifications, or any other radiologic finding that would localize the prior tumor site. Clips can be dislodged or lost if the specimen is sliced first. If no radiologic findings mark the tumor bed, the surgeon should place a suture at the pretreatment site of the carcinoma. If the specimen is a mastectomy, it is helpful to also provide a clock location and the distance from the nipple.

The gross appearance of a tumor bed after a marked response to NAT can be quite subtle and may consist of only an ill-defined area of fibrotic tissue (Fig. 56-1). Residual cancer may not be visible (due to low cellularity) or may consist of multiple small tan foci scattered throughout the fibrotic tumor bed.

The pathologist requires information about the number, size, and location of carcinomas prior to treatment in order to determine the best method to sample the specimen. At least one section per centimeter of the pretreatment carcinoma size of the tumor bed is suggested (7). If this sampling does not reveal residual invasive carcinoma, additional sampling may be considered to confirm a pCR.

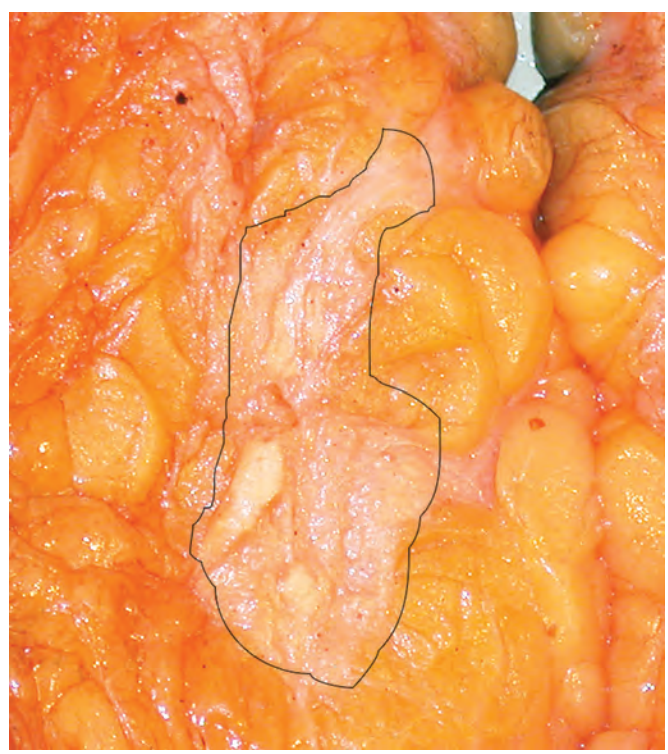

FIGURE 56-1 All that remains of this invasive carcinoma after chemotherapy is an ill-defined area of white fibrous tissue (outlined). A clip placed prior to treatment would be necessary to recognize this area as the prior tumor site. Extensive sampling and microscopic evaluation of this area did not reveal residual carcinoma and a pathologic complete response was confirmed.

Involvement of chest wall (skeletal muscle) or skin prior to treatment should be evaluated by sampling the areas of prior tumor involvement. These areas should be marked by the surgeon. Patients with inflammatory carcinoma should have additional areas of skin sampled. However, clinically evident skin changes often resolve during treatment and dermal lymphovascular invasion is frequently no longer seen.

Failure to find and adequately sample the tumor bed can result in an erroneous conclusion that there has been a pCR. Inaccurate information about tumor response may adversely affect patient care, evaluation of clinical trials, and interpretation of research results. If no residual cancer is present, the pathology report should clearly document the gross and microscopic identification of the tumor bed.

Gross Evaluation of the Lymph Node Specimen

The examination of lymph node specimens after treatment is the same as for specimens in the absence of treatment. All lymph nodes are identified grossly and separately evaluated by placing in designated cassettes and/or by inking nodes in different colors. Some studies report slightly fewer nodes after NAT, although other studies report similar numbers. Nodes may be more difficult to identify after NAT due to atrophy and fibrosis as a result of toxic effects of chemotherapy on normal lymphocytes. This effect could vary for different types of chemotherapy.

The nodes are thinly sliced (0.2 to 0.3 cm) and all slices are processed for microscopic examination. The use of additional levels through the paraffin blocks or immunohistochemical studies have not been shown to add useful prognostic information if the nodes appear negative on the initial H&E section. However, if scattered atypical cells are present, immunohistochemical stains for cytokeratin may be useful to identify the cells as residual carcinoma.

MICROSCOPIC EVALUATION OF BREAST CANCERS

All pathologic prognostic factors significant for untreated carcinomas are also important for carcinomas that have undergone treatment prior to surgery. However, many of these factors are more difficult to assess after neoadjuvant therapy (7,8). In addition, the changes induced by the treatment also have prognostic importance. Although NAT protocols use a wide variety of chemotherapeutic regimes, typical changes are seen in the majority of cancers with any type of treatment. In future NAT studies with new therapeutic agents, pathologists should report any new or unusual types of tumor response.

Tumor Bed

The tumor bed consists of dense hyalinized stroma with fibroelastosis, often infiltrated by foamy histiocytes, lymphocytes, and hemosiderin-laden macrophages. It does not have the appearance of normal fibrotic breast tissue. The size of the tumor bed is generally about the size of the pretreatment cancer, although moderate increase or decrease in size are reported. The tumor bed never completely disappears but could be significantly small and subtle in rare occasion, and must be identified in order to document a pCR.

Ductal Carcinoma *In Situ* (DCIS)

For unknown reasons, in some patients the invasive carcinoma responds to treatment, but the associated DCIS does not. Residual DCIS can mimic invasive carcinoma on MRI, as it may continue to be associated with increased enhancement.

Many definitions of pCR allow residual DCIS (9,10). Thus, it is very important to distinguish residual invasive from *in situ* carcinoma. DCIS after treatment may show marked nuclear atypia and may be intermingled with normal ductal cells and histiocytes. In difficult-to-interpret lesions, immunohistochemical studies to demonstrate myoepithelial cells associated with DCIS are helpful. Pathologists always must be provided with information about prior therapy in order to avoid misinterpreting residual *in situ* carcinoma in a sclerotic tumor bed as invasion. In addition, it may be difficult to distinguish atypical hyperplasia with nuclear atypia due to treatment effect from residual DCIS at margins.

Size of the Invasive Carcinoma

In cases of a minor response to therapy in which the gross carcinoma remains identifiable by palpation, a narrow rim of fibrosis may be present around the edge of the tumor. These carcinomas typically remain highly cellular. With marked response, multiple small foci of invasive carcinoma, or scattered cells, are present throughout the tumor bed (Fig. 56-2). In the absence of a pCR, the entire tumor bed would need to be excised to ensure complete removal of all foci of carcinoma.

Providing a measurement of tumor size is often difficult. The size of the entire tumor bed without notation of cellularity may overestimate residual carcinoma when there has been a marked response. Alternatively, reporting only the size of the largest single focus when multiple foci are present may underestimate tumor burden. Judgment must be used in individual cases to choose the best size for AJCC T classification (11–13). It may also be useful for the pathologist to report the number of foci and/or the number of blocks with residual carcinoma. Because size is difficult to quantify, cellularity is also a useful parameter to assess response.

Cellularity of the Invasive Carcinoma

There is often a marked decrease in cellularity of the carcinoma, even when there is not a marked decrease in size. However, carcinomas prior to treatment also vary greatly in cellularity and a change in cellularity can only be determined with certainty if the pretreatment carcinoma is available for comparison (Fig. 56-3). Tumor cellularity is used in some systems for the evaluation of response (Table 56-1; e.g., Miller-Payne, Residual Cancer Burden [RCB]) (14,15).

Histologic Appearance and Grade of the Invasive Carcinoma

The majority of cancers do not change in appearance after treatment, except for diminished cellularity. A few cancers may appear to be of higher grade (generally due to enlarged tumor cells with pleomorphic and bizarre nuclei from treatment effect) and in rare cases the cancer may be of lower grade due to a decrease in the mitotic index. A change in grade can only be assessed by comparing the pre- and post-treatment specimens. The prognostic significance of change in grade after therapy is unknown.

Lymphovascular Invasion (LVI)

In some cases a complete response occurs for invasive carcinoma in the stroma but LVI remains. This finding confers a poor prognosis (16). Tumor cells in lymphatics should be included when determining post-treatment cellularity.

In contrast, the skin changes of inflammatory carcinoma often resolve with treatment and dermal LVI may no longer be seen.

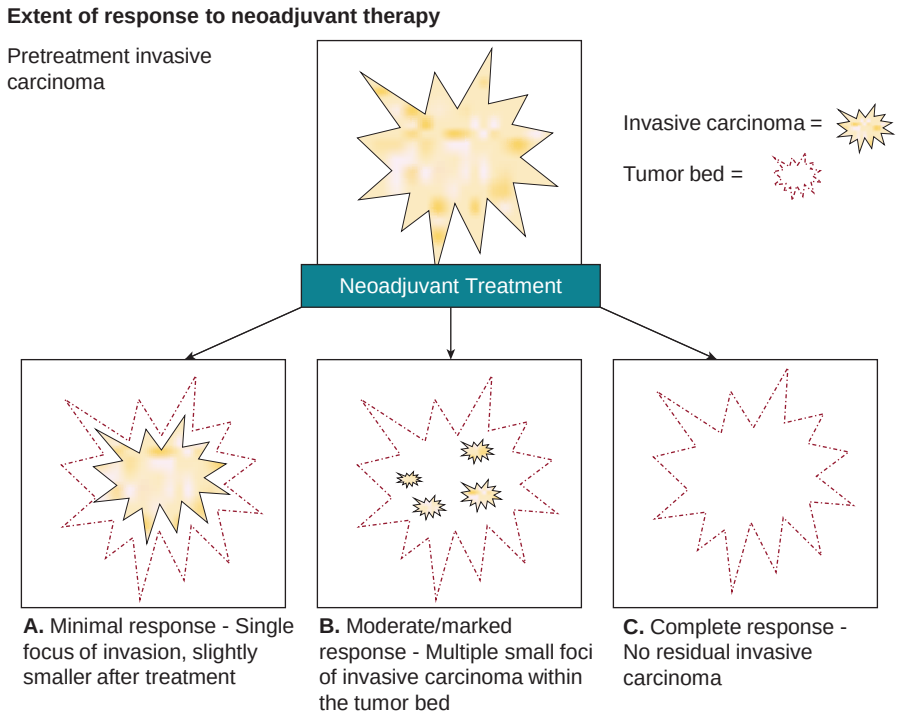

FIGURE 56-2 The initial response to treatment results in a narrow fibrotic rim and a slight decrease in tumor size **(A)**. This may be the only evidence of treatment effect in poorly responsive cancers. When a more marked response is present, the residual tumor is present as small nests or scattered individual cells across the tumor bed **(B)**. Cellularity and the number of tumor foci are methods to communicate the extent of residual cancer. In some cases, there will be no residual invasive carcinoma present **(C)**. However, this can only be ascertained if the prior tumor site is marked with a clip and the area is identified on gross examination.

Margins

Margins can be more difficult to evaluate after NAT. The extent of the tumor bed can be difficult to determine on imaging by the radiologist, grossly by the surgeon, and microscopically by the pathologist when there has been a pronounced response to treatment. The significance of tumor bed at the margin is unclear in patients with a pCR. If there is residual invasive carcinoma or DCIS within the tumor bed, tumor bed at the margin indicates the possibility that all carcinoma has not been removed and this finding should be reported.

Lymph Node Metastases

The response in the breast and in the lymph nodes is generally similar. However, the response in the lymph nodes is more predictive of survival than the response in the breast (17,18).

Metastases with little or no treatment response are easily identifiable. If there has been a marked response, only scattered tumor cells may be present in a fibrotic scar or associated with a prominent histiocytic infiltrate (Fig. 56-4). In nodes with a complete response, only fibrous tissue may remain. However, about one-third of pretreatment

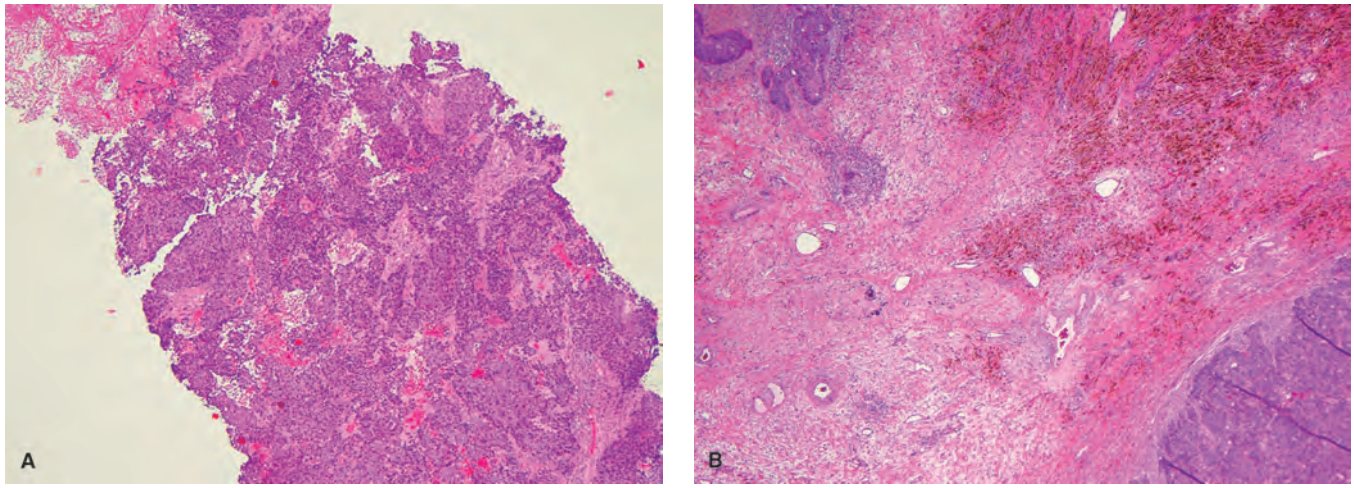

FIGURE 56-3 The most common therapy-related change in cancers is a decrease in cellularity. Before treatment, this high-grade invasive ductal carcinoma is highly cellular (>90%) and focal necrosis is present on the core needle biopsy **(A).** After treatment, the excision shows multiple nests of tumor within a tumor bed with fibrosis and hemosiderin deposition **(B)**.

TABLE 56-1

Systems for Evaluating Breast Cancer Response to Neoadjuvant Therapy

Name of System	*Factors Evaluated for Breast Carcinoma*	*Factors Evaluated for Lymph Node Metastases*	*Definition of pCR*	*No. of Categories of Response*
NSABP B-18 (20)	Treatment effect	Present/absent Size of metastasis	No invasive carcinoma	Three in breast
Sataloff (17)	Treatment effect	Present/absent Treatment effect	Total or near total therapeutic effect	Four
Pinder (8)	% Residual carcinoma	Present/absent Response	No invasive carcinoma in breast and nodes	Five in breast Four in nodes
Miller-Payne (14)	Percent reduction in cellularity compared to the pretreatment carcinoma	Not included	No invasive carcinoma in breast	Five
Modified Nottingham Prognostic Index (MNPI) (29)	Size Post-treatment grade	Present/absent Number	Most favorable class can include residual carcinoma	Continuous value divided into three classes
AJCC (y) (11)	AJCC T — post-treatment	AJCC N — post-treatment	No invasive carcinoma in breast or nodes (including ITCs)	Six
AJCC (y) — pre- and post-treatment (12)	AJCC T — pre- and post-treatment ER status, Grade	AJCC N — pre- and post-treatment	No invasive carcinoma in breast or nodes (including ITCs)	Six
Neoadjuvant Response Index (NRI) (13)	Change in AJCC T	Change in AJCC N	No invasive carcinoma in breast and nodes	Continuous value from 0 to 1
Residual Cancer Burden (RCB) (15)	Size of tumor bed in two dimensions and % cellularity of invasive carcinoma	Present/absent Number, Size	No invasive carcinoma in breast and nodes	Four (but also calculates RCB as a continuous value)

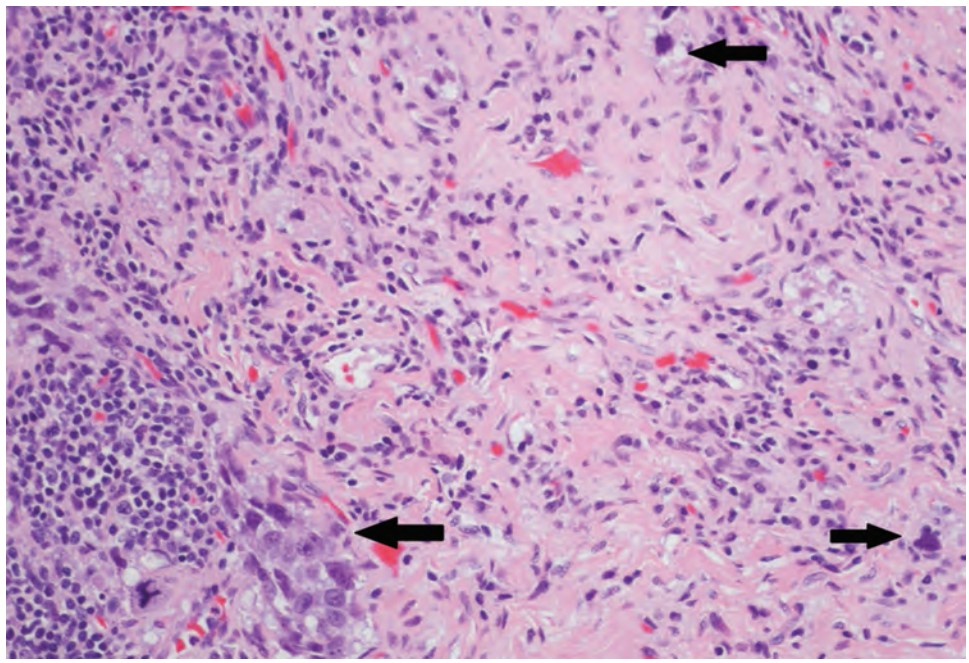

FIGURE 56-4 Lymph node metastases in the absence of therapy are typically highly cellular. After treatment, a marked response may be present. In this case the residual metastatic tumor cells (*arrows*) are surrounded by fibrous scarring, indicative of treatment effect. However, any residual carcinoma in nodes is a poor prognostic factor.

documented lymph node metastases completely resolve leaving only a normal-appearing lymph node (19). Therefore, the nodal status prior to treatment (i.e., whether or not the cancer had metastasized to nodes or not) cannot be determined with certainty in all patients if the nodes are only examined after treatment.

The significance of the size of a metastatic deposit in a lymph node depends on whether or not the patient has received NAT. In the absence of treatment, patients with macrometastases (> 0.2 cm) have a worse prognosis compared to patients with micrometastases or isolated tumor cells (ITCs). However, small metastases in treated patients are indicators of incomplete response and these patients have the same prognosis as patients with macrometastases (18,20,21). Immunohistochemical stains for keratin on nodes negative on H&E stains have not been shown to have prognostic importance, but only small numbers of patients have been studied (22,23). According to current AJCC guidelines, these nodes are classified as yp N0 (i+), but this finding precludes classifying the response as pCR.

Tumor Markers

In the majority of cases, ER, PR, and HER2 results remain the same before and after treatment. Changes occur more frequently if therapy targeting the marker is used (24,25). Changes in marker status may occur due to several reasons (Fig. 56-5):

Tumor heterogeneity with limited tumor sampling. The amount of tumor available for evaluation either before or after treatment may be very limited. Small sample size may result in differences in interpretation. However, in the absence of treatment the results on core needle biopsies are concordant with the results on excision greater than 95% of cases for ER and HER2 (24). NAT results in an increased number of cases with discordant results, depending on whether or not targeted therapy is used for the marker evaluated.

Multiple cancers/tumor heterogeneity with selection by treatment. Treatment is often more effective for cancer cells expressing targetable markers. For example, in about one-third of patients, residual carcinomas after HER2 targeted therapy no longer exhibit HER2 overexpression by immunohistochemistry or fluorescence *in situ* hybridization (FISH) (25). Because gene amplification is no longer present, this is likely due to selection of HER2 negative clones rather than temporary downregulation of gene expression. Loss of HER2 after targeted therapy has been reported to be associated with a poorer prognosis (25).

A core needle biopsy may not detect ER positivity in the pretreatment cancer. However, if an ER-positive subclone (or second ER-positive cancer) is present prior to treatment (but not detected by core needle biopsy), this component of the carcinoma may remain after treatment as hormone receptor–positive cancers are less likely to demonstrate a complete response to chemotherapy.

Change due to treatment. In some cases therapy likely alters gene expression. For example, over 70% of carcinomas that express PgR are found to be PgR negative after treatment with an aromatase inhibitor (AI), but similar changes are not seen for ER (24). In contrast, fewer than 10% of cancers become PgR negative after treatment with tamoxifen. An AI results in lower estrogen levels, causing downregulation of ER-regulated genes. It is likely that loss of PgR is a change in gene expression rather than selection of a PgR-negative subclone. This change has not been clearly linked to treatment response or survival.

When there has been an alteration in tumor markers after treatment, it is not known whether the pre- or post-treatment expression profile will be more predictive of the pattern in future recurrences or distant metastases. The clinical significance of the loss of a marker is unclear as the loss may be transient (if due to changes in gene expression) or may not occur in all residual or metastatic carcinoma (if due to selection by the treatment). Therefore, loss of a marker after therapy should not be used as an indication to withdraw targeted therapy.

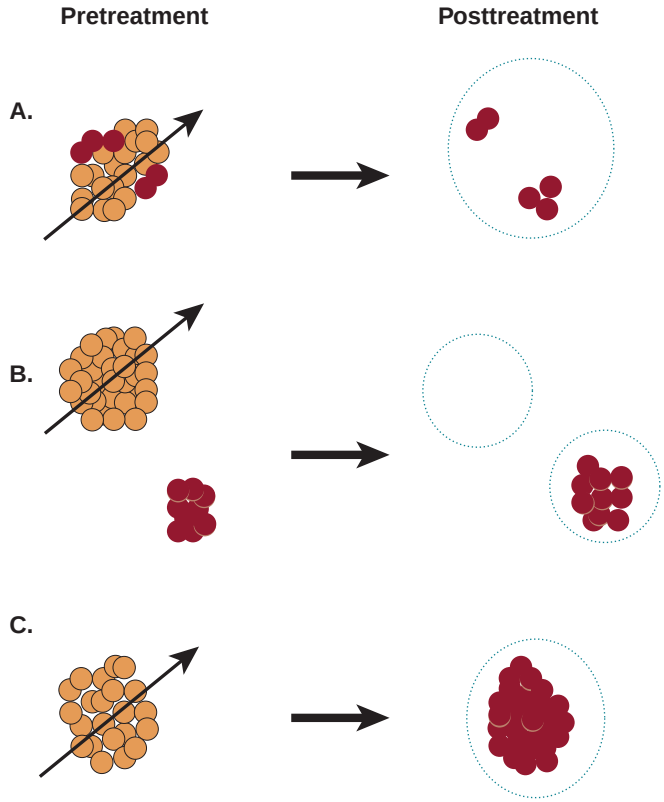

FIGURE 56-5 The results for biologic markers (e.g., ER, PR, HER2) on pretreatment core needle biopsy (*thin arrows*) may be different from the post-treatment residual carcinoma in the tumor bed (*dotted circles*). Carcinomas can be heterogeneous for biologic markers as represented by yellow circles (positive or negative) and red circles (opposite result). **(A)** Heterogeneity may not be detected initially and it is possible for treatment to select for subclones of cells with a different expression pattern. **(B)** Some patients may have multiple cancers with different expression patterns with different responses to treatment. **(C)** In some cases, treatment may cause a change in gene expression in tumor cells. It is unknown if such changes would be transient or permanent.

In contrast, gain of a marker may identify an additional treatment modality that would be beneficial to the patient. For example, patients with carcinomas negative for ER and PgR prior to treatment but positive after treatment benefit from hormonal therapy and have an improved prognosis (24,26). HER2-negative cancers that are found to be HER2 positive after treatment are very rare (<10% of cancers after NAT) and there are too few patients to determine if there is a benefit of HER2 targeted therapy.

Changes in proliferation as determined by immunoperoxidase studies for Ki-67 (MIB-1) have been suggested as a means to measure response to therapy, in particular for hormonal agents, as inhibition of proliferation is the goal of

treatment and pCR is uncommon. Decreased proliferation after treatment is predictive of improved survival (27).

SYSTEMS FOR EVALUATING PATHOLOGIC RESPONSE

Numerous systems for classifying the pathologic response of breast cancers to treatment have been developed and shown to be predictive of disease-free and overall survival (Table 56-1). All of the systems recognize a category of pCR and a category of little or no response. The challenge is to classify the 55% to 80% of carcinomas that undergo a partial response. The number of categories of partial response range from one to four, or the degree of response may be expressed by a continuous variable. The systems vary according to the definition of pCR, evaluation of the breast and/or lymph nodes, extent of residual cancer versus a change in the extent of cancer, and the use of additional non-treatment-related factors, discussed next.

Definition of pCR

A pCR is the most straightforward category of response to define and is often used to compare the results of trials of NAT. A common definition of pCR requires no residual invasive carcinoma in the breast and no metastatic carcinoma in the lymph nodes (9–11). Some systems allow an "almost pCR" (i.e., minimal residual disease). However, any amount of residual disease is challenging to quantify and it would be difficult to define such a category consistently across multiple studies and different observers. A true pCR should be recognized as a separate clearly defined category.

Residual DCIS decreases disease-free survival (due to local recurrences) but not overall survival (2,28). Therefore, in many systems residual DCIS does not preclude a pCR in the breast. Distinguishing DCIS from treatment-related nuclear atypia in areas of epithelial hyperplasia may be difficult in some cases. The issue of whether or not nodes with isolated tumor cells should be included as a pCR is also debated. The existing data support that small metastases after treatment have the same prognostic importance as larger metastases, although additional studies using immunohistochemistry to find single cells may not add additional information (20–23). Isolated tumor cells currently would not be considered a pCR in the nodes.

Breast and/or Lymph Node Evaluation

Some systems only evaluate response in the breast (e.g., Miller-Payne) whereas others evaluate both the breast and the lymph nodes (e.g., AJCC (y), Pinder, RCB, Neoadjuvant Response Index [NRI]) (8,11–15). Because of the prognostic importance of nodal response, systems that do not include this information will misclassify some node-positive patients as having a good prognosis. However, if a positive node is excised before treatment, systems that require evaluation of response in the nodes cannot be accurately assessed.

Residual Cancer or Change Due to Treatment

Some systems, such as RCB, only quantify the amount of cancer remaining after treatment (15). In order to determine the degree of response, one would need to know the equivalent RCB group prior to treatment. Other systems compare the pretreatment carcinoma to the post-treatment carcinoma to give a direct evaluation of response (e.g., Miller-Payne, AJCC (y), NRI) (11–13). These latter systems require knowledge of the pretreatment cellularity (Miller-Payne) or the pretreatment clinical stage (AJCC (y) or NRI).

Features Evaluated

No method utilizes all available prognostic factors. Most methods use either tumor size or tumor cellularity as the predominant factor for response in the breast and the presence of metastases in the lymph nodes. Treatment response in the nodes may or may not be included. Other features used by some methods are ER status, grade, and AJCC stage (Table 56-1). Factors such as LVI and HER2 status have not been incorporated.

Hormonal Therapy or Chemotherapy

In the majority of studies, classification of tumor response has been developed to evaluate cancers treated with chemotherapy. Cancers treated with neoadjuvant endocrine therapy often decrease in size clinically with prolonged treatment, but pCR is rare and does not identify a group with an improved prognosis. The preoperative endocrine prognostic index (PEPI) is a system specifically designed for neoadjuvant endocrine therapy (27). This system uses post-treatment tumor size (AJCC T1/2 vs. T3/4), nodal status (positive or negative), ER status (positive or negative), and Ki-67 score to divide patients into three risk groups.

The optimal system that employs all aspects of response has not yet been developed. Additional studies will be required to compare current systems, to create improved systems with better predictive value, and to determine the reproducibility of the categories.

CONCLUSIONS

NAT is being used more commonly in early-stage breast cancers and may become the standard of care for patients eligible for systemic therapy. NAT provides valuable information for patients, clinicians, and researchers. The pathologist plays a key role in determining the extent and types of response to therapy. To obtain the maximum amount of information about treatment effect, careful pretreatment tumor and lymph node sampling and close communication among surgeons, pathologists, radiologists, and medical oncologists is mandatory.

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CHAPTER 57

Local-Regional Therapy following Systemic Treatment

Thomas A. Buchholz and Kelly K. Hunt

CHAPTER CONTENTS

INTRODUCTION

The sequencing of systemic treatments prior to performing definitive breast cancer surgery has become increasingly common. This approach, often referred to as neoadjuvant systemic therapy, was once reserved for patients who presented with inoperable disease. The initial studies of neoadjuvant chemotherapy demonstrated high response rates and success in converting inoperable disease to disease more amenable to modified radical mastectomy. After this initial success, the focus of research concerning neoadjuvant treatments moved toward investigating whether neoadjuvant chemotherapy could permit breast-conservation therapy in selected patients whose local-regional disease at the time of initial diagnosis would require mastectomy. This strategy also proved to be successful and as clinicians became more familiar with its use, neoadjuvant systemic treatments were extended to patients with early-stage breast cancer. Indeed, some practitioners currently prefer the neoadjuvant approach for any patient for whom chemotherapy is known to be indicated as part of treatment based on the stage of disease or biologic parameters of her disease at the time of diagnosis.

As neoadjuvant treatments have become more common, a number of questions concerning optimizing local-regional therapy have arisen. As noted, one of the first of these questions concerned whether a greater percentage of patients could be safely treated with breast conservation if systemic treatments were given prior to surgery. This question has been the subject of large randomized phase III trials, the results of which consistently have indicated that breast-conservation rates are higher with neoadjuvant chemotherapy use (1). On the basis of these trials, neoadjuvant chemotherapy is now considered to be an appropriate standard for patients who desire a breast-conserving approach but who present with a large primary tumor or unfavorable tumor-to-breast-size ratio.

More recent local-regional treatment clinical trials for patients treated with neoadjuvant chemotherapy have focused on the management of the axilla. Specifically, a number of studies have evaluated whether sentinel lymph node surgery can safely be performed after neoadjuvant treatments rather than at the time of diagnosis for patients who present with clinically lymph node-negative disease. Performing sentinel lymph node surgery after chemotherapy rather than before could decrease overall rates of required axillary dissections. This is because a lower percentage of patients would have pathologically positive sentinel lymph nodes if they first were treated with systemic treatments (i.e., some patients with microscopically positive lymph nodes would have these foci of disease eradicated by the neoadjuvant treatment). Subsequently, surgical trials have investigated whether postchemotherapy sentinel lymph node surgery could be used in patients who present with clinically positive lymph nodes, in the hope that some of these patients who subsequently become clinically lymph node–negative after tumor response to neoadjuvant systemic treatment can avoid an axillary dissection.

The increased use of neoadjuvant chemotherapy has also raised a number of questions within the field of radiation oncology. Indications for radiation and treatment field designs have been historically based on the pathological extent of disease. For example, decisions concerning the use of radiation for regional lymphatic treatment and indications for postmastectomy radiation have historically been based on the number of positive lymph nodes, something that cannot be accurately determined with clinical staging. The ASCO and ASTRO consensus statements regarding the use of postmastectomy radiation recommend the use of radiation for patients with four or more pathologically involved lymph nodes and these recommendations were based on data from patients treated with surgery first (2,3). Neoadjuvant systemic treatment has the potential to change the pathological extent of the disease in the primary tumor site and the regional lymphatics in nearly all patients and it is unclear how these changes should affect radiation treatment decisions. Therefore, neither the ASCO nor the ASTRO consensus statements were able to address what are appropriate indications for postmastectomy radiation use for patients treated with neoadjuvant chemotherapy.

This chapter will focus on local-regional treatments for patients treated with neoadjuvant systemic therapies. We will review the randomized and nonrandomized data from studies investigating the use of breast conservation after neoadjuvant chemotherapy or hormonal therapy, evaluate the role of sentinel lymph node surgery for patients treated

with neoadjuvant systemic treatments, and review indications for postmastectomy radiation and regional lymph node radiation for patients treated with neoadjuvant treatments. In aggregate these data will highlight that there remain many controversial areas of local-regional treatment management for patients undergoing neoadjuvant systemic treatments. However, local-regional treatment after neoadjuvant chemotherapy remains a very exciting area of clinical research in that data from the initial studies suggest neoadjuvant therapy has the potential to further personalize local-regional treatment decisions. Specifically, it may be feasible to selectively use aggressive local therapies for patients with a poor response to chemotherapy while minimizing the morbidities associated with local-regional treatments for patients with an excellent response. The newly proposed clinical trials to investigate this hypothesis will also be reviewed.

BREAST CONSERVATION

The clinical response rates of primary tumors to neoadjuvant chemotherapy approach 80% to 90%, depending on the biological subtype of disease (4). Potentially, this could convert a large tumor that would require mastectomy into a size that is eligible for a breast-conserving approach. In addition, for patients with moderate-size tumors, the response may permit a more optimal aesthetic outcome after breast-conservation therapy. For both of these considerations to be feasible, the volume of surgical resection would have to be smaller and directed at the residual nidus rather than the original extent of disease.

In some instances, neoadjuvant chemotherapy successfully shrinks large primary tumors to smaller volumes such that the residual nidus of tissue can be resected with good or excellent aesthetic outcomes. However, in other cases tumors respond but the residual disease is diffuse, multifocal, and scattered throughout the original tumor volume. In the early 1990s investigators from MD Anderson examined 143 mastectomy specimens from patients given neoadjuvant chemotherapy to determine patterns of residual disease and their relationship to clinical factors. Only 23% of tumors had clinical and pathological features that would have predicted success with breast conservation. Important criteria included resolution of skin edema, favorable clinical response to neoadjuvant treatment, lack of multicentricity, and lack of extensive lymphovascular space invasion (5). These data highlighted that breast-conservation surgery would be feasible in only selected patients and that careful selection criteria should be used. These data were supported by the heterogeneity of outcome seen in the initial clinical trials, which varied according to the selection criteria used for their populations. For example, studies that included patients with positive surgical margins or inflammatory breast cancer reported higher rates of local recurrence (6,7). In addition, higher rates of local recurrence were noted in studies that attempted to eliminate surgery completely for the patients who achieved complete clinical resolution of disease (8). In contrast, the studies that had more stringent selection criteria and well-coordinated multidisciplinary teams reported excellent outcomes (9,10).

These institutional experiences helped set the stage for two large randomized trials that directly compared the outcome of patients treated with neoadjuvant chemotherapy versus adjuvant chemotherapy. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 study randomized 1,523 patients with operable breast cancer to 4 cycles of doxorubicin and cyclophosphamide (AC) either before or after surgical treatment (1,11,12) and the European Organisation for Research and Treatment of Cancer (EORTC) 10902 trial randomized 698 patients to 4 cycles of fluorouracil, epirubicin, and cyclophosphamide chemotherapy to be given as neoadjuvant or adjuvant treatment (13). Because the trials did not have an exclusive focus on rates of breast conservation, both studies included patients who were considered candidates for initial breast conservation and candidates who would require an initial mastectomy. The summary of the results of both studies are shown in Table 57-1. Both studies found that rates of breast conservation were higher in the neoadjuvant chemotherapy arm compared to the adjuvant chemotherapy arm (1,11,13). In the B-18 study, the improvement in breast-conservation rates from 60% to 68% for patients treated with neoadjuvant chemotherapy showed that 20% of initial mastectomy candidates (8% of 40% patients) could undergo breast-conservation surgery after neoadjuvant chemotherapy. As shown in Table 57-1, both studies reported that the overall ipsilateral breast recurrence risk in patients treated with neoadjuvant chemotherapy was not statistically different from that in patients treated with surgery first (1,11,13). However, in the B-18 study, the breast recurrence rate in a subset of patients who initially would have required a mastectomy but were treated with breast conservation after a favorable

TABLE 57-1

Outcome of Breast-Conservation Therapy in Randomized Prospective Clinical Trials Comparing Neoadjuvant and Adjuvant Treatments

Trial	*Breast-Conservation Rates*	*Local-Regional Recurrence Rates (first events only)*	*Survival Rates*
NSABP B-18 (51)			
(1,523 patients)			16 y
Neoadjuvant	68%	13%	55%
Adjuvant	60%	10%	55%
		p = .21	p = .90
EORTC 10902 (52)			
(698 patients)		10-year estimate	10 y
Neoadjuvant	35%	20%	64%
Adjuvant	22%	20%	66%
		HR 1.0–1.1	p = .54
		p = .97	

response to neoadjuvant chemotherapy was twice that of the patients with smaller tumors who were treated with surgery first (15.7% vs. 7.6%, respectively) (1). In addition, a meta-analysis of the 9 randomized studies comparing neoadjuvant and adjuvant chemotherapy reported that the use of neoadjuvant chemotherapy was associated with an increase in the relative risk of local-regional recurrence relative to adjuvant chemotherapy (relative risk [RR] 1.22, 95% confidence interval [CI] 1.04–1.43) (14). However, this analysis may have less relevance to modern treatment approaches in that it included trials in which surgery was not performed and radiation alone was used as the sole local-regional treatment. In the trials in which surgery was not used after neoadjuvant treatment, the relative risk was 1.53 and the 95% CI was 1.11 to 2.10) (14).

A second and more recent meta-analysis by Mieog and colleagues examined 10 studies and also demonstrated that overall survival was not different between patients receiving neoadjuvant versus adjuvant chemotherapy (HR 0.98, 95% CI 0.87–1.09) (15). In terms of the question of safety of breast-conserving therapy (BCT) after chemotherapy the meta-analysis reported that the mastectomy rate was decreased by 17% in patients receiving neoadjuvant chemotherapy. It is likely that this is an underestimation of the rate of downstaging as many of the women in these studies were likely breast-conserving therapy candidates before they received neoadjuvant chemotherapy. However, the rate of conversation from mastectomy to breast conservation depends in part on the T stage of disease. Ironically, it is the larger T3 tumors that have a higher conversation rate to breast conservation than the T1 or T2 tumors. This is because most T1 or T2 tumors are candidates for breast conservation at the time of diagnosis and it is factors beyond tumor size (e.g., diffuse microcalcificaitons throughout the breast) that lead to recommendations for mastectomy. These factors may be more difficult to overcome with neoadjuvant chemotherapy. In the B-18 trial the breast-conservation rate was no marked different between the adjuvant and neoadjuvant arms for the patients with T1–T2 disease; however, the use of neoadjuvant chemotherapy in the population with T3 disease resulted in an increase in the rate of breast conservation from 3% to 22% (11). Similarly, in the EORTC10902 trial, they looked at the surgical plan prior to starting chemotherapy in the group randomized to neoadjuvant chemotherapy and prior to starting chemotherapy 23% of patients who were thought to require mastectomy were able to have breast-conserving therapy (13). The meta-analysis by Mieog and colleagues showed that there were no differences in local-regional recurrences for patients receiving neoadjuvant or adjuvant therapy when stratified by the type of surgery performed (15). They also looked at patients in the EORTC trial and NSABP-18 trial who were downstaged to breast conservation and found no difference in local-regional recurrence rates for patients who were planned to undergo breast conservation and those who were downstaged enough to become breast-conservation candidates.

Studies from the Istituto Nazionale Tumori in Milan and the University of Texas MD Anderson Cancer Center (9,10) have provided additional data suggesting breast conservation is safe for appropriately selected patients with larger primary tumors that respond favorably to neoadjuvant chemotherapy. The Milan group noted an 85% breast-conservation rate in 536 patients treated with neoadjuvant chemotherapy for a primary tumor 2.5 cm in diameter or larger and reported an excellent 8-year rate of breast recurrence of 6.8% (9). In the initial MD Anderson series, 340 carefully selected patients were treated with breast-conservation therapy after showing a favorable response to chemotherapy (10) had a 5- and 10-year local recurrence rates were 5% and 10%, respectively, despite the fact that 72% of patients initially had clinical stage IIB or III disease. These investigators identified four factors that were independently associated with breast cancer recurrence and local-regional recurrence: clinical N2 or N3 disease, lymphovascular space invasion, a multifocal pattern of residual disease, and residual primary tumor larger than 2 cm in diameter (10). Eighty-four percent of patients had none or just one of these factors and the recurrence rate at 10 years in this group was only 4% (16). In contrast, the 4% of patients with three of these factors had a recurrence rate of 45%. Women with primary clinical T3 or T4 disease were at very low risk of recurrence if the tumor shrank to a solitary nidus or showed a pathologic complete response (pCR), but among patients with T3 or T4 tumors that left a multifocal pattern of residual disease, the breast cancer recurrence rate was 20% (10).

When interpreting the local-regional outcome results of breast conservation after neoadjuvant chemotherapy for patients with advanced disease, it is important to consider that patients with stage III breast cancer are at risk for local-regional recurrence even when mastectomy is performed. In addition, patients with advanced disease are at significant risk for distant metastases, which is an additional incentive to avoid removing the entire breast when breast-conserving surgery can be done with acceptably low recurrence rates. To compare local-regional treatment outcomes with those achieved with mastectomy, the investigators from MD Anderson Cancer Center applied the four prognostic criteria associated with breast recurrence in patients treated with neoadjuvant chemotherapy and breast conservation to a cohort of patients treated with neoadjuvant chemotherapy, mastectomy, and postmastectomy radiation (17). These investigators found that for patients who had none or one of these factors, the results with either local-regional treatment approach were excellent and equivalent. Among patients with two factors, a nonsignificant trend was evident toward fewer local-regional recurrences with mastectomy, and for the small cohort of patients with three or four factors, mastectomy with postmastectomy radiation provided a statistically significant benefit compared to breast conservation.

The previously described MD Anderson Prognostic Index based on the factors of clinical N2–N3 disease, lymphovascular invasion, residual pathologic tumor size greater than 2 cm and multifocal residual disease on pathology was more recently validated in an independent patient dataset (18). This study utilized a contemporary population of 551 women who had neoadjuvant chemotherapy, mastectomy, or breast-conserving surgery and radiation treated from 2001 to 2005 and who were not included in the original analysis. For patients undergoing breast-conserving therapy the 5-year local-regional recurrence-free survival rates were 92%, 84%, and 69% when the prognostic index was 0 (n = 91), 1 (n = 82), 2 (n = 38) or 3 or 4 (n = 13) (p = .01). Similar to the previous results, the 5-year local-regional recurrence-free survival rates were similar between patients undergoing mastectomy or breast conservation when the prognostic score was 0, 1, or 2, but mastectomy had an improved local-regional outcome when the prognostic index score was 3 or 4.

A common question raised with respect to performing breast-conserving therapy after neoadjuvant chemotherapy is what volume of breast tissue should be resected. Some tumors will shrink concentrically while others form more of a honeycomb pattern with small pockets of residual disease over the volume of original tumor size. To evaluate this, Boughey et al. studied whether preoperative chemotherapy was able to reduce the volume of tissue excised and the number of breast operations performed (19) and reported that in

patients with T2 or T3 tumors, significantly less tissue was resected when patients received neoadjuvant chemotherapy ($p < .004$ for volume of tissue resected). At a median follow-up time of 33 months there were only two cases of ipsilateral breast recurrence, one in the neoadjuvant group and one in the adjuvant group, leading them to conclude that it is not necessary to excise the entire prechemotherapy volume of tissue. Therefore, using chemotherapy in the preoperative setting can afford a better overall cosmetic outcome for patients.

Recently, the NSABP updated its experience of breast conservation after neoadjuvant chemotherapy by combining the data from such patients enrolled on B-18 and B-27 and retrospectively analyzing their outcome. The 10-year local-regional recurrence rate was 10.3% in the 1,100 patients treated with neoadjuvant chemotherapy, lumpectomy, and whole breast irradiation (20). In a multivariate analysis, age under 50, positive clinical nodal status, and pathological positive lymph nodes and lack of a complete response in the breast predictive of higher rates of local-regional recurrence. The highest rates of local-regional recurrences were in patients who presented with clinically positive lymph nodes and were found to have pathologically positive lymph nodes after neoadjuvant chemotherapy.

Finally, a recently published study from MD Anderson evaluated the outcome of 2,984 patients who underwent segmental mastectomy and whole breast radiation over a period of approximately 20 years and compared those who underwent surgery first ($n = 2,331$) versus those who had surgery after neoadjuvant chemotherapy ($n = 652$) (21). Due to selection biases, the neoadjuvant group had a higher percentage of patients who were younger, had more advanced stage of disease, had high-grade disease, and had estrogen-receptor (ER)- negative tumors. Neoadjuvant chemotherapy resulted in a pathologic complete response in 20% of patients and downstaging in many others as evidenced by the fact that 93% of patients presented with clinical stage II or stage III disease and only 46% had stage II or stage III disease on final pathology ($p < .001$). With a median follow-up of over 7 years in both groups, the local-regional recurrence-free survival rates were excellent in both groups. Specifically, the 5- and 10-year local-regional recurrence-free survival rates in patients undergoing surgery first noted to be 97.1% and 94.3%, respectively, and in patients receiving neoadjuvant chemotherapy they were 93.4% and 90.3%, respectively. Multivariate analysis revealed that age less than 50, clinical stage III disease, grade III disease, and either ER-negative disease or patients with ER-positive disease who did not receive hormonal therapy were factors associated with local-regional recurrence. Additionally, multifocal disease on final pathology, the presence of lymphovascular invasion, and close or positive margins were also significant factors. When neoadjuvant chemotherapy was added to the model it was not significant, suggesting that after controlling for these other adverse factors there was no difference with respect to local-regional recurrence in patients receiving neoadjuvant chemotherapy compared to those who undergo upfront surgery.

The investigators also evaluated local-regional recurrence-free survival rates by presenting clinical stage and found there were no differences in recurrences among the stage I, stage II, or stage III patients with respect to treatment sequence. Finally, they then evaluated patients by the number of those adverse factors that were identified on multivariate analysis and found that the majority of patients had none of these factors present or only one or two factors present. There were no significant differences in local-regional recurrence-free survival in patients with zero, one, two, or three factors, between the surgery first and neoadjuvant chemotherapy patients. There were too few patients with four, five, or six adverse factors for meaningful analysis. They therefore concluded that neoadjuvant chemotherapy downstages a significant number of patients with clinical stage II or stage III disease and that appropriately selected patients can achieve high rates of local-regional control with breast-conserving therapy with either upfront surgery or neoadjuvant chemotherapy. Finally, their data indicated that the local-regional recurrence after breast conservation was driven by biologic factors and not the timing of chemotherapy delivery.

Our institutional approach is to utilize ultrasound of the breast and regional nodal basins at diagnosis in addition to diagnostic mammography. A clip is placed to mark the primary tumor site and the patient is followed with ultrasound imaging during the chemotherapy treatment. At the completion of chemotherapy repeat ultrasound and mammogram are performed to evaluate for any residual mass or other radiographic abnormality. Calcifications associated with the primary tumor, residual radiographic abnormalities, and the marker clip are targeted for resection with a margin of normal tissue. We perform intraoperative assessment of the specimen using radiographic and pathologic correlation. A whole specimen radiograph is obtained and the segmental resection specimen is then marked for superior, inferior, medial, lateral, anterior, and posterior margins with different colors of ink. After the specimen is inked, it is sectioned and radiographed and correlated with gross pathologic examination (Fig. 57-1). This allows for intraoperative identification of areas in which additional margin reexcision may be beneficial.

NEOADJUVANT HORMONAL THERAPY

There are fewer data concerning the long-term outcome of patients treated with hormonal therapy prior to surgery. In part this is because most patients treated with neoadjuvant systemic treatments for ER-positive breast cancers have disease extent that necessitates both chemotherapy and hormonal treatments. However, interest in neoadjuvant hormonal therapy has increased after reports from studies that found patients with ER-positive disease have a lower probability of achieving a pCR with chemotherapy compared to those with ER-negative disease (22). In fact, in patients with lobular breast cancer, in whom over 90% of tumors are ER-positive, the rates of pCR with neoadjuvant chemotherapy is 5% or less (23). In addition, some patients with ER-positive breast cancer that is locally advanced and/or lymph node positive at presentation will have significant comorbid medical conditions and therefore not be ideal candidates for neoadjuvant chemotherapy. For such patients, treatment with neoadjuvant hormonal therapy is a reasonable option (24).

Responses to neoadjuvant hormonal therapy occur over a longer period of time compared to those seen with neoadjuvant chemotherapy. The rates of pCR with hormonal therapy are lower than typically reported in neoadjuvant chemotherapy trials but comparable to the rates achievable with neoadjuvant chemotherapy in patients with ER-positive disease. After aromatase inhibitors became available for postmenopausal patients with ER-positive disease, neoadjuvant hormonal therapy trials were developed to directly compare the activities of various agents. A 330-patient randomized trial conducted in the United Kingdom (IMPACT trial) compared 3 months of anastrozole, tamoxifen, or the combination and found response rates of 36% to 39%, with

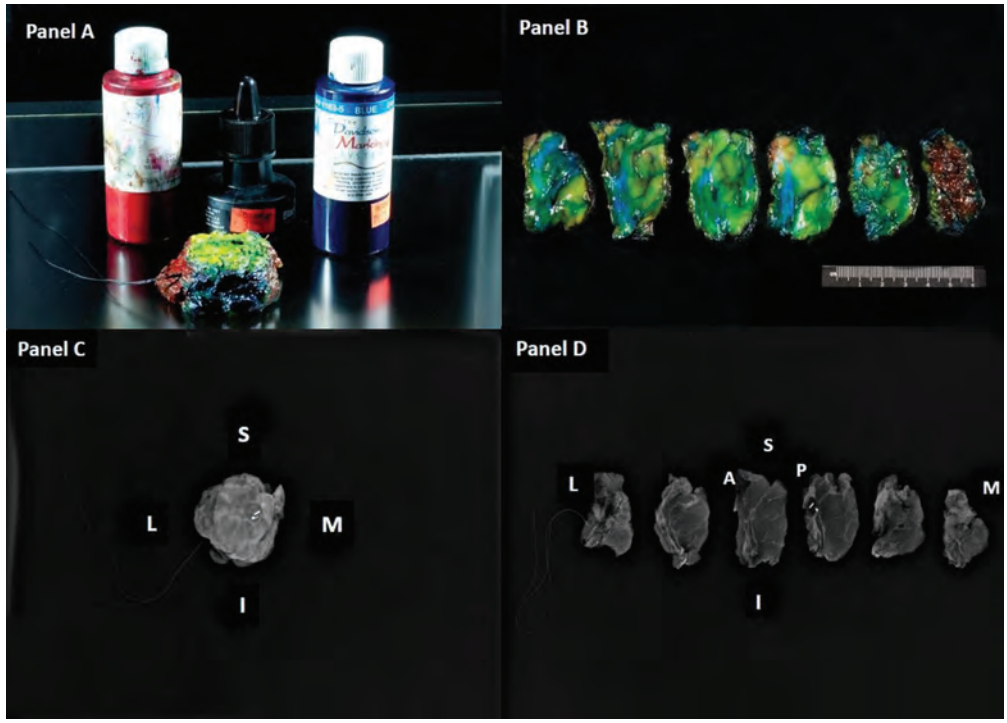

FIGURE 57-1 Specimen processing of the partial mastectomy specimen after neoadjuvant chemotherapy. Panel A demonstrates the partial mastectomy specimen that has been inked with different colors to denote the margins of resection. Panel B demonstrates the partial mastectomy specimen following sectioning. Grossly there are no significant abnormalities that would suggest residual tumor. Panel C demonstrates the whole specimen radiograph which illustrates the clip that was placed at the time of the initial tumor biopsy and the radioactive I-125 seed that was placed after chemotherapy for intraoperative tumor localization at the time of surgery. Panel D demonstrates the sectioned specimen radiograph and illustrates the clip and the I-125 radioactive seed in the fourth section. There are some densities noted in the superior aspect of the specimen and around the clip that will be targeted for pathologic assessment to determine if there is residual disease following chemotherapy. A, anterior; I, inferior; L, lateral; M, medial; S, superior; P, posterior.

only 1% to 3% achieving a clinical complete response (25). In the subgroup of 124 patients who were not candidates for breast conservation at diagnosis, the rates of breast conservation after 3 months of neoadjuvant hormonal therapy were highest in the anastrozole alone arm. An Italian trial randomized patients to 3 months of anastrozole versus tamoxifen and also noted a higher rate of breast conservation after treatment with anastrozole alone versus tamoxifen alone. The overall response rates were similar to those in the UK study (26). Eiermann and colleagues conducted a multicenter phase III trial (P024 trial) comparing 4 months of neoadjuvant tamoxifen or letrozole for women with ER-positive disease who not felt to be candidates for breast conservation at the time of initial diagnosis. Breast-conserving surgery was achieved in 45% of patients in the letrozole group compared with 35% in patients who received tamoxifen (p = .022) (27). Letrozole was effective in tumors with all levels of ER expression, whereas tamoxifen was effective only in tumors with higher levels of ER expression (28). Ellis and colleagues later described the Preoperative Endocrine Prognostic Index (PEPI), a tool for assessing long-term clinical outcomes based on response to preoperative endocrine therapy. The PEPI score was developed utilizing patients from the P024 trial and validated with patients from the IMPACT trial (29). The four components of the PEPI score include pathologic size of the primary tumor, pathologic nodal status, posttreatment Ki-67 level, and posttreatment ER status (Allred score). The PEPI score stratified patients with respect to relapse-free and breast cancer specific survival outcomes and identified a very favorable group (PEPI 0) that may not benefit from chemotherapy.

In the American College of Surgeons Oncology Group (ACOSOG) Z1031 trial, investigators compared the aromatase inhibitors anastrozole, letrozole, and exemestane head to head in a neoadjuvant trial of 16 weeks of aromatase inhibitor therapy in patients with stage II or III ER-positive breast cancer (28). There were 377 postmenopausal women with strongly enriched (Allred score 6–8) ER-positive tumors enrolled with the primary end point being clinical response. The three agents were similar in terms of their clinical response rates and overall 51% of patients who were deemed to be mastectomy-only candidates at registration and 83.1% of those thought to be marginal candidates for breast conservation were able to have breast-conserving surgery after aromatase inhibitor therapy. Gene expression profiling demonstrated that luminal A tumors were more likely to have favorable characteristics after neoadjuvant endocrine therapy; however, some had increases in Ki-67 on therapy suggesting that this approach could be used to triage patients to alternative treatment strategies after

short-term endocrine therapy exposure. This approach was used in the Z1031 cohort B study which routed patients with a Ki-67 over 10% after 2 to 4 weeks of neoadjuvant aromatase inhibitor therapy to neoadjuvant chemotherapy versus immediate surgery. This strategy is also incorporated in the Alternate trial, a phase III trial randomizing patients to neoadjuvant therapy with anastrozole, fulvestrant, or the combination which is expected to open to accrual in the summer of 2013. A 4- or 12-week tumor biopsy with a Ki-67 level over 10% will be used to categorize patients as having "endocrine resistant" tumors who will then be triaged to neoadjuvant chemotherapy. The PEPI score will be validated in the patients with "endocrine responsive" tumors who will continue on the neoadjuvant endocrine therapy for 6 months prior to proceeding to surgery. Surgical outcomes and the ability to increase breast-conservation rates with a longer course of endocrine therapy in patients with tumors enriched for favorable biologic characteristics are important secondary end points of this trial.

APPROACH TO THE AXILLA AFTER NEOADJUVANT THERAPY

In addition to demonstrating higher rates of breast conservation, an interesting finding of the NSABP B-18 study was that fewer patients in the preoperative chemotherapy arm had pathologically positive axillary nodes (40%) as compared with the patients who underwent surgery first (58%). Traditionally, axillary lymph node dissection (ALND) has been utilized for posttreatment axillary staging and regional control in patients receiving neoadjuvant chemotherapy. As more patients with operable breast cancer are being offered systemic treatment in the neoadjuvant setting, controversy has arisen with respect to the most appropriate axillary staging procedure and the timing of that intervention. Since imaging studies have not proven to be sufficiently sensitive in detecting subclinical involvement of nodes in patients with a clinically node-negative axilla, sentinel lymph node (SLN) surgery has been suggested as a tool for staging the axilla in patients planned for neoadjuvant chemotherapy. There continue to be two camps with respect to the timing of SLN surgery, those that favor pretreatment SLN surgery and those that favor posttreatment SLN surgery. The advantages to performing SLN surgery prior to chemotherapy are that it offers classical TNM staging and the false-negative rate is well established for SLN surgery in the upfront surgery setting. The disadvantages are that the patient will require two operations (upfront SLN surgery and posttreatment primary tumor resection). If the SLN is positive, the patient will be committed to ALND and one loses the ability to assess response in the axillary nodes to chemotherapy. The points in favor of performing SLN surgery following neoadjuvant chemotherapy include one operation for the primary tumor and the nodal basin, fewer positive lymph nodes after chemotherapy which results in fewer ALNDs (less morbidity), and the ability to assess response in the breast and axilla to the preoperative regimen (prognostic information). The disadvantages of using SLN surgery after chemotherapy are that the effect of chemotherapy on lymphatics is unknown, the reported false-negative rates are higher in this setting than in those with upfront surgery, and it is unclear which patients should receive nodal radiation (loss of prognostic information).

The largest single-institution experience with sentinel lymph node surgery after neoadjuvant chemotherapy was reported from MD Anderson Cancer Center by Hunt et al. In this study there were 3,746 patients with clinically node-negative invasive breast cancer who underwent sentinel node biopsy between 1997 and 2007. Of these patients, 3,171 (84.7%) underwent SLN surgery as a first intervention and 575 (15.3%) underwent SLN after chemotherapy (30). A sentinel node was identified in 3,690 (98.5%) patients and the identification rate was higher when a combination or dual-agent mapping technique was utilized versus single-agent (99% vs. 97.5%, $p < .0001$). The identification rate was slightly improved in patients undergoing surgery first (98.7%) versus patients undergoing chemotherapy first (97.4%) but there was no impact on identification rates with respect to age, T size, histology, tumor location, diagnostic biopsy type, or surgery type. The false-negative rates were assessed in patients who had SLN surgery and also planned for completion ALND. In the surgery-first group there were 22 false-negative events in 542 patients for a rate of 4.1%. In the chemotherapy-first group there were 5 false-negative events in 84 patients for a rate of 5.9%. There was no statistically significant difference between the false-negative rates in the surgery-first group versus the chemotherapy-first group ($p = .39$). The authors did find that a false-negative event was more likely when fewer than two sentinel nodes were removed ($p = .001$) and when blue dye alone was used for the mapping procedure ($p < .0001$). There was no impact of age, T size, location, biopsy type, surgery type, or timing of sentinel lymph node surgery on false-negative rates. Similar to the NSABP-18 trial this study noted that patients undergoing surgery first had a higher incidence of positive SLNs stage for stage when compared with patients undergoing chemotherapy first. This was most significant in the patients with T2 tumors who had a rate of 36.5% ($p < .0001$) positive SLNs versus 20.5% in patients undergoing chemotherapy first and in patients with T3 tumors where the positive SLN rate was 51.4% in those with upfront surgery versus 30.4% in patients receiving chemotherapy first ($p = .04$). Along with these differences in nodal positivity rates, the authors also noted that the need for ALND was lower in patients undergoing chemotherapy first versus those undergoing surgery first in those with both T2 and T3 tumors. Importantly, there was no difference in local or regional recurrence rates between the two groups with a median follow-up of 47 months in the surgery-first group and 55 months in the chemotherapy-first group.

Mamounas and colleagues reported a retrospective analysis on SLN surgery in 428 patients enrolled in NSABP B-27, a multicenter trial that included patients who presented with either clinically node-negative or clinically node-positive disease prior to chemotherapy (31). They found a false-negative rate of 11% but noted that it decreased to 8% when radiocolloid was utilized. There was no statistically significant difference in the false-negative rates between clinically node-positive and clinically node-negative patients (12.4% vs. 7.0%, respectively, $p = 0.51$) but there was no requirement to document that palpable nodes were positive with needle biopsy at the time of registration.

The results of a prospective multicenter trial examining the role of SLN surgery after neoadjuvant chemotherapy were reported by Classe, et al. (32) These investigators studied both clinically node-negative and clinically node-positive patients who had lymphatic mapping and SLN biopsy performed with a combination of radiocolloid and blue dye. The identification rate was 90% and the false-negative rate was 11.5%. The investigators noted that patients with palpable axillary nodes (N1) had a lower identification rate (81.5% vs. 94.6%, $p = .008$) and a higher false-negative rate compared with patients with clinically negative nodes (N0) (15% vs. 9.4%, $p = .66$).

There have been two meta-analyses performed evaluating SLN biopsy after chemotherapy, the first reported by Xing

et al. (33), who included 21 studies in their analysis and a total of 1,273 patients. The identification rates ranged from 72% to 100% with a pooled estimate of 90%. The false-negative rates ranged from 0% to 33% with a pooled estimate of 12%. Based on the summary of their results, the authors concluded that SLN biopsy was reliable for surgical staging following neoadjuvant chemotherapy. A more recent meta-analysis from Kelly et al. (34) examined studies published between 2000 and 2007 which included a total of 24 studies with 1,799 patients. The identification rate was 89.6% and the false-negative rate was 8.4%. Again the authors concluded that SLN surgery was a reliable tool for assessing the lymph node status following the use of neoadjuvant chemotherapy.

Although the NSABP B-27 subgroup analysis and the French multicenter study included patients with clinically node-positive breast cancer, the majority of studies examining the use of SLN surgery after chemotherapy have been in clinically node-negative patients. The population of patients presenting with node-positive disease confirmed at diagnosis prior to administration of neoadjuvant chemotherapy has been less well studied with respect to accuracy of SLN surgery. It has been well documented that patients with positive lymph nodes can be converted to lymph node–negative with neoadjuvant chemotherapy and this rate has increased with combination anthracycline- and taxane-based chemotherapy regimens (4,35). Dominici et al. recently reported that 74% of patients with *HER2*-positive breast cancer converted to node-negative disease after receiving an anthracycline and taxane regimen concurrently with trastuzumab (36). With increasing pCR rates in the axillary nodes and the fact that these patients will receive adjuvant radiation therapy as a component of their treatment, there has been significant interest in exploring the role of SLN surgery in staging the axilla following chemotherapy in patients who initially present with confirmed node-positive disease.

One of the first reports on the use of SLN surgery after chemotherapy in patients with node-positive disease at diagnosis was from Shen et al. (37). In this retrospective analysis, 69 patients were treated between 1994 and 2002 and of these 56 had SLN surgery with completion ALND. There were 10 false-negative events in the 40 patients with residual node-positive disease after chemotherapy for a false-negative rate of 25%. This high false-negative rate suggested that SLN surgery was not reliable in this patient population. On pathologic assessment of the SLNs, it was noted that patients without any treatment effect (fibrosis, ghost cells, etc.) were more likely to have a false-negative SLN. A follow-up study by Alvarado et al. (38) analyzed this question further with a series of 150 patients treated between 1994 and 2010 who all had proven axillary lymph node metastasis at diagnosis and then received neoadjuvant chemotherapy. The identification rate was 93% in this group of patients and in 111 patients who had sentinel lymph node dissection and axillary lymph node dissection performed, there were 15 false-negative events for a rate of 20.8%. It did appear that patients who had normal nodal morphology by ultrasound examination after chemotherapy had a lower false-negative rate; in addition, multivariate analysis revealed that fewer sentinel lymph nodes removed (less than two) and small initial tumor size were associated with a false-negative event.

The use of SLN surgery after neoadjuvant chemotherapy in patients with initial node-positive disease has been studied in two large prospective trials recently reported in abstract form at the San Antonio Breast Cancer Symposium. The American College of Surgeons Oncology Group (ACOSOG) Z1071 trial was a phase II study that included women with clinical T0 to T4, N1–2, M0 breast cancer receiving neoadjuvant chemotherapy who had node-positive disease documented by fine-needle aspiration or core needle biopsy (39). Following chemotherapy all patients had SLN surgery with completion ALND. The primary end point of the trial was the false-negative rate which was predetermined to be 10% as an acceptable false-negative rate in this patient population. There were 756 patients enrolled from 2009 to 2011. The false-negative rate in women with clinical N1 disease with two or more SLNs removed was 12.8%. This rate was reduced to 11.1% when a combination blue dye and radiocolloid technique was utilized. The investigators concluded that SLN surgery following chemotherapy was a useful technique for staging the axilla after chemotherapy when surgical standards were utilized including dual tracer technique and removal of more than two SLNs.

Another study that was recently reported was from the German SENTINA (SENTInel NeoAdjuvant) trial group (40). This was a four-arm prospective multicenter trial evaluating the timing of SLN biopsy in patients receiving neoadjuvant chemotherapy. The patients were categorized into four different groups according to the clinical staging of the axilla prior to chemotherapy treatment. Patients with a clinically node-negative axilla underwent SLN biopsy before chemotherapy and if the SLN was negative they had no further surgery after chemotherapy (arm A). If the SLN was positive (arm B) the patients had SLN biopsy again after chemotherapy. Patients who were clinically node-positive prior to chemotherapy (cN1) had SLN biopsy if they converted to clinically node-negative with chemotherapy (arm C) and had ALND if they remained clinically node-positive after chemotherapy (arm D). The false-negative rate in arm C patients was 14.2%. In a multivariate analysis the number of SLNs removed was a significant predictor of the false-negative rate. In the patients who had SLN biopsy before and after chemotherapy (arm B) the false-negative rate was 51.6%. The results of SLN surgery after chemotherapy in multicenter trials are summarized in Table 57-2.

In conclusion, sufficient data exist to demonstrate that sentinel lymph node surgery after neoadjuvant systemic treatment is an appropriate standard of care for patients who present with clinically negative lymph nodes. This technique offers the advantages of improved convenience and costs in avoiding a separate surgery prior to neoadjuvant treatment and results in fewer overall axillary lymph node dissections. For patients who present with clinically positive lymph nodes who convert to lymph node–negative disease after neoadjuvant systemic treatment, the use of sentinel lymph node surgery without an axillary dissection remains controversial and should be used selectively. It is clear in the patients who present with clinically node-positive disease that surgical technique is critical in lowering the false-negative rate of SLN surgery after chemotherapy.

IMPACT ON RADIATION TREATMENT DECISIONS

It has been established that adjuvant radiation after mastectomy and regional lymph node irradiation benefit a large percentage of breast cancer patients with lymph node–positive breast cancer. Meta-analyses of the trials evaluating patients treated with mastectomy indicated that adjuvant radiation significantly reduced recurrence and improved survival for patients with lymph node–positive disease and did not provide a clinically relevant benefit for patients with lymph node–negative disease (41,42). In addition, the recently presented Canadian MA.20 trial that evaluated patients treated with breast conservation, most of whom had lymph node–positive disease, showed a lower rate of

TABLE 57-2

Multicenter Studies Evaluating Sentinel Lymph Node Surgery after Neoadjuvant Chemotherapy

Authors	*Year*	*Stage/Eligibility*	*Method of Lymphatic Mapping*	*No. of Patients*	*No. of Node-Positive Patients*	*No. with SLN Identified*	*ID Rate*	*No. with FN SLN*	*FN Rate (%)*
Tafra et al. (53)	2001	Predefined protocol for SNB	Blue dye + radiocolloid	29	15	27	93%	0	0
Mamounas et al. (31)	2005	TI-3, N0-1 No predefined protocol for SNB	Blue dye, radiocolloid, or combination	428	140	363	85% Blue dye: 77% Radiocolloid: 90% Combination: 88%	15	11% Blue dye: 14% Radiocolloid: 5% Combination: 9%
Classe et al. (32)	2009	T0-3, N0-1	Blue dye + radiocolloid	195	52	176	90% cN0: 94.6% cN1: 81.5%		11.5% cN0: 9.4% cN1: 15%
Boughey et al. (39)	2012	T0-3, N1	Recommended blue dye + radiocolloid	756	382	639 cN1: 605 cN2: 34	92.7% cN1: 92.9% cN2: 89.5%	39	cN1: 12.6%
Kuehn et al. (40)	2012	T0-3, N0-1		1,737			Arms A & B: 99.1% Arm C: 80.1%		Arm C: 14.2%

SLN, Sentinel lymph node; ID, identification rate, FN, false negative; cN0, clinically node negative; cN1, clinically node positive, N1; cN2, clinically node positive, N2.

local-regional recurrence and improvement in disease-free survival for patients randomized to breast and regional lymph node radiation versus radiation just directed to the breast (43). However, none of the patients entered into these important randomized trials were treated with neoadjuvant systemic treatments, therefore how the response to chemotherapy should affect radiation treatment decisions remains in question.

When neoadjuvant chemotherapy was introduced in breast cancer management it predominantly was used in patients with locally advanced, inoperable, and inflammatory breast cancer. For such patients, radiation treatment to the breast or chest wall and the regional lymph nodes was considered to be an important component of treatment. However, more recently neoadjuvant chemotherapy has been commonly used in earlier-stage disease, which has raised new questions regarding the indications for radiation therapy. For patients with clinical stage I or II disease, historically the decision to administer radiation therapy after mastectomy or its use to treat regional lymphatics was made predominantly on the basis of the pathological extent of disease. As noted previously, neoadjuvant chemotherapy changes the extent of pathological disease in 80% to 90% of cases, and fewer data are available to determine how the posttreatment pathological information should guide decisions regarding radiation treatment. One of the initial studies to investigate this question compared the local-regional recurrence risk associated with the pathological extent of disease after neoadjuvant or adjuvant systemic treatments, mastectomy and no postmastectomy radiation. This study reported that for any pathological lymph node status or primary tumor size the local recurrence was higher among patients treated with chemotherapy first compared to those treated with surgery first (44). This is not particularly surprising; in the neoadjuvant chemotherapy group, the pathologic examination represented residual disease after treatment, whereas in those treated with surgery first, the extent of disease represented untreated cancer. However, these findings imply that the risk of local-regional recurrence for patients given neoadjuvant chemotherapy is determined by both the pretreatment clinical stage and the extent of residual disease as determined by pathologic assessment after chemotherapy.

Information concerning potential indications for postmastectomy radiation therapy for patients treated with neoadjuvant chemotherapy is limited and derived from retrospective analyses. The largest data source for determining predictors of local-regional recurrence in patients treated with neoadjuvant chemotherapy and mastectomy comes from the retrospective study of 1,946 patients treated on the NSABP B-18 and B-27 trials (20). In both of these studies, radiation use was not recommended for patients treated with mastectomy. The 10-year rate of local-regional recurrence for these patients was 12.6%. In a multivariate analysis, clinical T3 disease, clinically node-positive disease, pathologically positive lymph nodes after neoadjuvant chemotherapy, and lack of a complete response of the breast primary were independent predictors of local-regional recurrence. For patients who presented with T1 or T2 disease, the risk of local-regional recurrence was over 10% if pathologically positive lymph nodes were present after neoadjuvant chemotherapy but much lower if lymph nodes were negative after neoadjuvant chemotherapy. For patients with T3 disease, lymph node status after chemotherapy again predicted for local-regional recurrence. Cohorts with a less than 10% local-regional recurrence rate included those with clinical T3N0 disease and who had pathologically negative lymph nodes and those with T3N1 disease who had a pathological complete response.

Limited data are also available concerning the efficacy of postmastectomy radiation in patients treated with neoadjuvant chemotherapy. One of the first published studies investigating this issue compared the outcomes of 579 patients who received neoadjuvant chemotherapy, mastectomy, and radiation therapy with those of 136 patients who were treated with neoadjuvant chemotherapy and mastectomy (45). Patients in this study had been treated in prospective trials but radiation therapy was not a randomized variable in any of the trials, so significant imbalances in the prognostic factors were present between the two groups. Patients with worse disease characteristics were more often referred for and treated with radiation therapy, as evidenced by the higher percentage of patients with stage III clinical disease stage in the radiation group. Despite this, the local-regional recurrence rate was found to be significantly lower in the group treated with postmastectomy radiation therapy than in the group treated with neoadjuvant chemotherapy and mastectomy without radiation (10-year local-regional recurrence rates were 8% and 22%, respectively, $p = .001$). For patients with clinical stage III disease or extensive disease after chemotherapy, radiation led to significant improvements in local-regional recurrence and overall and cause-specific survival rates. Multivariate analyses indicated that use of radiation was independently associated with a lower risk of local-regional recurrence (hazard ratio [HR] for not receiving radiation therapy 7.0, $p < .0001$) and a lower risk of death due to breast cancer (HR for not receiving radiation therapy –2.03, $p < .0001$) (45).

The same group of investigators has also shown that among patients with stage III disease who achieved a pCR, the local-regional recurrence rate for those treated with radiation therapy was 7% versus 33% for those who did not receive radiation therapy ($p = .040$) (46). Radiation use in these patients was also associated with an improvement in survival. Finally, this group also tried to address which patients given neoadjuvant chemotherapy for clinical stage II breast cancer should receive radiation therapy. They examined 132 such patients who had not received radiation therapy and found that the small number of patients with clinical T3N0 disease and those with four or more positive lymph nodes had high rates of local-regional recurrence (47). However, the 42 patients with clinical stage II disease who had one to three positive lymph nodes after neoadjuvant chemotherapy had a relatively low rate of local-regional recurrence (5-year rate of 8%).

Investigators from the University of Miami also examined the outcome of postmastectomy radiation in 464 patients treated with neoadjuvant chemotherapy. They reported a local-regional recurrence rate of 6%, but noted that advanced presenting clinical stage, a high degree of residual pathological disease after neoadjuvant treatment, and ER-negative disease all independently predicted for higher rates of local-regional recurrence (48).

Additional retrospective analyses of single-institution small studies were recently compiled in a critical review performed in an attempt to provide further insights into radiation indications (49). This study identified 24 relevant studies, 23 of which were retrospective and conducted in single institutions. The authors reported the following cohorts of patients had low risk of local-regional recurrence without radiation and therefore could potentially be spared postmastectomy radiation: patients over the age of 40 with clinical stage II, estrogen-receptor-positive disease with pathologic zero to three positive nodes without lymphovascular invasion or extracapsular extension. This study provides recommendations that are consistent with an early statement of the science report for the National Cancer Institute (50).

In aggregate, these findings suggest that recommending postmastectomy radiation therapy is reasonable for all patients with clinical stage III disease and those with positive lymph nodes after treatment with neoadjuvant chemotherapy. Clearly, however, additional studies are needed to quantify the local-regional recurrence risk for patients who present with T1 or T2 disease and have zero to three positive lymph nodes after neoadjuvant chemotherapy.

Future Directions

A major potential advantage of using neoadjuvant systemic treatments would be to permit the tailoring of local-regional treatment recommendations based on disease response. Specifically, based on the data available to date it is reasonable to ask whether patients with a very favorable response could potentially avoid the toxicities of more aggressive local-regional therapies. Two recently activated phase III trials investigate this concept; one with respect to axillary management and one with respect to avoidance of postmastectomy or regional lymph node radiation.

The recently approved axillary management trial is being led by the Alliance Group (A11202 trial). This trial will study patients who present with node-positive disease and who continue to have positive SLNs after chemotherapy despite no longer having clinical evidence of gross residual lymph node disease. Patients will be randomized to the current standard of care of performing axillary lymph node dissection plus breast or chest wall and nodal irradiation versus avoidance of axillary lymph node dissection and use breast or chest wall and nodal irradiation to eradicate potential residual microscopic disease within the undissected lymph nodes. If this trial is able to achieve equivalence results, the avoidance of an axillary dissection for patients will likely result in less patient morbidity and lower costs.

The radiation trial for patients being treated with neoadjuvant chemotherapy is being led by NSABP and RTOG (NRG 9353 trial). This study will enroll patients with initial node-positive disease who convert to node negative with chemotherapy (determined by SLN surgery or ALND). Eligible patients for this study will include those with clinical T1-3N1 disease who have pathologically negative lymph nodes after neoadjuvant chemotherapy. All patients treated with breast conservation will receive radiation to the breast and the study will randomize these patients to the addition or omission of regional lymph node radiation. For patients treated with mastectomy, randomization will be between radiation to the chest wall and draining lymphatics versus no radiation. The schema of these trials is shown in Figure 57-2.

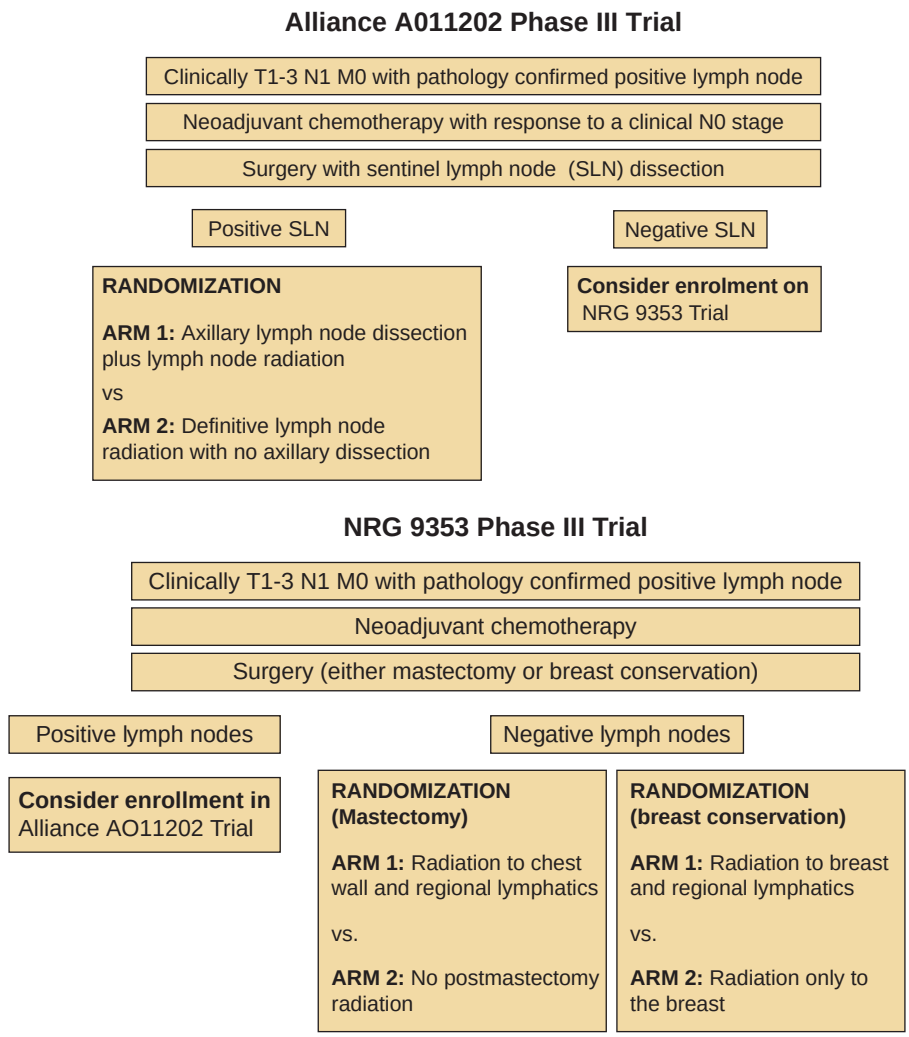

FIGURE 57-2 Schema of the Alliance A11202 trial and the NRG 9353 trial.

MANAGEMENT SUMMARY

- Preoperative or neoadjuvant systemic therapy has been shown to increase the use of breast-conserving therapy and can decrease the use of axillary dissection.
- The use of preoperative systemic therapy in patients with operable breast cancer has created new challenges for breast surgeons and radiation oncologists. There are as yet few results from randomized clinical trials testing local treatments.
- Clinical and radiological assessment of the extent of primary cancer before and after preoperative chemotherapy is important. Physical examination, mammography, and ultrasonography are the standard methods of assessment, but their performance characteristics in predicting a pathologic complete response are not optimal.
- MRI may provide a better means to assess response. Studies are underway to test this. Other newer imaging methods are being tested as well.
- A core needle biopsy should be performed on all suspicious abnormalities found in the ipsilateral and contralateral breasts before chemotherapy. Radiopaque clips should be placed within all malignant tumors to provide localization for subsequent surgical removal.
- Surgical resection of the tumor bed to confirm the clinical or radiographic impression of complete response is an essential part of management.
- SNB can be performed either before or after preoperative chemotherapy. There are potential advantages and limitations with each approach, but increasingly SNB after neoadjuvant systemic is the standard of care for patients who present with clinically negative lymph nodes.
- The use of SNB after neoadjuvant systemic therapy for patients who present with clinically positive lymph nodes who convert to negative nodes is currently under investigation.
- In patients treated with breast-conserving surgery, clearly negative margins of resection should be obtained. Even in patients with a pathological complete response in the breast, breast RT should be used.
- For patients treated with mastectomy, chest wall and regional nodal RT should be considered for patients who present with clinical stage III disease or have histologically positive axillary nodes after preoperative chemotherapy. With some possible exceptions, patients with clinical stage I or II disease at presentation who have a pCR after preoperative chemotherapy do not require PMRT. The use of PMRT in patients with clinical stage I or II disease at presentation who have negative nodes but residual disease in the breast is uncertain.

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CHAPTER 58

Locally Advanced Breast Cancer

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CHAPTER CONTENTS

DEFINITION

Locally advanced breast cancer (LABC) remains an important public health problem and a challenging management problem around the world (1). In groups of women who participate in periodic screening programs, the incidence of LABC is lower than 5%, whereas in medically underserved areas of the United States, and in many developing countries, LABC represents 40% to 60% of newly found malignant breast neoplasms (2–3). It can be estimated that between 400,000 and 550,000 new cases of LABC are diagnosed around the world every year.

LABC includes large primary tumors (>5 cm, T3 in the AJCC Cancer Staging System) (4), tumors of any size associated with skin or chest wall involvement (T4), tumors with fixed or matted axillary lymph nodes (N2), and those with involvement of the ipsilateral infraclavicular and supraclavicular lymph nodes (N3). Operationally, even moderate-sized tumors, 3 to 5 cm in size, located in a small breast are best treated with similar combined-modality approaches. The management of patients with LABC has evolved substantially over the past four decades, and this chapter will summarize current therapeutic options.

HISTORICAL PERSPECTIVE

Adjuvant systemic treatments have become integral components of the curative management of primary breast cancer (5). Postoperative adjuvant chemotherapy, hormone therapy, and trastuzumab produce highly significant reductions in odds of recurrence and death from breast cancer for patients of any age, with node-negative or node-positive tumors. The effectiveness of systemic therapy varied markedly, however, based on predictors of therapeutic benefit. Thus, only patients with estrogen and/or progesterone receptor-positive breast cancer benefit from endocrine therapy; only patients with overexpression or amplification of HER2 benefit from trastuzumab. In addition, the efficacy of chemotherapy is several-fold greater in patients with negative hormone receptors than in patients with positive hormone receptors.

Randomized trials designed for stage III breast cancer suggested that adjuvant systemic therapies also decreased the probability of recurrence and death in this group of patients (6). Most of the information about the management of LABC is based on phase II trials. Therefore, the levels of evidence on which many of the recommendations made in this chapter are based are lower than the levels of evidence that support adjuvant systemic therapy.

Historically, patients with LABC treated with surgery only fared poorly: although surgical resection was technically possible in most patients with LABC, 10 years after diagnosis more than 80% of patients had succumbed to the disease (6). On the basis of this experience, Haagensen and Stout defined the concepts of operable and inoperable breast cancer (7).

Subsequent to Haagensen's landmark publication, patients with inoperable tumors were treated with radiation therapy alone or associated with surgical resection (6). However, the large doses of radiation necessary to optimize local control, were often associated with long-term complications, including skin and chest wall fibrosis, skin ulceration, pulmonary fibrosis, rib necrosis or resorption, brachial plexopathy, and lymphedema of the arm (8,9).

It was on this background that the initial combined modality treatment approaches were developed, in parallel with the postoperative adjuvant chemotherapy programs.

There is general agreement that combinations of systemic and local/regional therapies represent the standard of care for all patients with LABC.

DIAGNOSIS AND STAGING

Most LABCs are easily palpable and even visible. Many represent neglected primaries present for months or sometimes years before the initial diagnosis. Patients may be aware of the breast or lymph node abnormality, but because of fear, denial, or lack of access to appropriate healthcare, they delay seeking medical attention. However, some LABCs present with diffuse infiltration of the breast and without a dominant mass. On mammographic or sonographic assessment they often appear as large areas of calcification, or parenchymal distortion; sometimes skin thickening is also present. Occasionally, even large lesions are mammographically and sonographically silent and magnetic resonance imaging (MRI) is needed for definitive imaging.

A core needle biopsy usually establishes the histologic diagnosis; incisional biopsies are seldom required. Some recommend a full-thickness skin biopsy (punch biopsy) when inflammatory breast cancer (IBC) is suspected. However, although the presence of dermal lymphovascular tumor emboli is pathognomonic of IBC, lack of dermal involvement does not exclude it. If an experienced cytopathologist is available, the diagnosis of malignancy can be confirmed by fine-needle aspiration cytology (FNAC); nuclear grade, flow cytometry, estrogen- and progesterone-receptor status and HER-2/neu can all be assayed on FNAC samples, and so can most other proposed prognostic indicators (Ki-67, etc.). However, FNAC cannot differentiate invasive from noninvasive tumors. If palpable regional nodes exist, a positive fine-needle aspirate of a node confirms the presence of invasive breast cancer. Once the diagnosis is established, the extent of tumor involvement needs to be ascertained. Bilateral mammogram serves to assess the known primary tumor and to rule out the presence of multifocal and multicentric disease and synchronous bilateral cancer or contralateral metastases. Sonography serves to further define tumor dimensions and to detail any regional lymph node involvement. Sonographic examination preferably should include, in addition to the breast and axillary area, the infraclavicular, supraclavicular, and internal mammary lymph node chains. The extra-axillary nodal basins are commonly involved in LABC. Our recent review of 865 patients with LABC staged by ultrasound showed a 37% probability of infraclavicular, supraclavicular, or internal mammary involvement (10). For lesions poorly defined by mammography or sonography, MRI can be helpful. Bilateral MRI is used at some institutions for baseline assessment of extent of tumor involvement, additional foci of cancer, and following neoadjuvant systemic therapy to assess response to therapy. This is particularly true of some subtypes of breast cancer that are frequently mammographically occult, such as invasive lobular cancer or inflammatory breast cancer. Accurate imaging evaluation at baseline and following systemic therapy is critical to guide optimal local/regional therapy planning and for assessment of response. A biochemical survey, chest radiograph, and bone scan complement a complete physical examination, with quantitative documentation of all palpable abnormalities. Abdominal imaging (computerized tomography [CT] or sonography) is recommended to rule out intraabdominal metastases. Areas of increased radionuclide uptake on bone scan are assessed by radiographs, MRI, or CT scanning. Other tests are indicated only by specific symptoms or for investigational purposes. Increasingly, positron emission tomography (PET) combined with CT is also being employed to assess extent of disease and rule out metastatic deposits at the time of diagnosis.

DEVELOPMENT OF COMBINED MODALITY STRATEGIES

Systemic therapy was introduced in the management of inoperable breast cancers more than 40 years ago (11,12). Surgery or radiotherapy, or both, followed systemic therapy in these trials. For optimal utilization of all treatment modalities, all interested specialists (radiologist, pathologist, and surgical, radiation, and medical oncologists) should review the diagnostic data, examine the patient, and determine the optimal type and sequence of therapies before any treatment is implemented. Treatment strategies that include neoadjuvant systemic therapy have several potential advantages: early initiation of systemic therapy, *in vivo* assessment of response, and reduction in the extent of primary tumor and regional lymphatic metastases. The potential (theoretical) shortcomings include delay in local treatment, induction of drug resistance, and unreliability of clinical staging. The practical advantages have exceeded, by far, the disadvantages. The ability to monitor response to therapy by serial measurements of the primary tumor, and the reduction in tumor volume that often permits breast conservation, are the two major clinical advantages of these treatment strategies. However, neoadjuvant systemic therapy also represents an unparalleled research platform, facilitating biomarker discovery, such as identification of predictors of response, pharmacodynamics markers of response (early tumor changes that predict response), and biomarkers associated with residual, therapy-resistant disease. Further, neoadjuvant systemic approach can allow for testing of the efficacy of novel combination therapies, expediting drug development.

Neoadjuvant Chemotherapy (NACT)

The first clinical trials with NACT (also called induction chemotherapy, primary chemotherapy, or preoperative chemotherapy) started in the late 1960s, but the earliest reports were published in the 1970s (11,12). Since then, multiple reports have documented the effectiveness of primary systemic therapy in patients with LABC (summarized in reference 6). Most reports of combined modality therapy of locally advanced breast cancer are based on anthracycline-containing combination chemotherapy regimens (see also Chapter 44, Adjuvant Chemotherapy). Administration of combination chemotherapy produces major reductions in tumor volume in 60% to 90% of patients. Tumor reduction has been consistently documented in both the primary tumor and the enlarged regional lymph nodes (6,11–18,). Although mixed responses (response in the primary tumor and no response in the regional lymph nodes, or vice versa) have been reported, they are uncommon (18–20). Clinical complete remissions have been reported in 10% to 20% of patients with LABC treated with anthracycline-containing combination chemotherapy regimens (6,18–21). Response rates, and especially complete response rates, improve if a taxane is added, especially in sequential regimens. The median number of cycles required to achieve a partial remission was reported to be four, and for a complete remission, five (13). Pathological complete remission (pCR) (20–21) is uncommonly obtained with chemotherapy in ER positive tumors, and is rare after neoadjuvant endocrine therapy. Since the introduction of trastuzumab, a number of reports indicated that, in combination with chemotherapy, trastuzumab produces pCR rates ranging from 20% to 70% in HER2-amplified or overexpressing breast cancers (22). Clinical measurements of breast masses

are often inaccurate, and there is substantial interindividual variation among examiners (23). Therefore, imaging methods are often used to more reliably document extent of disease (24). The combination of physical examination with either mammography or ultrasound gives measurements that closely approach those achieved by histopathology, and it reduces error rates in serial monitoring of response to systemic therapy (24). MRI may also be used to determine extent of disease (25). The determination of clinical complete remission requires that no residual disease be present by physical examination and by imaging (mammography and/or ultrasound) in the breast or regional lymph nodes (17). Even following these criteria, only half to two-thirds of patients thought to have a clinical complete remission are found to have a pathologic complete remission (i.e., no residual disease) (17,18,20,21,24). Furthermore, a third of patients with no residual disease by histologic examination will have residual clinical or imaging abnormalities that preclude the diagnosis of clinical complete remission. Patients who achieve a histologically documented complete remission have a markedly improved long-term prognosis compared with patients who achieve incomplete or no responses (17,21,26). Furthermore, these patients are often excellent candidates for breast-conserving strategies, with or without surgical intervention (27). In recent years, in addition to refinements to the sequential evaluation of extent of disease during therapy utilizing mammography, sonography, and MRI, positron emission tomography (PET) has been evaluated. Several authors have reported that not only does PET (usually in combination with CT, PET/CT) identify metastatic lesions not found by other imaging modalities (28) but also it is a very sensitive tool to monitor the functional status of the tumor. Thus, changes in PET imaging, such as marked reductions in standardized uptake values, are under evaluation for early determination of response to neoadjuvant systemic therapy (29).

Most initial reports of combined-modality treatment of LABC were based on anthracycline-containing combination chemotherapy regimens, such as doxorubicin, and cyclophosphamide (AC) or fluorouracil, doxorubicin/epirubicin, and cyclophosphamide (FAC or FEC). Over the past two decades, multiple reports have documented the benefits of the use of anthracycline and taxane combinations (27,30,31). These newer regimens were reported to have marked antitumor activity, with overall response rates in the 80% to 95% range. Unfortunately, the reported clinical and pathologic complete remission rates were only modestly higher than those reported with older combinations. Table 58-1 summarizes prospective randomized trials that compare anthracycline- and taxane-containing regimens with anthracycline-containing combinations without a taxane (26–27, 30–40). In several randomized trials in which a taxane was administered sequentially, after the initial four cycles of an anthracycline/cyclophosphamide-containing neoadjuvant regimen, a significant increase in pathologic complete remission was reported (26,32). In a small, multicenter trial conducted on patients with LABC, the increase in clinical and pathologic complete response rate was associated with improved disease-free and overall survival rates (32–41). Of note, both responders and nonresponders to the initial anthracycline-containing combination benefited from crossover to docetaxel. The National Surgical Adjuvant Breast and Bowel Project (NSABP) protocol B-27 included a crossover to docetaxel after four cycles of neoadjuvant doxorubicin and cyclophosphamide (AC); the addition of docetaxel resulted in significant increases in overall and complete response rates, pathologic complete response rates, and increased breast-conserving surgery rates (26). However, while there was a borderline improvement in relapse-free survival, the primary endpoint of the study, improved disease-free survival, was not significantly altered. However, this study was underpowered to detect clinically significant differences in survival. It is estimated that for each 10% increase in pCR rate a 2.6% improvement in survival might be observed (26). Other drugs under investigation in the neoadjuvant setting are gemcitabine, vinorelbine, platinum analogs, ixabepilone, eribulin, trastuzumab, pertuzumab, trastuzumab emtansine, bevacizumab, and lapatinib. Single-agent trastuzumab was reported to achieve a 23% partial response rate after three weeks of treatment in patients with LABC in one study and a 45% response rate in another (42,43). In combination with a taxane or vinorelbine, or two-drug combination chemotherapy regimens, clinical CR rates of 24% to 59% were reported (22,44,45). The corresponding pCR rates ranged from 18% to 45%. In a small randomized trial of sequential paclitaxel followed by fluorouracil, epirubicin, and cyclophosphamide, with or without trastuzumab, pCR rate increased from 26% to 65% with the addition of trastuzumab (46). These results

TABLE 58-1

Randomized Phase III Studies Comparing Anthracycline- and Taxane-Containing Regimens with Anthracycline-Containing Combinations without Taxanes

Author (Ref. no)	*n*	*Clinical stage*	*Treatment*	*ORR (%)*	*pCR (%)*
Smith et al. (32)	162	IIB, III	CVAP vs. CVAP + docetaxel	64 vs. 85 ($p = .03$)	15 vs. 31 ($p = .06$)
Vinholes et al. (33)	407	IIIA, IIIB	Docetaxel + doxorubicin vs. FAC	72 vs. 63 ($p = .0056$)	16 vs. 11
Luporsi et al. (34)	90	II, III	FEC vs. ET	72 vs. 84	24 vs. 24
NSABP B-27 (26)	2411	II	AC vs. AC + T + surgery vs. AC + surgery + T	85 vs. 91	14 vs. 25
Evans et al. (35)	365	II, III	AC vs. AT	78 vs. 88	12 vs. 8
Buzdar et al. (36)	174	II–IIIA	Paclitaxel vs. FAC	80 vs. 79	8 vs. 14
Dieras et al. (37)	247	IIA, IIB, IIIA	AC vs. AT	10 vs. 16	66 vs. 83
Green et al. (38)	127	I, II, IIIA	T q 3 weeks vs. weekly T	18 vs. 31	N/A N/A
Untch et al. (39)	475	II, IIIA+B	Dose-dense sequential E to T, vs. standard ET	18 vs. 10	N/A N/A

CVAP, cyclophosphamide, vincristine, doxorubicin, prednisone; FAC, 5-fluorouracil, Adriamycin (doxorubicin), cyclophosphamide; FEC, fluorouracil, Epirubicin, cyclophosphamide; ET, Epirubicin, paclitaxel; AC, Adriamycin (doxorubicin) and cyclophosphamide; AT, doxorubicin, docetaxel; T, paclitaxel; ORR, overall response rate; N/A, not available.

TABLE 58-2

Effective and Well-Tolerated Induction Chemotherapy Regimens

Regimen—Drugs	*Doses, Route, and Day of Administration*	*Frequency and Number of Cycles*
Dose Dense AC-T		
Cycles 1–4		
Doxorubicin	60 mg/m^2 IV, day 1	Every 2 weeks × 4 cycles
Cyclophosphamide	600 mg/m^2 IV, day 1	Every 2 weeks × 4 cycles
Perfilgrastim	6 mg SQ, day 2	Every 2 weeks × 4 cycles
Cycles 5–8		
Paclitaxel[a]	175 mg/m^2 IV, day 1	Every 2 weeks × 4 cycles
PACLITAXEL/FAC		
First 3 months		
Paclitaxel[b]	80 mg/m^2 IV, day 1	Every week × 12 weeks
Final 3 months		
5-Fluorouracil	500 mg/m^2 IV, day 1	Every 3 weeks × 4 cycles
Doxorubicin	50 mg/m^2 IV, day 1	Every 3 weeks × 4 cycles
Cyclophosphamide	500 mg/m^2 IV, day 1	Every 3 weeks × 4 cycles
TAC		
Docetaxel	75 mg/m^2 IV, day 1	
Doxorubicin	50 mg/m^2 IV, day 1	Every 3 weeks × 6 cycles
Cyclophosphamide	500 mg/m^2 IV, day 1	Every 3 weeks × 6 cycles
Perfilgrastim	6 mg SQ, day 2	Every 3 weeks × 4–6 cycles
TC		
Docetaxel	75 mg/m^2 IV, day 1	Every 3 weeks × 4–6 cycles
Cyclophosphamide	600 mg/m^2 IV, day 1	Every 3 weeks × 4–6 cycles
REGIMENS WITH TRASTUZUMAB		
DOSE DENSE AC-TH		
Cycles 1–4		
Doxorubicin	60 mg/m^2 IV, day 1	Every 2 weeks × 4 cycles
Cyclophosphamide	600 mg/m^2 IV, day 1	Every 2 weeks × 4 cycles
Perfilgrastim	6 mg SQ, day 2	Every 2 weeks × 4 cycles
Cycles 5–8		
Paclitaxel	175 mg/m^2 IV, day 1	Every 2 weeks × 4 cycles
Trastuzumab	4 mg/kg IV, day 1, followed by 2 mg/kg IV	Weekly for 1 year
TCbH		
Docetaxel	75 mg/m^2 IV, day 1	Every 3 weeks × 6 cycles
Carboplatin	AUC = 6 IV, day 1	Every 3 weeks × 6 cycles
Trastuzumab	8 mg/kg IV, day 1, followed by 6 mg/kg	Every 3 weeks for 1 year

[a]Paclitaxel, 80 mg/m^2 IV every week × 12 weeks can be substituted.
[b]Docetaxel, 100 mg/m^2 IV every 3 weeks × 4 cycles can be substituted (before or after FAC).

were confirmed by a larger randomized trial that included 235 patients with HER-2/neu-positive primary breast cancer (47). A large, multicenter confirmatory study has completed accrual patients with T2 and T3, HER-2-positive breast cancer (ACOSOG protocol Z1041). Gianni and collaborators also reported the initial results of a four-arm randomized trial comparing neoadjuvant docetaxel plus trastuzumab with docetaxel plus pertuzumab, docetaxel plus both antibodies, or the two antibodies without chemotherapy (48). Pathological complete remission rates were 31%, 23%, 49%, and 18%, for the four arms, respectively, indicating that combining the two antibodies with chemotherapy provides the best result, while the two antibodies without chemotherapy were able to eradicate the primary tumor in almost 20% of patients.

Table 58-2 lists the more commonly used effective and well-tolerated neoadjuvant chemotherapy regimens.

NEOADJUVANT ENDOCRINE THERAPY

Most of the clinical investigation with neoadjuvant systemic therapy was conducted with cytotoxic therapy. More limited information is available about neoadjuvant endocrine therapy (see also Chapter 55, Preoperative Endocrine Therapy for Operable Breast Cancer). For patients with estrogen receptor-positive (ER+) breast cancer neoadjuvant endocrine therapy is an appropriate option. The initial trials used tamoxifen and included patients selected on the basis of old age or comorbidity that precluded chemotherapy (49,50). The

results suggested that neoadjuvant endocrine therapy was therapeutically effective and produced marked reduction in tumor volume in 40% to 60% of patients. A significant minority of tumors progressed during neoadjuvant endocrine therapy; thus, close monitoring is required so that early progressors are identified promptly and appropriate regional therapy (or crossover to chemotherapy) can be implemented. Several studies also concluded that tamoxifen alone was insufficient therapy for patients with primary and locally advanced breast cancer, and that appropriate surgery and/or radiation therapy was needed for optimal local and systemic control (51,52). Endocrine therapy should be restricted to patients with hormone receptor–positive breast cancer. More recent trials compared selective aromatase inhibitors with drugs in the same family or with tamoxifen (53). Greater antitumor efficacy was observed with aromatase inhibitors compared to tamoxifen (53). In general, response to neoadjuvant endocrine therapy occurs in 35% to 50% of patients with hormone receptor–positive breast cancer, but fewer than 5% achieve pCR. Response rates to neoadjuvant endocrine therapies in this setting are lower than response rates to anthracycline/taxane based chemotherapy in unselected patients with LABC (52); pCR rates with neoadjuvant chemotherapy for patients with ER+ breast cancer are observed in 5% to 14%, several-fold lower than for patients with ER– breast cancer. Early progression is observed more frequently after neoadjuvant endocrine therapy (12% to 17%) (53) than after neoadjuvant chemotherapy (5% to 10%) (6). The poor prognosis for patients with LABC indicates that all treatment modalities are needed for optimal results, so all patients with positive estrogen and/or progesterone receptor assays should receive adjuvant endocrine treatment as part of multidisciplinary therapy. Whether there is a subset of patients with hormone receptor–positive LABC that does not benefit from, and therefore does not require, NACT is under active investigation.

Considerations for Imaging

A common denominator underlying clinical decisions about appropriate surgical treatment for LABC is the importance of accurate imaging. It is important at initial presentation to estimate tumor size and determine if the patient is a good candidate for NACT. During and after NACT, imaging of the primary tumor and the axillary lymph nodes is used to assess treatment response and aid in surgical planning.

Standard Imaging Modalities After NACT

Mammography and US have been shown to offer accurate predictions of pathologic tumor size in patients with small invasive ductal carcinomas without an extensive intraductal component, provided the patients have not received NACT (54,55). In patients who have received NACT, however, there have been widely disparate reports on the accuracy of these imaging approaches for predicting residual pathologic tumor size (24). Overall, as reviewed in the report from Chagpar and colleagues (54), physical examination appears to be at least as accurate as mammography or US in estimating residual tumor size, with correlation coefficients ranging from 0.42 to 0.73, compared to a range of 0.33 to 0.65 for mammography and 0.29 to 0.60 for US. However, the false negative rate associated with physical examination has been reported to be almost 60% (54), indicating that many small tumors might be missed using this approach. Similarly, the false positive rates from US and mammography may be 50% or higher, suggesting that these imaging approaches may pick up inflammatory or fibrotic changes induced by chemotherapy. The mixed reports about the usefulness of US and mammography in assessing residual tumor size have driven the search for more accurate imaging modalities. There is interest in using magnetic resonance imaging (MRI), as well as new approaches involving functional imaging and the tools of nanotechnology as well as additional refinements to mammography and US.

MRI for the Assessment of NACT Response

MR images of breast lesions are captured before and after the injection of a gadolinium-based contrast agent. Because malignant lesions are typically more vascular than benign lesions, they tend to take up the contrast agent faster. They can also be distinguished from benign lesions by having spiculated rather than smooth edges. MRI originally suffered from an unacceptably high rate of false positives, but improved algorithms for combining morphologic and kinetic data have greatly improved this picture, with specificity now ranging from 81% to 99% (55) (see Chapter 13). MRI is especially being pursued as an early predictor of pCR. Data from the ACRIN 6657/I-SPY trial demonstrated that change in MRI tumor measurements after one cycle of anthracycline-based NACT was a better predictor of pCR than clinical examination (56).

MRI may allow a more precise estimation of residual tumor than mammography or ultrasound (56,57). Despite its sensitivity, however, the ability of MRI to detect a complete pathologic response has shown great variability in different series, presumably because the limits of detection for MRI do not allow the identification of very small foci of *in situ* or invasive disease. For this reason, a negative report on MRI should be evaluated conservatively, and properly used only to assess a patient's candidacy for breast-conserving therapy (BCT). Further, a larger tumor extent on MRI in a patient who is eligible for breast conservation based on mammography or ultrasound should also be interpreted with caution. For this reason, several institutions, including MDACC, only selectively use MRI for patient management.

Other Approaches to Breast Imaging

Positron emission tomography (PET) produces images that reflect metabolic and physiologic functions occurring in living cells. A positron-emitting radionuclide is attached to a molecule (such as ^{18}F-fludeoxyglucose = FDG) that is ingested or metabolized at a high rate in the rapidly growing cancer cells. FDG-PET is very specific for the detection of malignant breast tumors, and problems with spatial resolution and "noise" from normal tissue can be reduced by using a small parallel pair of detector heads placed directly above and below the breast (58). A general problem with PET is the lack of anatomical specificity. This problem can be resolved by running the scan concurrently or sequentially with an alternate anatomical imaging modality. Andrade and colleagues (59) used hybrid PET/CT imaging to assess response to neoadjuvant chemotherapy in 45 patients with primary breast cancer. They were able to demonstrate a sensitivity of 90.9% and a specificity of 83.3% for the prediction of clinical response by PET/CT. Mammography can also be used as an anatomical imaging adjunct for PET; using the small parallel detector heads, the scan can be run concurrently or sequentially with mammography without releasing the breast compression (58) (see Chapter 14).

APPROACHES TO LOCAL THERAPY

The administration of NACT as the first modality of treatment, before surgical therapy is instituted, is favored by most experts for the management of stage III and most large stage II breast cancers (60). NACT results in major objective

responses and downstaging for approximately 70% to 95% of patients (6,14,17,18,61). Only 3% of patients experience tumor progression during NACT (62), this rarely (0.5%) leads to an increase in the scope of surgery required or inoperability (63). Surgical therapy may require a total mastectomy or only breast-conserving surgery (also referred to as wide excision, lumpectomy, or quadrantectomy), both with an axillary surgery (see also Chapters 33, Mastectomy; 35, Breast-Conserving Therapy, and 38, Axillary Dissection).

Considerations for Breast-Conserving Surgery

The use of NACT has become standard management for patients with LABC, in part because it frequently reduces the size of the primary tumor enough to allow previously inoperable tumors to become operable. For selected patients, (i.e., complete resolution of skin edema [peau d'orange], adequate reduction in the tumor size, no extensive intramammary lymphatic invasion, absence of extensive suspicious microcalcifications, and no evidence of multicentricity), BCT can be an appropriate local treatment option. In patients meeting these criteria, the local recurrence rate and 10-year overall survival after BCT are equivalent to those seen in early stage breast cancer patients (64).

As with any curative breast cancer surgery, the primary goal is to completely remove the tumor with negative margins. This is a potential problem in LABC patients treated with NACT because approximately 30% of these patients (and up to 60% of those treated with trastuzumab) will achieve a clinical complete response, making it difficult to locate the tumor site during surgery (65). In addition, nearly two-thirds of the patients with a clinical complete response will prove to have residual tumor on final pathology, so it is critically important to be able to precisely localize and remove the original tumor site and ensure that the surgical specimen has clean margins (65). This can be accomplished by the placement of a metallic marker in the tumor under US or mammographic guidance either at initiation of therapy (65), or when the tumor has shrunk to less than 2 cm in size during chemotherapy. Placement of two or more markers should be considered for multifocal disease in patients who are interested in breast conservation.

If the marker(s) is placed before the initiation of NACT, the tumor may shrink eccentrically, leaving the marker on the edge of the residual tumor, rather than in the epicenter. Platinum is preferable to the stainless steel rods that were originally used because it is more compatible with MRI. The marker is inserted with a long needle and a blunt stylet under US guidance. Alternatively, we may use stereotactic clips, which are much smaller in size. Mammography is performed immediately after marker implantation to precisely document the position of the marker in relation to the tumor.

At the beginning of surgery a guide wire is inserted by the radiologist under US or mammographic guidance to indicate the location of the marker. Bracketing with two or more guidewires is used for patients with extensive calcifications or multifocal disease at the onset. Surgical excision does *not* attempt to remove the pre-chemotherapy volume of tumor. Rather, the goal is to remove any residual lesion with 1 cm of clear margins or, if there is no detectable residual lesion, a 2-cm specimen with the metal coil in the center. When the specimen is removed, the orientation is designated. Margins are inked; a multicolor inking system may be used to identify the superior, inferior, lateral, medial, anterior, and posterior surfaces (Fig. 58-1). In pathology, a specimen radiograph is

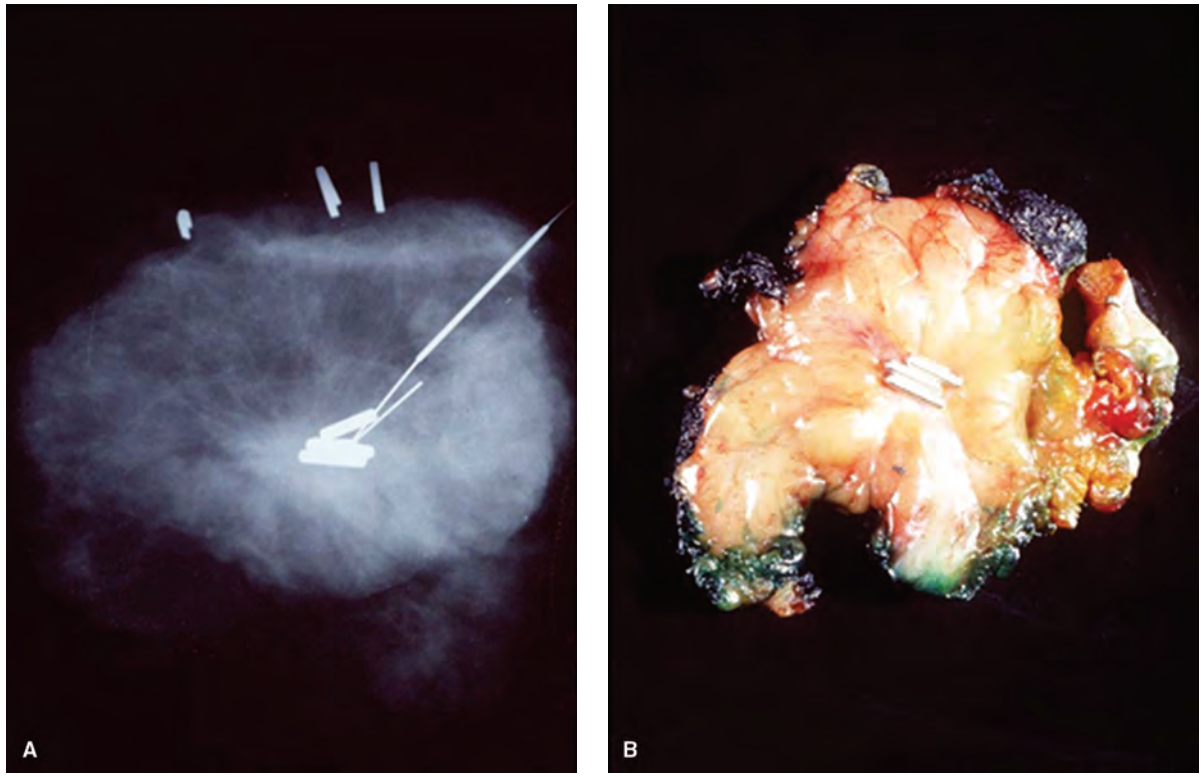

FIGURE 58-1 **(A)** Specimen radiograph showing position of metal markers and guidewire inside the excised specimen. **(B)** Metal markers in the sectioned specimen. (Photographs courtesy of Dr. Henry Kuerer and Dr. Peter Dempsey.)

taken to verify the presence of the marker within the excised specimen. While the patient is still in surgery, the specimen may be sectioned, with the order of all sections maintained so that the site of any positive or close margin can be identified and the surgeon can remove additional tissue from this area to obtain a negative margin.

The clinical definition of LABC has traditionally included tumors of any size that are associated with skin or chest wall involvement, classified as T4 in the AJCC Cancer Staging System (4). Classification of a tumor as T4b indicates the presence of noninflammatory skin changes, including edema, ulceration of the skin of the breast, or presence of satellite skin nodules confined to the same breast. Such skin involvement has been associated with a poor prognosis, and these patients traditionally have been recommended for mastectomy, under the assumption that local failure rates would be unacceptably high with BCT. However, emerging data suggests that carefully selected patients with noninflammatory T4b disease may be candidates for breast conservation.

Shen and colleagues (66) looked at local control and long-term survival in 33 patients with noninflammatory T4b disease treated with breast conservation therapy. The median tumor size at study entry was 7 cm (range 2–12 cm), and all patients had one or more types of skin involvement. After a median of 4 cycles of neoadjuvant chemotherapy (NACT), 28 patients had a complete or partial clinical response, and 28 patients showed a complete resolution of skin changes. At a median follow-up time of 91 months, only five patients (6%) had developed a locoregional recurrence (LRR), similar to rates observed in patients without noninflammatory skin involvement who received BCT after NACT. The 5-year overall survival rate was 78%, superior to most published survival data for patients with noninflammatory T4b disease, likely reflecting the careful selection criteria that were used.

This demonstrates that skin involvement at presentation is not an absolute contraindication for BCT, especially when found in combination with superficial smaller tumors and if negative margins can be achieved. This is true even for selected patients with skin ulceration, among the most alarming of symptoms and one that is usually associated with long-neglected locally advanced disease. For example, tumors of the inframammary fold can be quite small (≤1 cm) and present with skin ulceration. The direct skin involvement might occur as a result of the tumor's location very close to the skin surface. These patients can be treated conservatively with en bloc excision of the involved skin if the tumor demonstrates direct tumor invasion/ulceration, with favorable outcomes.

There have been concerns about the risk of LRR with breast-conserving surgical treatment (BCST) after neoadjuvant chemotherapy. However, multiple studies have demonstrated that BCT for locally advanced breast cancers after NACT is feasible and, if appropriate selection criteria are applied, safe and associated with high local control rates (14,67–70). When patients who underwent surgery after NACT were evaluated at MDACC, clinical N2 or N3 disease, residual pathologic tumor size more than 2 cm, a multifocal pattern of residual disease, and lymphovascular space invasion in the specimen were associated with higher risk of LRR in two independent cohorts (63,71). For patients undergoing BCT, the 5-year LRR-free survival rate was 92% if patients had none or only one poor prognostic factor, 84% when they had two unfavorable factors, and 69% when they had three or four factors. The 5-year LRR-free survival rates were similar between patients undergoing mastectomy or BCT when patients had 0, 1, or 2 poor prognostic factors. In patients who had 3 to 4, the 5-year LRR-free survival was significantly lower for patients treated with BCT compared with mastectomy (69% vs. 93%, p = .007) (71). Although, these factors do not represent absolute contraindications for BCT, they highlight a high-risk patient group in whom caution should be exercised in local-regional treatment planning.

Considerations for Management of the Axilla after NACT

LABC encompasses patients with clinical N2/N3 as well as clinically N0 patients with large primary tumors. Ultrasound of the regional node basins with percutaneous biopsy of suspicious nodes can assist in better regional staging of patients with LABC in several ways: in patients who have clinically node-negative axillae, by identifying, ultrasonographically, suspicious nodes that are involved and demonstrating their involvement by biopsy, and in patients with clinically node-positive disease, pathologically confirming nodal involvement as well as by determining extent of regional nodal involvement by assessing supraclavicular, infraclavicular, and internal mammary lymph node basins.

SLNB has become widely accepted and used because it offers accurate assessment with a substantially reduced occurrence of the morbidities usually associated with complete axillary lymph node dissection (e.g., edema, reduced mobility, pain, etc.). Most studies in SLNB have been performed in patients with early stage disease. However, there is increasing experience with use of SLNB in patients with clinically node-negative tumors with larger, non-inflammatory breast cancers. Although there was some initial controversy about use of SLNB in patients who were initially clinically N0 and then underwent NACT, a meta-analysis has demonstrated acceptable SLNB false-negative rates in such patients (72) and studies have shown adequate local-regional control with SLNB only in initially clinical N0 patients who underwent SLNB after NACT (73).

Patients with pathologically demonstrated nodal involvement at presentation are offered axillary lymph node dissection at completion of NACT, even if they have a complete clinical response in the breast and axilla. However, with the increasing utilization of targeted therapies, it is likely that pCR rates in the axilla will increase over the next decade. Notably, it has been shown that 74% of HER2 positive patients with axillary metastases confirmed by ultrasound-guided FNAC who received trastuzumab-containing NACT followed by breast surgery with complete axillary lymph node dissection were found to have a complete axillary response (74). ACOSOG Z1071 evaluated the role of sentinel node biopsy following NACT in women with clinically node-positive disease at presentation, and cooperative group studies are planned to determine the feasibility of less invasive strategies in selected patients with clinical nodal involvement and subsequent NACT.

Considerations for Reconstructive Surgery

Many patients with LABC will become good candidates for BCT after NACT, but some will still need or prefer to undergo a mastectomy. Current reconstructive techniques using autologous tissue flaps offer excellent cosmetic results without compromising long-term outcomes (see Chapter 36). Ideally, breast reconstruction can be carried out during the same surgery as the mastectomy, lessening the cost and the risk of multiple surgeries. However, there are potential restrictions to immediate reconstructions in patients with LABC that both physician and patient need to understand and discuss.

Patients with LABC are known to have a high risk of chest wall recurrences following mastectomy alone (75). For this reason, most are recommended for radiation therapy

(RT) of the chest wall and the axilla following surgery. The optimal sequencing of RT and reconstruction is controversial. Immediate breast reconstruction can be an important factor in recovery, contributing to a more positive body image. On the other hand, there has been concern that a reconstructed chest mound might interfere with the delivery of the proper radiation dose, especially to the internal mammary nodes, or that there might be volume loss and asymmetry in the flap as a side effect of the RT.

A report by Tran and colleagues (76) examined both early and late complications from RT in patients with a free transverse rectus abdominis myocutaneous (TRAM) flap breast reconstruction. Of 102 patients in the study, 32 had immediate TRAM flap reconstruction before RT and 70 had RT before delayed TRAM flap reconstruction. Mean follow-up times for the immediate reconstruction and delayed reconstruction groups were 3 and 5 years, respectively. There was a slightly higher rate of early complications from RT in patients who received delayed reconstruction, but the differences were not significant. Late complications, including fat necrosis, volume loss in the flap, and contracture in the flap, were significantly more common in patients with immediate reconstruction. Fat necrosis occurred in 44% of patients with immediate reconstruction compared with 9% of patients with delayed reconstruction. No patients with delayed reconstruction experienced volume loss or contracture, versus 88% and 75%, respectively, of patients receiving immediate reconstruction.

Foster and coworkers (77) argue that immediate breast reconstruction has minimal morbidity and that complications tend to be minor. Their study involved 35 patients who received immediate Transverse Rectus Abdominis Myocutaneous (TRAM) flap reconstruction followed by RT. At a minimum follow-up time of 1 year, they reported fat necrosis in 3 patients, two of whom developed volume loss of the flap and required additional surgery. Two patients had cellulitis, one developed a periumbilical hernia, and one experienced fascial laxity of the lower abdomen. Although the median follow-up time was 48 months, no data were presented about long-term cosmetic outcomes. In addition, there was no comparison group of patients who received RT prior to a delayed reconstruction.

Although most authors acknowledge that radiotherapy to an immediate reconstruction may impair the final cosmetic outcome for some patients, until recently there was no information about the impact of immediate reconstruction on radiotherapy planning. An MDACC study compared 110 patients who had mastectomy with immediate reconstruction and postoperative radiotherapy with contemporaneous stage-matched patients who had undergone mastectomy without intervening reconstruction (78). Each of the radiotherapy plans were assessed for completeness of coverage and avoidance of adjacent critical structures. Of the radiotherapy plans scored after reconstruction, 52% had compromises compared with 7% of matched controls ($p < .0001$). Left sided radiotherapy plans had larger compromises after immediate reconstruction than right sided ones. Because of this, the potential for compromised Post Mastectomy Radiation Therapy (PMRT) planning should be considered when deciding between immediate versus delayed reconstruction.

Overall, the timing of reconstructive surgery has remained somewhat controversial for patients who are known to need PMRT at the onset. At MD Anderson Cancer Center, reconstruction is either deferred until after the completion of RT in patients with LABC who receive a mastectomy, or performed with a tissue expander to facilitate preservation of the breast skin envelope, with the intent of subsequently performing an autologous reconstruction.

ROLE OF RADIATION THERAPY IN LABC

Comprehensive irradiation is an effective therapy to eliminate occult deposits of tumor in local and regional tissues after surgical removal of macroscopic tumor. Patients with stage III breast cancer have a 30% to 50% risk of local-regional recurrence when surgery or radiation is used as the sole local treatment (11,16,17,79,80). This level of risk indicates the need to administer radiation therapy after a total mastectomy and certainly after breast-conserving surgery (see also Chapters 35 and 42). For operable stage III breast cancer, the postoperative administration of chemotherapy and radiotherapy resulted in improved local control and overall survival rates, compared to the use of either adjuvant treatment alone. Advanced regional nodal involvement, poor response to chemotherapy, ER- tumors, extracapsular tumor, and involvement of the skin or nipple are associated with particularly high locoregional recurrence rates (81). For local/regional treatment to be effective, it must encompass all the volumes at risk, and it must eliminate any tumor cells therein. For LABC, this means treating the entire soft tissue of the chest wall, including any residual breast tissue, the surrounding skin, the connective tissue, and the regional lymphatics. Most local recurrences occur on the chest wall, followed in order of frequency by the axillary and supraclavicular chain and, infrequently, the internal mammary chain. Failure in the dissected axilla is unusual, provided no gross disease remains (82). In the presence of known residual disease, higher doses of radiation therapy are required, with the consequent increase in acute and long-term complications. For this reason, if there is residual disease after induction chemotherapy, surgical excision is preferred, particularly for disease that is larger than 1cm, followed by radiotherapy.

From a technical perspective, successful treatment planning results in field arrangements that accomplish the following four objectives:

1. Broad coverage of the chest wall;
2. Inclusion of the undissected nodal basins including the internal mammary, axillaryapical, and supraclavicular nodes;
3. Minimization of lung irradiation; and
4. Minimization of heart irradiation.

Most commonly, the chest wall is treated at MD Anderson Cancer Center with lateral tangential fields of 6-MV or combined 6- and 18-MV photons abutted to a medial electron beam field. Alternate field arrangements using only electrons or only photons may be used for treatment of patients with appropriate anatomic configurations. CT planning with heterogeneity correction is routine, but inverse-planned Intensity Modulated Radiation Therapy (IMRT) is not favored by the MD Anderson Breast Radiation Oncology group because of the limitations of current planning software to accurately model the dose in thin chest walls and the tendency for these plans to result in irradiation of large regions of the uninvolved thorax. In locally advanced breast cancers the internal mammary chain will contain tumor in more than 25% of patients subjected to Internal Mammary Chain (IMC) dissection (83). Thus, an adjacent, matching electron beam field is typically used to treat the lymph nodes of the internal mammary chain. With this technique, the left ventricle can be completely excluded from the irradiated volume, and a maximum of 2 to 3 cm of lung is treated (Fig. 58-2). Alternatively, a series of electron beam fields can be used to treat the chest wall and internal mammary nodes. The undissected lymphatics of the axillary apex and supraclavicular fossa are treated with low-energy photons or electrons. This field may frequently need to be expanded in patients with advanced presentations (especially if known supraclavicular

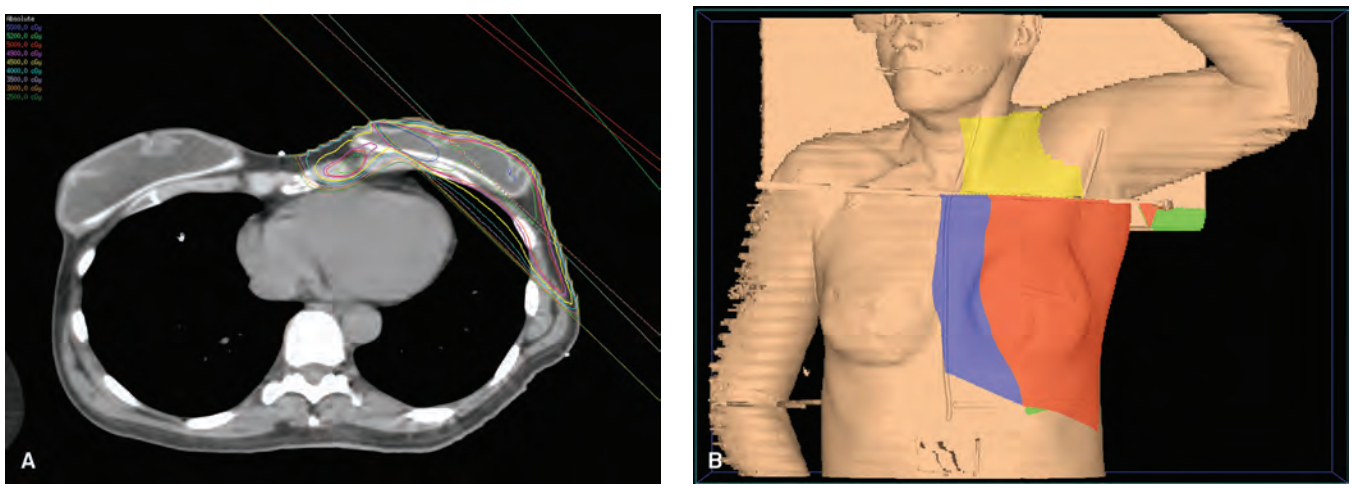

FIGURE 58-2 **(A)** Left postmastectomy radiotherapy isodose distribution. Use of multiple adjacent fields allows minimization of heart and lung volume. A tissue expander, placed at mastectomy, has been deflated to optimize radiotherapy planning. **(B)** Left postmastectomy radiotherapy field projections.

adenopathy has been documented) to cover all regions at risk (84). Fifty Gray is delivered in 25 fractions, followed by a boost to the chest wall, to a total dose of at least 60 Gy. Areas of initial nodal involvement not removed at surgery are also treated to 50 Gy followed by electron boosts to the site of original disease to achieve a total dose of 60 Gy for a complete response and 66 Gy for minimal residual disease. At these higher doses, care should be employed to avoid sensitive structures like spinal cord or brachial plexus. Combined-modality therapy offers excellent local control to 90% or more of those with stage IIIB or IIIC breast cancer who have no gross residual disease, and an even higher proportion of those with stage IIIA disease (17). However, if any part of the multidisciplinary treatment strategy is suboptimal, it compromises the efficacy of the entire program. All patients with Stage III breast cancer should receive postmastectomy RT even if a pathologic complete response is achieved by initial chemotherapy. Patients with clinical stage II breast cancer at the time of diagnosis and residual positive lymph nodes after neoadjuvant chemotherapy should also be considered for postmastectomy radiation therapy.

Unfortunately, a small minority of patients with advanced breast cancer will not respond to initial therapy. These patients present a difficult management problem because of tumor ulceration, necrosis, and superinfection, or regional consequences in the neck or brachial plexus. Radiotherapy, with or without concurrent chemotherapy, is an important tool to provide local symptom palliation for these individuals.

SEQUENCING TREATMENT MODALITIES

There are many possible ways to combine or sequence the therapeutic modalities used for breast cancer. The high incidence of distant metastases in patients with LABC makes the early introduction of systemic therapy imperative. Whether simultaneous chemotherapy and radiotherapy result in improved local and distant control compared to sequential administration of chemotherapy and radiotherapy remains to be established (85). Therefore, most combined-modality strategies for inoperable LABC start with induction chemotherapy, usually with an anthracycline and taxane-containing multidrug regimen. The extensive experience our group has acquired over the past four decades suggests that neoadjuvant chemotherapy followed by surgical resection, adjuvant chemotherapy, and consolidation radiotherapy is a well-tolerated, safe, and effective sequence of therapies for patients with LABC (17). In recent years, we have modified this sequence slightly on the basis of two important observations: the first, that the ability to monitor response (or lack of response) to systemic chemotherapy helps guide treatment. If there is no response, or progression of the tumor is demonstrated, the treatment being used can be stopped so that additional toxicity can be avoided, and another, non–cross-resistant chemotherapy regimen can be introduced. The second observation indicates that both responders and nonresponders to neoadjuvant chemotherapy benefit from a fixed crossover to another, non–cross-resistant regimen (32). Therefore, we now administer all chemotherapy before surgical resection, and we consistently use two chemotherapy regimens in sequence: FAC and a taxane-containing regimen. We and others have documented an increase in overall and pathologic complete response rates with this approach and have reduced the percentage of patients with primary resistance to neoadjuvant chemotherapy (26,32,38). Whether this increase in response is related to longer duration of chemotherapy or to the introduction of a second chemotherapy regimen has not been fully defined, although the limited data that exist seem to support the second explanation. Increased frequency and quality of objective responses is usually associated with down staging, thus facilitating the surgical procedure, and sometimes permitting breast conserving surgery even in patients with LABC. Whether administering all chemotherapy before surgery is better than administering some before and some after surgery has not been definitely established. The only large, prospective trial where these two approaches could be compared was NSABP B-27. In this study there was a trend favoring giving all chemotherapy up front, although this difference was not definitive (26). Because B-27 included only operable breast cancer, the relevance of these results to LABC is uncertain. It can also be stated that there is no apparent superiority (be it conceptual or empirical) to administering some chemotherapy before and reserving some for postoperative administration.

TABLE 58-3

Selection Criteria for Breast-Preserving Surgery after Neoadjuvant Chemotherapy

Patient desires BCT
Availability of radiotherapy
Family and/or social support systems available
Resolution of skin edema
Healing of skin ulceration
Residual solitary tumor size of <5 cm
No collagen vascular disease
No extensive intramammary lymphatic invasion
Absence of extensive suspicious microcalcifications
No known evidence of multicentricity
Clear surgical margins

The addition of trastuzumab to the preoperative treatment of patients with HER2-positive breast cancer has further increased overall and complete response rates (22,44–48). The addition of trastuzumab to multimodality treatment has also improved locoregional control. Adjuvant endocrine therapy should be administered to all patients with hormone receptor–positive breast cancer.

There are multiple patient and tumor characteristics that must be considered in the process of selecting candidates for breast-conserving therapy. There are very few absolute contraindications to breast-conserving therapy, although each of the factors listed may increase moderately the risk of recurrence within the breast. Selection of patients with LABC for breast-conserving therapy should be done with caution, and implemented only by groups with experience in combined-modality therapy. The MD Anderson Cancer Center criteria to select patients for breast-conserving surgery after neoadjuvant chemotherapy or endocrine therapy are listed on Table 58-3. All criteria must be fulfilled before breast-conserving surgery is offered.

The radiotherapeutic technique for breast conservation in patients with LABC is particularly challenging because the target volume extends beyond the intact breast to include the regional lymphatics. This involves the use of multiple adjacent fields. Ideally, the use of noncoplanar beams with precise matching techniques is used when photon fields abut one another. Typically, the breast and undissected lymphatics will be treated to a dose of 50 Gy in 25 fractions over five weeks' time, followed by a 10-Gy boost to the tumor bed, which had been marked intraoperatively with clips. In patients with LABC downstaged with systemic therapy, our current practice is to design treatment fields on the basis of the original extent of disease.

TOLERANCE AND TOXICITY

Combined modality regimens have been well tolerated, and no increase in surgical complications has been reported (86). Over the past two decades we have elected to administer all chemotherapy (usually eight to nine cycles, or 24 to 27 weeks) before the surgical intervention. The expected acute toxic effects of combination chemotherapy are observed with the same frequency and intensity as in the postoperative adjuvant setting (18,26). In studies with simultaneous radiotherapy and chemotherapy, slight increases in hematologic toxicity and enhancement of acute radiation effects (erythema, moist desquamation) have been reported. Simultaneous administration of chemotherapy (especially anthracycline-containing regimens) and radiotherapy impairs, to some extent, the cosmetic results of breast-conserving therapy. Although some impairment of cosmesis is also observed with the sequential use of chemotherapy and radiotherapy, this effect is not clinically important for most patients (87). For patients with left breast cancer, synergistic cardiac toxicity is a danger with simultaneous anthracycline and radiation therapy (88). Sequential administration of chemotherapy and radiotherapy, a modification in radiotherapy techniques, and careful attention to the total dose of anthracyclines minimizes the risk of cardiac toxicity. The administration of doxorubicin by 48- or 96-hour continuous infusion schedules, the use of a cardiac protector (such as dexrazoxane), or using a less cardiotoxic anthracycline (epirubicin or a liposome-encapsulated anthracycline) also reduces the risk of cardiac toxicity substantially.

SURVIVAL EFFECTS OF COMBINED MODALITY STRATEGIES

The bulk of the information regarding the multidisciplinary treatment of stage III and LABC was obtained from uncontrolled phase II trials; therefore, the effects of the various components of these treatments on survival are tentative at best, and definitive conclusions might not be reached. For patients with inoperable stage III or inflammatory breast cancer, randomized trials including a control arm without systemic therapy will never be conducted. The results of phase II trials compare favorably to the outcomes of historical control series, or literature controls, suggesting higher 5- and 10-year survival rates, especially for the worst prognostic subgroups (6) or for patients with supraclavicular lymph node involvement (17,89), and patients with T4 primary lesions. Figure 58-3A shows the disease-free survival of patients with stages II, IIIA, and IIIB treated at MD Anderson Cancer Center with induction chemotherapy followed by surgery, radiotherapy, and adjuvant chemotherapy, with a maximum follow-up now exceeding 20 years. Figure 58-3B shows the overall survival curves from the same three groups of patients. The median relapse-free and overall survival times for patients with stages II and IIIA breast cancer treated with combined-modality therapy at our institution have not been reached at 240 months. This is in contrast with a median relapse-free survival of 102 months for similar stage IIIA patients treated with surgery and radiotherapy at our institution in earlier years. Similarly, the median overall survival has not been reached for patients with stages II and IIIA breast cancer treated with chemotherapy, surgery, and radiotherapy, whereas it was 140 months for patients treated without systemic therapy. It is generally accepted that patients with stage III breast cancer treated with local therapy followed by postoperative adjuvant chemotherapy have a significant relapse-free (5,90) and overall survival advantage over those treated with only local therapy. The results of randomized trials comparing neoadjuvant (or preoperative) chemotherapy with postoperative chemotherapy in operable breast cancer, suggest that the two approaches are therapeutically equivalent (18,91,92) (Table 58-4).

In both studies, the chemotherapy regimen given before or after surgery was the same. In both studies, the relapse-free survival and overall survival curves of the neoadjuvant and adjuvant chemotherapy-treated groups were superimposable. No randomized trials comparing preoperative to postoperative systemic therapy have been conducted in patients with LABC. As both randomized trials in operable breast cancer included patients with T3 lesions, it is unlikely that the results of similar trials conducted in patients with LABC would be any different.

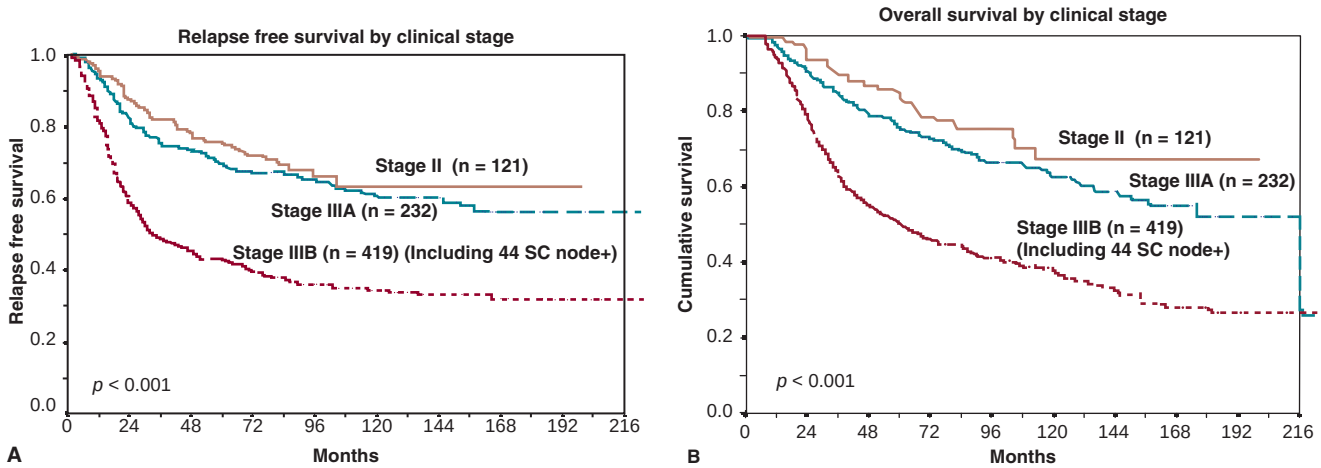

FIGURE 58-3 Patients with stages II, IIIA, and IIIB breast cancer were treated with three to four cycles of neoadjuvant chemotherapy (FAC), followed by surgical resection, radiotherapy, and adjuvant chemotherapy between 1973 and 1995 on four consecutive prospective clinical trials (n = 772 [including 44 patients with supraclavicular of infraclavicular lymph node involvement at the time of diagnosis]). **(A)** Relapse-free survival curves. **(B)** Overall survival curves.

For decades it was considered that patients with ipsilateral supraclavicular or infraclavicular lymph node involvement at presentation had overt metastatic disease and were incurable. Brito el al. reported that such patients treated with combined modality treatments such as those described for LABC in this chapter have outcomes similar to other patients with LABC, and that 32% survive without evidence of recurrence or progression for 10 years or longer (89). As a result of that observation and confirmation from other studies, patients with supraclavicular involvement at presentation, but no other evidence of distant metastases were moved to the Stage III category in the most recent edition of the AJCC Staging Manual (4).

PROGNOSTIC FACTORS

The ability to predict outcome changes with the efficacy of the treatments used. For LABC treated with regional therapies only, large tumor size, presence of involved axillary lymph nodes, involved supraclavicular lymph nodes, skin edema, inflammatory breast cancer, diffuse primary tumor, and short duration of symptoms were predictive of decreased relapse-free and overall survival rates (7,93,94). Evaluation of the prognostic value of axillary lymph node involvement after NACT showed that the number of involved nodes was the best predictor for both relapse and death in a multivariate analysis (95). The pathologic nodal subgroups of 0, 1 to 3, 4 to 10, and greater than 10 positive lymph nodes after NACT predicted a prognostic distribution similar to that found in previously untreated patients. Other important and independent factors found in this study by multivariate analysis were clinical tumor stage at presentation, clinical response to NACT (Fig. 58-4), and menopausal status. Other investigators have reported clinical response to NACT, or its surrogate, histologically detected extent of residual disease, as an important prognostic indicator (96).

Response (and especially complete response) to NACT was reported to occur significantly more often in patients with poorly differentiated tumors (96,97). Response rates were also higher in patients with hormone receptor–negative tumors (98). Provocative data from pilot studies suggested that responses were more common in patients with aneuploid tumors and in those with high proliferative fraction (99,100). Retrospective analyses of randomized clinical trials have suggested that tumors that overexpress the HER-2 oncoprotein might be relatively resistant to the CMF combination and to hormonal therapy with tamoxifen (101), while higher doses of doxorubicin might be more effective in this same group (102).

TABLE 58-4

Survival of Patients with Stage II–III Breast Cancer after Combined Modality Programs Based on Neoadjuvant Chemotherapy Followed by Local Treatment

					Survival %	
Reference	*Treatment Program*	*No. of Patients*	*% Rendered Disease-Free*	*Median Survival (months)*	*3 Year*	*5 Year*
Fisher (91)	CT → S	760	100	NR	90	80
	S → CT	763	100	NR	90	80
Van der Hage (92)	CT → S	350	100	NR	90	85
	S → CT	348	100	NR	87	82

Results of Randomized Trials

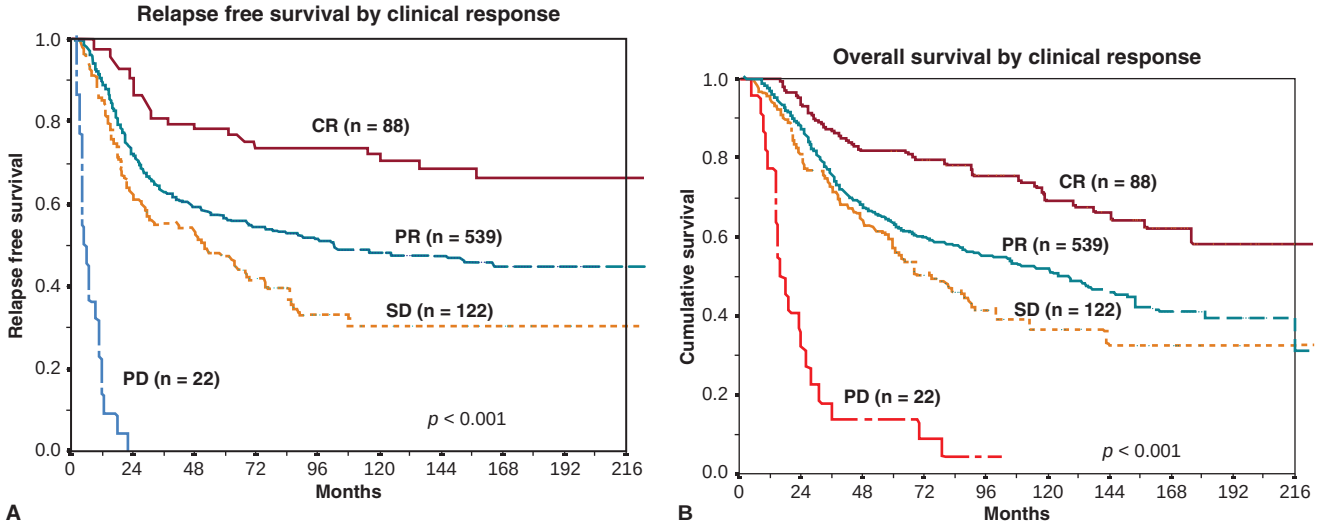

FIGURE 58-4 Clinical response to neoadjuvant chemotherapy (n = 771; response could not be evaluated in one patient). **(A)** Correlation with relapse-free survival. **(B)** Correlation with overall survival. CR, clinical response; PR, pathology response; SD, stable disease; PD, progressive disease.

Other studies have assessed the prognostic importance of various factors in terms of relapse-free and overall survival. Initial TNM stage, clinical tumor size, clinical nodal stage, and histologic grade have been shown to correlate with both endpoints in univariate analyses (13,17,36). In multivariate analyses, histologic/nuclear grade, both clinical and surgical nodal stages, initial tumor size, and response to neoadjuvant chemotherapy were significant predictors of disease-free survival (17,93,95), whereas tumor size, nodal status, grade, and response to neoadjuvant chemotherapy correlated with overall survival (17,93,95). The most important predictor of outcome in our institutional experience is pathologic complete response, defined as complete absence of residual invasive cancer in the surgical specimen, including the axillary lymph nodes (Fig. 58-5). A recent meta analysis conducted by the FDA reached identical conclusions (103).

Local control is related to response to neoadjuvant chemotherapy and to initial stage of the disease (Fig. 58-6). Although our initial clinical trials suggested that a mastectomy should be performed if the tumor was (or became) operable, more recent clinical trials offered the option of breast-conserving surgery if downstaging was of sufficient magnitude. Our experience confirms that if selection criteria are strictly followed, optimal local control can be obtained after neoadjuvant chemotherapy and breast-conserving surgery.

PROSPECTS FOR THE FUTURE

Much progress has been made in the management of locally advanced breast cancer, but much remains to be accomplished. The taxanes (paclitaxel, nab-paclitaxel, and docetaxel) have been effectively incorporated into the management of metastatic breast cancer, and multiple reports suggest that they contribute to the curative regimens in locally advanced and early breast cancer. Anthracycline–taxane combinations are effective in locally advanced breast cancer. New cytotoxic agents, with demonstrated antitumor efficacy against metastatic breast cancer, continue to be developed (104): gemcitabine, capecitabine, liposomal

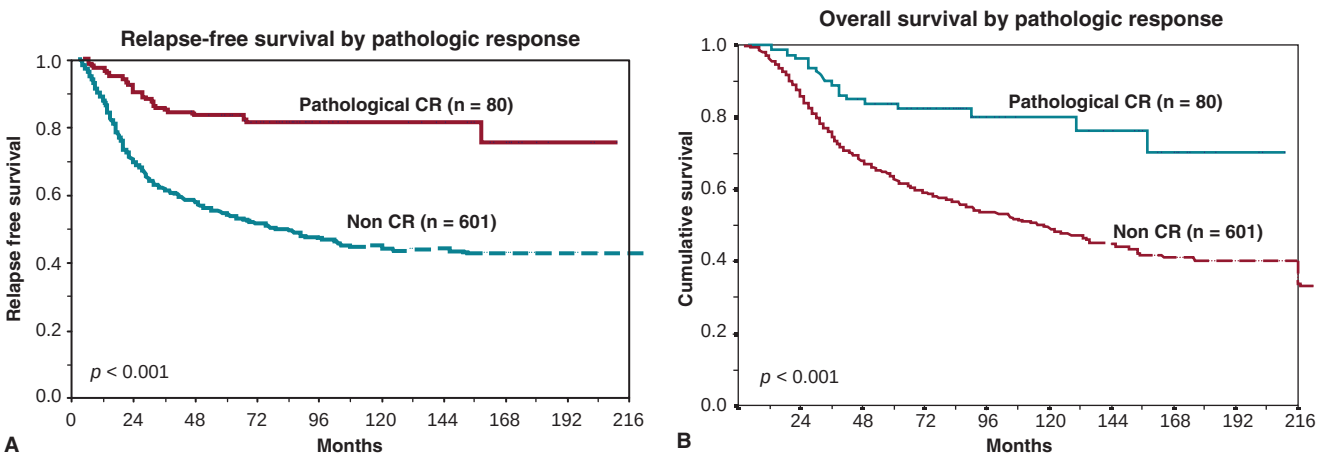

FIGURE 58-5 Pathologic complete response (n = 681; 91 patients did not have surgical resection). **(A)** Correlation with relapse-free survival. **(B)** Correlation with overall survival. CR, clinical response; PR, pathology response; SD, stable disease; PD, progressive disease.

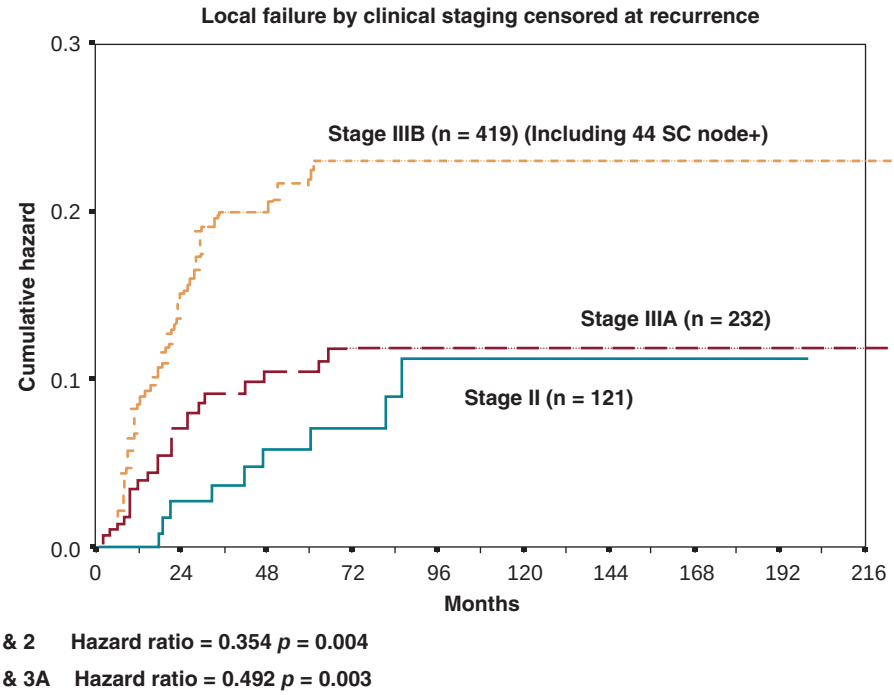

FIGURE 58-6 Cumulative rate of local/regional recurrence as first event by clinical stage (n = 772). Patients who developed distant metastases without local/regional recurrence were censored at the time of the metastases.

doxorubicin preparations, several antifols, ixabepilone, and eribulin have shown modest activity, in the 20% to 45% range, in metastatic breast cancer and clinical investigation is ongoing in the neoadjuvant and adjuvant setting.

While progress in the development of cytotoxic agents continues, there is increased emphasis on the development of molecularly targeted therapy. Trastuzumab (Herceptin), a monoclonal antibody against the extracellular domain of the HER-2 oncoprotein demonstrated clear-cut antitumor activity in patients with HER2-amplified (or overexpressed) metastatic breast cancer (105) and resulted in significant prolongation of overall survival in combination with chemotherapy in randomized clinical trials (105). The mature results of six multicenter, randomized clinical trials of trastuzumab used in the adjuvant setting demonstrate that the addition of trastuzumab to chemotherapy reduces annual odds of recurrence by about 50% and annual odds of death by one-third. The addition of trastuzumab to neoadjuvant chemotherapy of patients with HER2-positive operable or locally advanced breast cancer led to significant increases in the proportion of patients achieving a pathological complete remission, in some cases as high as 65%. Other HER2-directed agents, including the tyrosine kinase inhibitor lapatinib and pertuzumab, also reported to have important clinical activity in metastatic and locally advanced breast cancer and synergize with trastuzumab, resulting in enhanced antitumor efficacy (22,44,46–48). Studies testing lapatinib alone and in combination with trastuzumab in the neoadjuvant and adjuvant settings are ongoing. A randomized trial of pertuzumab in combination with trastuzumab and chemotherapy compared to trastuzumab and chemotherapy in the neoadjuvant setting demonstrated significantly increased pCR rates for the double antibody arm. On that basis, the FDA granted accelerated approval to trastuzumab and pertuzumab combined with docetaxel in the neoadjuvant setting. A large, adjuvant trial focused on the same question is currently ongoing.

The efficacy of sequential local and systemic treatments in combined modality therapy for locally advanced breast cancer makes these approaches the standard of care for these high-risk groups of patients (Fig. 58-7). Using these approaches as a platform, ongoing trials assess the efficacy of limited surgery, both breast-conserving surgery and sentinel lymph node biopsy, in patients with LABC. Ongoing work is testing several modifications of radiotherapy technique to minimize toxicity without compromising outcome. There is renewed interest in assessing the contribution of neoadjuvant endocrine therapy in the multidisciplinary approach to LABC. There is need for developing more effective predictive markers for response to systemic therapy; candidate approaches under investigation include genomics and proteomics.

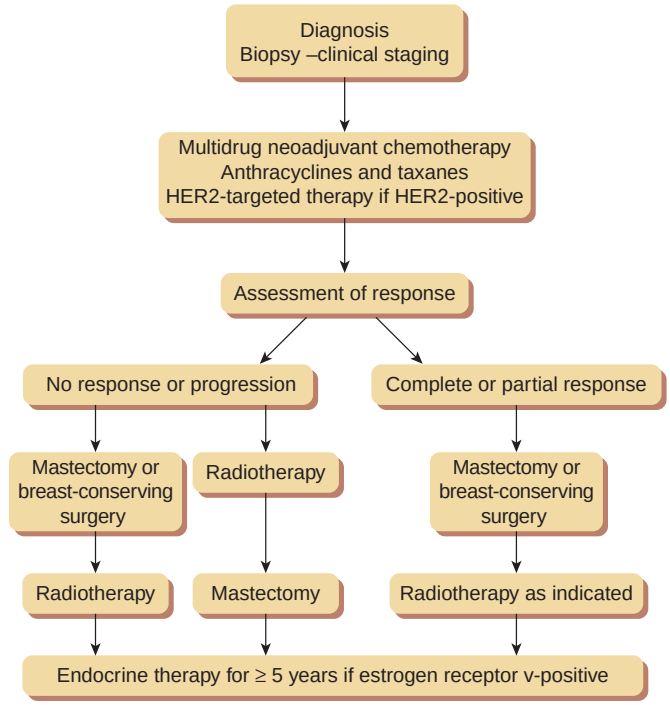

FIGURE 58-7 Flow diagram for the treatment of patients with locally advanced breast cancer.

The prevention of LABC might be the most effective approach to reduce mortality from this disease. Over the past 50 years, the frequency of LABC decreased to less than 5% of newly diagnosed breast cancer in populations with access to mammographic screening. Public and professional education emphasizing the importance of early diagnosis, the identification of women at high risk, and the systematic use of screening mammography might further decrease the frequency with which we find this high-risk lesion and contribute to the cure of breast cancer.

Combined-modality therapy that includes induction systemic therapy (chemotherapy with anti-HER2 agents and/or endocrine therapy for the properly selected subgroups) permits optimal local control with less radical surgical and radiotherapeutic intervention and leads to improved disease-free and overall survival rates. By downstaging primary and regional tumors, breast conservation becomes an option for many patients. In addition, the multidisciplinary management of stage III and locally advanced breast cancer provides an excellent biologic model to assess the effects of systemic therapy on the primary tumor. On the clinical side, this provides *in vivo* assessment of response, and the possibility of modifying subsequent therapy on the basis of this evaluation of response.

These strategies, developed for the management of LABC, are being successfully applied to earlier primary breast cancer.

MANAGEMENT SUMMARY

- Baseline physical exam, mammography, and ultrasound are essential to demonstrate tumor extent and identify multifocal, multicentric, and contralateral disease, if present. MRI might be needed in some patients to accurately define tumor boundaries. Staging for distant metastases at the onset can guide therapy.
- The regional lymph node-bearing areas should be carefully imaged, and suspicious nodes sampled with image-guided fine-needle aspiration biopsy.
- Close and continued interaction between all therapeutic and diagnostic specialists is needed to deliver optimal therapy.
- Combined-modality treatment, starting with neoadjuvant systemic therapy, represents the treatment of choice for patients with Stage IIIB breast cancer.
- Patients with triple-negative LABC should start with combination neoadjuvant chemotherapy.
- Any third-generation chemotherapy regimen that has been validated in the adjuvant setting can be appropriately used in the neoadjuvant setting.
- HER2-targeted therapy should be administered in combination with chemotherapy to all patients with HER2-positive cancers as an integral part of neoadjuvant treatment. Dual anti-HER2 inhibition with chemotherapy might be the optimal choice.
- Patients with hormone receptor–positive breast cancer, especially those with HER2-normal tumors with low proliferative rate, respond less well to chemotherapy; neoadjuvant endocrine therapy should be strongly considered.
- Patients who receive neoadjuvant systemic therapy should be closely monitored.
- Treatment must be individualized depending on molecular subtype of breast cancer and the response to, and the tolerance for, systemic therapy.
- Repeat imaging after the final dose of chemotherapy is indicated to assess response and determine appropriate surgical therapy. During treatment, if there is clinical uncertainty regarding disease progression, imaging may aid in the evaluation.
- Endocrine therapy should be administered following definitive local therapy to all patients with estrogen and/or progesterone receptor-positive cancers.
- Carefully selected patients with LABC can undergo breast-conserving therapy.
- Radiotherapy should be administered to all patients, even those with a pCR.
- For patients with locally advanced and inflammatory breast cancer, delayed autologous breast reconstruction is preferred.

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CHAPTER 59

Inflammatory Breast Cancer

Beth Overmoyer and Lori J. Pierce

CHAPTER CONTENTS

DEFINITION AND DIAGNOSTIC CRITERIA

Historical Perspective

The term "inflammatory breast cancer" (IBC) was first introduced by Lee and Tannenbaum in their sentinel 1924 manuscript, to describe a rare, rapidly progressing breast cancer with characteristic features of inflammation seen among 28 cases at Memorial Hospital (1). They discussed the grave prognosis of breast cancer when associated with inflammatory changes, as first described by Sir Charles Bell in 1812 (1a); "When a purple color is on the skin over the tumor accompanied by shooting pains, it is a very unpropitious beginning." Throughout time, this form of breast cancer was referred to as "mastitis carcinomatosa" (1b), "carcinoma mastitoides" (1c,1d), and "acute carcinoma of the breast" (1e,1f).

The historical identification of IBC is important as a reminder of the evaluation and acceptance of classic clinical criteria that differentiates it from other forms of locally advanced breast cancer (LABC). More recently, there has been increased awareness concerning the distinctive clinical and pathologic nature of IBC, which has resulted in earlier identification of the disease, enhanced understanding of its unique biologic elements, and utilization of these features to develop improved therapies resulting in a superior disease response. It is anticipated that a greater understanding of IBC will also lead to advances in the treatment of non-IBC, because successful treatment of a virulent form of disease in general, often results in therapeutic progress for less aggressive disease.

Clinical-Pathologic Characteristics

Inflammatory breast cancer is a rare subtype of breast cancer, accounting for 1%–5% of breast cancer in the United States (2,3). Between 1988 and 1990 and 1997 and 1999, the incidence of IBC increased from 2.0/100,000 women-years, to 2.5/100,000 women-years ($p < .001$), which translates into a rate of 1.23% per year (4). IBC can also rarely present in male patients, and all pathologic subtypes of invasive adenocarcinoma of the breast can be associated with IBC, though invasive ductal carcinoma is the most common type (5).

"Primary" IBC presents as LABC in a previously unaffected breast, characterized by a rapid onset of symptoms within approximately 3 months. This rapid onset of symptoms and signs distinguishes primary IBC from LABC with inflammatory changes. The clinical features of IBC consist of enlargement of the breast with associated tenderness and warmth, often without a palpable mass (Fig. 59-1). Extensive nodal involvement is often clinically assessable, involving fixed ipsilateral axillary, supraclavicular, and internal mammary nodal groups, as well as frequent extension to contralateral axillary lymph nodes (6,7). Erythema of the skin,

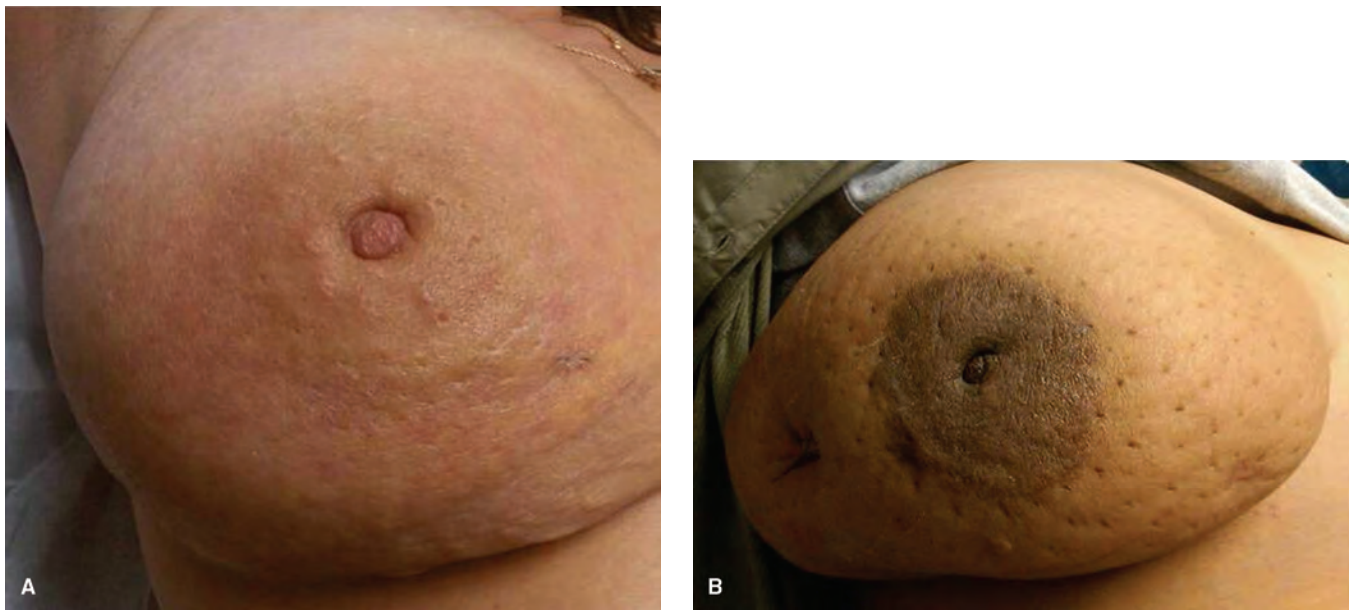

FIGURE 59-1 Classic clinical features of inflammatory breast cancer. **(A)** Erythema, edema (peau d'orange). **(B)** Enlargement of the breast.

involving approximately one-third or more of the breast can vary in character from faint pink, to red or purple; either diffuse or developing in a serpiginous fashion (8). The extent of erythema may eventually extend into the contralateral breast via dermal lymphatic extension. Edema or induration of the skin, with pitting of the hair follicles, is often described as peau d'orange (orange peel-like in consistency) (6,9). Ulceration of the skin and/or nipple is quite rare. This classic appearance of the breast is not due to inflammatory infiltrates, but rather to lymphatic occlusion from tumor emboli present in the papillary and reticular dermis of the skin. Pathologic confirmation of dermal lymphatic involvement is not required for the diagnosis of IBC, and because of skip regions within the breast, dermal lymphatic invasion can be confirmed in only 75% of IBC skin biopsies. The irregularity of the dermal lymphatic involvement contributes to the characteristic feel of "ridges" within the breast.

Primary IBC is differentiated from "secondary" IBC which is clinically and biologically similar; however, secondary IBC arises as a breast cancer recurrence in the breast or chest wall of a patient with a previous history of treated non-IBC. In the past, there have been inconsistencies in the definition of IBC and this has complicated the analysis of epidemiologic studies and clinical trials. However, recently there has been a consensus agreement on defining the clinical characteristics of IBC which has permitted the differentiation from non-IBC LABC, and has improved the interpretation of clinical outcomes of IBC (10). Acceptable diagnostic criteria for IBC are based upon both clinical and pathologic features and include the International Classification of Disease for Oncology (ICD-0-2, 8530/3 for IBC) and the American Joint Committee on Cancer (AJCC) staging criteria (3,11). According to the AJCC staging criteria, the tumor in IBC is classified as T4d, and staged as IIIB, IIIC, or IV based upon extent of nodal involvement and evidence for distant metastasis.

Epidemiology

Based upon data from the Surveillance, Epidemiology, and End Results (SEER) Program, patients with IBC usually present at an earlier age compared with non-IBC LABC; approximate mean age at diagnosis 58 years and 66 years, respectively (3). The incidence of IBC increases to the age of 50 years, then plateaus, regardless of hormone receptor (HR) status, whereas the incidence of non-IBC continues to increase after age 50 years, especially among estrogen receptor (ER) positive disease (2,4). The incidence of IBC is higher among African American women compared with Caucasian women (3.91/100,000 women-years compared with 2.5/100,000 women-years, p <.001), and has geographic variation within the United States and globally (12). For example, SEER data from 1992–2002 demonstrated the frequency of IBC documented in the Los Angeles Tumor Registry as 2.45% whereas the frequency of IBC in the Connecticut Tumor Registry during the same period was 1.49% (4). Internationally, there is an increased frequency in the Middle East and Northern Africa, e.g., 11% occurrence in Egypt, 5%–7% in Tunisia (decreased from 50% using stringent diagnostic criteria), 10% in Pakistan, and 17.5% in Nigeria; versus 2.9% in Spain, 5.4% in France, and 0.6%–2% incidence in Italy (4,7,13–15). Other epidemiologic features that have been associated with a higher incidence of IBC include living in a high poverty county within the United States, having a high BMI (regardless of menopausal status, though there is a propensity of developing IBC while premenopausal), an earlier age of menarche, and earlier age of first full-term pregnancy (16–18). A familial or genetic linkage for IBC has not been borne out.

Approximately 30% of patients with IBC present with distant metastasis at the time of initial diagnosis (stage IV), based upon SEER data examined from 2004–2007 (19). Among individual institutions, the incidence ranges from 26% (City Hospital, Nottingham, UK) to 40% (MD Anderson Cancer Center); however, all data supports a significantly higher occurrence of stage IV disease at presentation with IBC than with non-IBC (20,21). Compared with non-IBC LABC, the 2-year breast cancer specific survival (BCSS) for IBC was 84% vs. 91% (p < .0001) (22). This translated into a hazard ratio of 1.43 risk of dying of breast cancer among patients with IBC vs. non-IBC LABC (p = .008). Among the SEER cases from 1990 to 2008, the median BCSS for non-IBC LABC was 13.4 years versus 4.75 years among patients with IBC (23).

These data support the importance of accurate diagnosis for IBC which carries a significantly poorer prognosis compared with non-IBC LABC.

Imaging

The imaging employed during the evaluation of IBC serves to identify the extent of disease within the breast and regional lymph nodes, determine spread to the ipsilateral pectoralis muscle or contralateral breast, to detect distant metastasis, and assess disease response to treatment. As in non-IBC, mammography is utilized as an initial diagnostic procedure, wherein the affected breast demonstrates skin thickening (from dermal lymphatic involvement), diffuse increased breast density, and trabecular distortion due to edema. Although most patients with IBC do not present with a palpable breast mass, in a large retrospective study of 80 patients with IBC, 80% of the patients displayed mammographic abnormalities in the affected breast, such as architectural distortion, asymmetry, multi-focal densities (masses), or suspicious calcifications (41%) (24). Microcalcifications often become more evident with effective treatment that results in a decrease in the density of the breast parenchyma (25). Occasionally, the mammographic findings are subtle and can only be detected by direct comparison with the contralateral breast. IBC appears to be a predominately unilateral breast disease, with previous reports of bilateral cancers now being attributed to non-IBC LABC.

Mammographic differentiation between IBC and non-malignant inflammation of the breast can be complicated by the patient's inability to undergo adequate compression of the breast due to pain. For this reason, ultrasonography is often utilized to assess skin thickening and regional lymph node involvement as well as identify areas within the breast that can successfully undergo biopsy via ultrasound guidance. In contrast to mammography, these abnormalities can be identified in 95% of patients with IBC (24). Ultrasound is more sensitive at detecting abnormal anatomic changes within the axillary lymph nodes, and color Doppler sonography can be used to assess intratumoral vascularity, however, microcalcifications cannot be detected via ultrasound.

A review of 4 studies evaluating the efficacy of magnetic resonance imaging (MRI) in IBC described skin thickening and enhancement (98% and 94%, respectively), and more commonly than a discrete mass, the parenchyma contained an infiltrative mass associated with a reticular/dendritic pattern of enhancement in 78% of patients (25). The retrospective study by Yang et al. found MRI detection of multiple breast masses with heterogeneous internal enhancement associated with a washout in 97% of their 80 patients (24). Overall, MRI was found to be the most accurate imaging modality for IBC, not only useful in detecting the primary cancer (98% vs. 68% with mammography), but also in imaging axillary lymph nodes and determining cancer involvement of the pectoralis muscle (26). In addition, MRI imaging posttreatment has the highest correlation with pathologic disease response compared with other modalities, such as mammography and ultrasonography (25).

The use of PET/CT (fused positron emission tomography and computed tomography) in breast cancer remains controversial; however, pretreatment imaging with PET/CT among patients with IBC has resulted in the detection of new areas of distant metastasis in 44% of 62 patients with IBC evaluated in one retrospective analysis (27). The extent of pretreatment nodal involvement detected by PET/CT imaging resulted in changes in the posttreatment radiation therapy fields in 18% and 14% of IBC patients in two independent retrospective analyses, though the clinical impact of these therapeutic modifications remains unknown. These data suggest that PET/CT may be considered as an imaging modality in the initial evaluation of IBC; however, confirmatory data is needed prior to recommending it as a standard approach (27,28).

The current armamentarium of breast imaging is associated with some ambiguity in the evaluation of IBC, both in terms of diagnostic information as well as confirming disease response. Novel molecular targeting agents are currently being explored in IBC with the goal of demonstrating more sensitive and specific non-invasive evidence of disease response to systemic treatment (29).

BIOLOGIC CHARACTERISTICS

Breast cancer is a heterogeneous disease characterized by expression of specific molecular markers that control the biologic phenotype of the disease. IBC has been shown to express specific molecular characteristics that are more uniformly associated with this disease, and have thus permitted the characterization of IBC based upon biologic criteria rather than from purely histologic or clinical classification. A greater understanding of these distinctive mechanisms that coordinate the progression of IBC will allow the development of more successful targeting agents designed specifically for this disease.

Gene Expression Profiling

High-throughput molecular technologies, such as DNA microarray-based expression profiling, have revealed the full complement of breast cancer cell-of-origin subtypes (i.e., Luminal A, Luminal B, basal-like, HER2-overexpressing) within IBC; however, IBC has a propensity for segregating into the more proliferative molecular subtypes, such as the basal-like (triple negative, i.e., ER-negative, PR-negative and HER2-negative) and HER2-overexpressing subtypes. Bertucci et al. first demonstrated the same heterogeneity of cell-of-origin subtypes within 37 IBC tumor samples and 1 IBC cell-line (SUM-149) (30). Compared with 44 non-IBC LABC tumor samples, 24% of IBC samples were HER2-overexpressing and 22% were basal-like, versus 14% HER2-overexpressing and 19% basal-like. These findings were confirmed in a subsequent analysis from Van Laere et al., wherein 16 pretreatment IBC tissue specimens exhibited all of the different cell-of-origin subtypes, yet 50% of the IBC samples segregated into the combined basal-like and HER2-overexpressing clusters compared with only 17% of the non-IBC samples (31). A principal component analysis of variability of gene expression in the entire sample set revealed that approximately 30% of the variation between IBC and non-IBC samples was related to the cell-of-origin subtype, suggesting the presence of other genetic factors that significantly contribute to the IBC phenotype.

Several investigators have attempted to discover a specific IBC gene signature; however, the results have been inconclusive. A RT-PCR analysis of mRNA expression among 36 pretreatment IBC tumor specimens identified 48 genes involved in cellular proliferation, signal transduction, apoptosis, and angiogenesis (32). Interestingly, the investigators found no difference in the expression of inflammatory cytokines, except IL-6, supporting the conclusion that the inflammatory characteristics of IBC were due to dermal lymphatic occlusion by tumor emboli and not by classical inflammatory mechanisms. They also identified a 3-gene expression signature that was associated with a poor prognosis in IBC. Van Laere et al. expanded their original work and identified an IBC signature that was associated with NF-κB activation, although the association of NF-κB target genes appeared to be linked to ER negative breast cancer as well as with IBC

(33,34). Within their IBC gene signature, several genes were identified that were linked to insulin-like growth factor (IGF) signaling, which is supported by several molecular analyses described later in this chapter.

The Baylor group identified a hyperproliferative gene profile involving fatty acid and lipid metabolism, the Bcl2-BAX apoptotic pathway, and genes associated with increased cell turnover (35). When their signature was compared with the Van Laere IBC signature, only 5 genes overlapped, and when the signature was compared with the Bertucci signature, only 1 gene was similarly over-expressed (30,33). Other studies examining specific IBC gene signatures have identified clusters of oncogenes that encode proteins involved in protein translation and transport, adaptation to hypoxia, and activation of mammalian target of rapamycin (mTOR) signaling (36,37). These heterogeneous gene profiles examined the tumor epithelium, whereas investigators from the National Cancer Institute (NCI) explored gene expression signatures among the tumor stroma of 52 IBC tissue specimens and found an enrichment of genes involved in intracellular protein transport and localization, protein secretion, mRNA translation, and GTPase signaling (38). The investigators proposed that the IBC phenotype was more easily distinguished by its stromal signature than the tumor epithelial signature. All of these studies demonstrate a significant heterogeneity within IBC, and although a specific IBC gene expression signature has not been established, these investigations have revealed certain molecular markers and signaling pathways that have consistently been linked to the pathophysiology of IBC.

Traditional Molecular Features: HER2, Hormone Receptor, TP53

Although there is a considerable focus on elucidating the unique biologic profile of IBC, the traditional molecular features of breast cancer play an important role in understanding the pathophysiology, prognosis, and treatment options associated with IBC. Clinical evaluation of patients with IBC supports the findings seen with gene expression profiles, i.e., IBC is more frequently found to be triple negative and HER2 positive (39,40). One-hundred and eight patients with LABC from the Leuven University Hospital in Belgium were identified and classified as IBC (49) or non-IBC (59), and compared with non-IBC LABC, IBC patients were more likely to have HER2 positive disease; 35% versus 19% (p = .07) (41). In a larger registry dataset from the California Cancer Registry (1999–2007), the receptor status and clinical outcome was assessed among 2,014 IBC patients, 1,268 non-IBC LABC patients, 3,059 patients with metastatic breast cancer (MBC) and 73,758 non-T4 breast cancer patients (42). Patients with IBC were more likely to have HR negative disease (both ER and PR negative) compared with the other groups of breast cancer patients: 40% (IBC), 31% (non-IBC LABC), 25% (MBC), 18% (non-T4); whereas IBC patients were more likely to have HER2 positive breast cancer: 40% (IBC), 35% (non-IBC LABC), 35% (MBC), 22% (non-T4). Patients with HR negative IBC had an inferior overall survival (OS) and BCSS compared with HR positive IBC, whereas HER2 status was not found to be prognostic for a worse OS among patients with IBC, but was prognostic for a more favorable BCSS (hazard ratio [HR] = 0.82). These associations, i.e., a more favorable prognosis with HR positive IBC and absence of an adverse prognosis with HER2 positive disease, are also supported by retrospective data from MD Anderson Cancer Center, the Institut Gustave Roussy, and the Aga Khan University Medical Center (7,43,44). The more favorable disease outcome associated with HER2 positive disease is attributed to the effective therapy with trastuzumab discussed later in this chapter.

In addition to an increased incidence of HER2 overexpression, IBC is often associated with a higher frequency of mutations in the tumor suppressor gene p53 (TP53) compared with non-IBC (7). Wild-type TP53 is intimately involved in maintaining genomic stability by functioning as a transcription factor for genes involved in cell-cycle progression, DNA repair, and apoptosis. Common TP53 mutations are missense or nonsense mutations, and often result in the accumulation of p53 protein in the cytoplasm or nucleus demonstrated by immunohistochemistry (IHC); however, direct complimentary DNA (cDNA) sequencing can also detect up to 20% of TP53 mutations that are not identified by IHC (45,46). Using these methods, Turpin et al. examined 161 patients from the Hospital Saint Louis and found 57% of the 63 IBC tumors exhibited TP53 mutations compared with 37% of the 27 non-IBC LABC (40). Another evaluation of the immunohistochemical profile of IBC using tissue microarray techniques found 45% of 86 IBC tumor specimens contained TP53 mutations versus 23% of the 552 non-IBC samples (39). This study also confirmed the increased incidence of triple negative IBC and HER2 positive IBC compared with non-IBC (54% vs. 24% and 40% vs. 12%, respectively). Some, but not all of the studies which demonstrate a prevalence of TP53 mutations in IBC have correlated this finding with an adverse prognosis (46–48). A single institution retrospective analysis from the MD Anderson Cancer Center found that among 59 patients with IBC, 58% had TP53 positive tumors which corresponded to a shorter 5-year progression-free survival (PFS) (35% vs. 55%) and OS (44% vs. 54%); neither were statistically significant (49). A similar retrospective examination from the Japanese Foundation for Cancer Research did not find such a correlation (50).

Distinctive Molecular Features: RhoC GTPase, WISP3

Recent investigations into the unique molecular properties of IBC have elucidated several genetic features that are critical to the development of its highly metastatic phenotype. RhoC GTPase is a member of the RAS superfamily of G proteins that are involved in several aspects of cellular function including cell cycle control, cell migration and epithelial cell polarity, cell survival, and angiogenesis (51). Dysregulation of these processes is associated with increased metastatic potential in pancreatic cancer, melanoma, and breast cancer. Original exploration of differentially expressed genes in IBC was performed on the triple negative IBC cell-line, SUM149 and validated among 29 IBC and 19 non-IBC tumor samples under the direction of van Golen et al (52). This search led to the demonstration of overexpression of RhoC GTPase in 90% of the IBC specimens compared with 38% of the non-IBC tumors (p = .0095). The overexpression of RhoC GTPase was 91% concordant with a decrease in expression of WISP3 (Wnt-1 inducible signaling pathway protein 3), a member of the CCN (Cyr61, CTGF, Nov) family of tumor suppressor genes that function to modulate insulin-like growth factor-1 (IGF-1) mediated cellular growth, and proliferation (53). WISP3 was originally named LIBC or "Lost in Inflammatory Breast Cancer" because it was expressed in only 20% of the IBC specimens examined compared with 79% of the non-IBC tumors (p = .0013) (52).

Overexpression of RhoC GTPase in transfected cell lines resulted in a phenotype that mimics IBC similar to the IBC cell-line SUM149, including its tumorigenic ability (54). These experiments led to a greater understanding of the potential role of RhoC as an IBC oncogene, in addition to its known

ability to stimulate angiogenesis, aid in the formation of stress fibers and focal adhesion, and to stimulate actomyosin-mediated cell contraction leading to increased cellular mobility. Recent data from the van Golen laboratory have also shown an increase in several PI3K/Akt signaling pathways due to a downstream effect of activated RhoC on PI3K/Akt-1 associated genes (55). These signaling pathways control cytoskeletal polarity and cellular mobility. C-Met activation may also contribute to enhance PI3K pathway signaling in IBC due to increased expression of c-Met expression in IBC (56).

Given the greater than 90% rate of concordance of WISP3 suppression with RhoC expression observed in human IBC, Kleer et al. transfected immortalized human mammary epithelial (HME) cells with antisense WISP3 constructs resulting in the inhibition of WISP3 and subsequent overexpression of RhoC (57). This molecular pattern of WISP3 modulating RhoC expression produced a statistically significant increase in cellular proliferation and in VEGF production. Transfection of the IBC cell-line SUM149 with WISP3 resulted in suppression of angiogenesis by reducing levels of VEGF, FGF2, and IL-6 (58). Restoration of WISP3 function also caused a decreased rate of cellular proliferation, anchorage-independent growth, and invasive capabilities manifested by reduced tumor formation when injected into athymic nude mice. One potential mechanism of WISP3 protein function is directly related to its secretion into extracellular spaces, thus functioning to regulate IGF-1 signaling leading to diminished growth of IBC cells (59). This constellation of function attributed to WISP3 supports its classification as a tumor suppressor gene of IBC.

The WISP3 negative/RhoC positive phenotype detected by both IHC and RT-PCR has consistently been found to be associated with IBC compared with non-IBC human tumor samples evaluated in Tunisia (26/41 = 66% of IBC vs. 10/86 = 12% non-IBC) (60). RhoC overexpression has also been demonstrated in 40/46 (87%) of Egyptian IBC tumor samples versus 11/64 (17%) of non-IBC tumors (61). This reliable molecular arrangement, seen in IBC, supports investigation into modifying the expression/function of RhoC or WISP3 as a therapeutic target (62).

The Pathophysiology of Tumor Emboli: E-cadherin, MUC-1, eIF4GI

The establishment of an IBC xenograft model (MARY-X) from a patient with IBC has been instrumental in elucidating some of the principal features of the pathophysiology of IBC. MARY-X was developed in 1999 and exhibited classical characteristics of erythema of the murine skin and tumor emboli exclusively involving lymphovascular spaces in nude/SCID mice (63). The carcinoma is triple negative but is EGFR (epidermal growth factor receptor) and TP53 positive. MARY-X overexpresses the membrane bound adhesion molecule E-cadherin and cell-surface MUC-1 glycoprotein up to 10–20 times greater than in non-IBC xenograft models. When further examined, the carcinoma within the lymphovascular spaces were spheroids, exhibiting significant homotypic tumor cell adhesion due to overexpression of E-cadherin along the entire membrane surface of the carcinoma (64). Although MARY-X overexpressed MUC-1, it was a dysfunctional protein, with decreased cell-surface sialyl-Lewis X/A residues which bind to E-cadherin. This contributes to the absence of tumor cell heterotypic adhesion to the endothelial cells causing visible retraction of the tumor emboli from the endothelial wall lining of the lymphovascular structures. The pattern of these effector molecules results in the ability of IBC to form tight adhesive tumor emboli that lack the ability to adhere to the endothelial wall of vasculature, thus enabling a more metastatic phenotype. Alpaugh et al. confirmed the overexpression of E-cadherin and MUC-1 in human IBC specimens and also found that the tumor emboli were retracted from the endothelial lining of the vasculature in these human samples (63–65).

The E-cadherin adhesion complex remains structurally and functionally intact in IBC, with overexpression of its associated α-catenin and β-catenin membrane-bound proteins as part of its E-cadherin/α,β-catenin functional axis (65). In MARY-X, when this axis is disrupted, the spheroids disassociate and apoptosis occurs suggesting that the intact E-cadherin/α,β-catenin functional axis is necessary for the survival of IBC cells. These characteristic spheroids are also present and functional in the pulmonary metastasis that develops in the MARY-X xenograft, supporting the hypothesis that this structural integrity is necessary and maintained throughout the progression to metastasis that occurs in IBC.

Gene amplification results in increased MUC-1 expression whereas alterations in other factors involved in mRNA transcription and translation contribute to the higher E-cadherin levels. eIF4GI is a translation initiation factor which, when combined with eIF4E and eIF4A, forms a complex (eIF4F—eukaryotic initiation factor 4E) that contributes to the initiation of cap-dependent mRNA translation (66). Silvera et al. examined 77 breast cancer samples and found overexpression of eIF4GI in 80% of the 37 IBC specimens (67). Through a series of studies performed on the SUM149 IBC cell line, suppression or silencing of eIF4GI resulted in a reduction of E-cadherin attached to the IBC surface membrane due to increased E-cadherin degradation. Increased stability of E-cadherin occurs with membrane association through its interaction with the protein p120 catenin. Silencing of eIF4GI also results in a reduction in the translation of p120 mRNA by more than 60%. Overexpression of eIF4GI appears to be essential for the development and survival of IBC tumor emboli and supports its invasive properties by promoting increased translation of mRNAs with internal ribosome entry sites (IRESs), such as the p120 mRNA.

The Stem-cell Phenotype of Inflammatory Breast Cancer

The MARY-X spheroids and tumor emboli have been likened to the human embryonal blastocyst which overexpresses the E-cadherin axis and is the source of embryonal stem cells (ES). This similarity in physiology, i.e., the presence of cellular anchorage independence and enhanced ability to migrate and metastasize, prompted several studies that demonstrated a strong association between IBC and breast cancer stem cells. MARY-X expresses the stem-cell marker phenotype which includes CD44+/CD24-/low (100% of cells), strong CD133 surface expression (>90% of cells), high activity of aldehyde dehydrogenase (ALDH) (23% of cells) (68). Molecular pathways which sustain the stem cell state, such as Notch signaling through the Notch 3 receptor, are also increased in MARY-X compared with non-IBC carcinomas that primarily utilize Notch 1 and Notch 4 expression to enhance Notch signaling (69). Increased tumorigenicity and self-renewal was primarily evidenced in the subpopulation of MARY-X which exhibited both high ALDH expression and enhanced Notch 3 signaling.

Xiao et al. also confirmed a higher level of CD133 membrane expression and Notch 3 nuclear expression in human IBC tumor samples compared with non-IBC samples (88% vs. 8%, and 76% vs. 8%, respectively), regardless of molecular subtype of IBC. The high prevalence of CD44+/CD24-/low phenotype among human IBC was confirmed by Polyak's laboratory where they examined tumor specimens from all

subtypes of IBC and found that >80% expressed the stem-cell phenotype of CD44+/CD24-/low, regardless of whether they were triple negative or of luminal subtype (70). In addition to the Notch signaling pathway, both the NF-κB/RAS/MAPK and the IL6/JAK2/STAT3 pathways have been found to play an important role in mammary stem cell survival and have enhanced activation in IBC, making them potential therapeutic targets for this disease (34,70–73).

Angiogenesis and Lymphangiogenesis in Inflammatory Breast Cancer

Early investigation of IBC determined this subtype of breast cancer to have significantly greater angiogenic and lymphangiogenic properties compared with non-IBC. Histologically, Colpaert et al. found a significant increase in microvessel density as determined by the Chalkley method ($p < .0001$), and a greater percentage of proliferating endothelial cells (EPC) among the 35 human IBC tumor specimens compared with 104 non-IBC specimens (19% vs. 11%, respectively, $p = .014$) (74). A correlation was found between EPC and expression of the hypoxia marker carbonic anhydrase IX (CA IX) on tumor emboli, whose transcription is regulated by hypoxia inducible factor 1 (HIF-1). This evidence suggests an adaptation to hypoxia within the IBC tumor emboli, supported by intense angiogenesis. However, hypoxic signals are not the sole stimulant of the intense angiogenesis seen in IBC. RhoC, which is overexpressed in IBC, is a potent activator of angiogenesis, and the overexpression of eIF4GI in IBC results in the increased translation of specific IRES containing mRNA that encode VEGF, regardless of hypoxic signals (75). IBC tumor cells express a genetic profile that is associated with survival during hypoxia even when it does not exist.

RT-PCR analysis of 16 IBC and 20 non-IBC tumor specimens revealed a significantly higher expression of the mRNA involved in the Ang1/Tie2 pathway among the IBC samples (Ang-1, Tie-1, Tie-2) (76). This pathway supports the survival of endothelial cells and vascular expansion. In addition, the mRNA expression of KDR (the receptor for vascular endothelial factor A [VEGF-A]) and FGF-2 was also significantly higher among the IBC specimens, supporting a more active angiogenic process among IBC compared with non-IBC. Other molecular profiling studies of IBC supported an increased expression of genes involved in angiogenesis (32). IBC is also associated with a higher expression of all of the lymphangiogenesis mRNAs (VEGF-C, VEGF-D, Flt-4, Prox-1, Lyve-1), supporting activation of the Flt-4 signal transduction pathway that induces lymphangiogenesis. This was confirmed by the demonstration of a greater percentage of proliferating lymphatic endothelial cells among the IBC specimens compared with the non-IBC specimens. Significant investigation is ongoing in determining whether the presence of IBC tumor emboli in lymphovascular spaces occurs by classic lymphovascular invasion, or whether the IBC tumor cells stimulate the formation of encircling vascular channels from adjacent myoepithelial cells or stromal stem cells; a process known as lymphovasculogenesis. Regardless of pathophysiology, the highly angiogenic presence in IBC lends itself as an excellent therapeutic target, as described later.

TREATMENT OPTIONS FOR INFLAMMATORY BREAST CANCER

The poor prognosis associated with IBC stimulated intensive research focusing on unraveling the unique molecular biology of this disease in an attempt to develop more specific and effective therapies. These novel therapies will be discussed later in this chapter. The current therapeutic armamentarium does not differ significantly from that utilized for non-IBC LABC and the next sections will review the current tri-modality approach to treatment.

LOCOREGIONAL THERAPY FOR INFLAMMATORY BREAST CANCER

Locoregional Treatment in Inflammatory Breast Cancer: An Historical Perspective

Early surgical series of patients presenting with clinical findings consistent with IBC in the pre-chemotherapy era demonstrated consistently poor outcomes despite aggressive surgical resection. Haagensen reported his initial experience with IBC in a series of 20 patients treated with radical mastectomy (77). Due to difficulty in achieving negative margins, the rate of locoregional failure (LRF) was high at 50%. Rates of systemic failure were higher, thus survival was poor with a median survival 15.5 months after surgery and no 5-year survivors. Similar results were reported by others as summarized by Treves in an editorial where a table of 6 radical mastectomy series revealed 4 of 262 patients survived 5 years when treated by radical mastectomy alone, translating into a cumulative 5-year OS of 1.5% (78). These results supported the classification of IBC as a categorically inoperable disease because, as noted by Haagensen, "when no cures can be expected, and no definite evidence of prolongation of life can be shown, it seems entirely unreasonable to treat these patents by radical mastectomy" (77).

These experiences led to radiotherapy (RT) as sole management of IBC. The extent and bulk of local-regional disease required the delivery of high radiation doses to extended radiation fields. The ability to tolerate treatment necessitated a protracted RT course pioneered by Baclesse in France (79). Fletcher and Montague at MD Anderson Cancer Center published results using a protracted course of up to 100 Gy over 12 weeks delivered initially with 250 kV orthovoltage prior to 1955 and later with Cobalt 60 teletherapy (80). Using this regimen, the authors reported a 40.5% rate of LRF in 47 patients with IBC with 18% alive at 3 years and 12% alive at 5 years. Increased rates of late complications including severe breast fibrosis, breast and chest wall necrosis, and brachial plexopathy were observed.

Despite the use of high doses of RT in patients with IBC, rates of local control remained disappointing. Dose response data from a series of 62 IBC patients treated at Massachusetts General Hospital demonstrated 14/15 failures when the total dose was less than 60 Gy, with increasing control with higher doses. However, despite doses in excess of 80 Gy, gross disease greater than 10 cm could not be controlled (81). Similarly, Perez et al. demonstrated poor tumor control with high dose RT, with approximately 50% LRF with doses of 70 to 75 Gy. In attempts to improve tumor control, preoperative RT was utilized to render locoregional disease operable followed by radical mastectomy (82). Zucali et al. reported the outcomes of 454 patients with inoperable Stage III disease treated with either RT alone or RT followed by radical mastectomy (83). The median survival in the overall series was improved with the combination of RT and surgery compared to RT alone (3.9 years vs. 2.1 years). Only 12 of 70 patients with IBC, however, were able to undergo surgery, and the median survival of the IBC patients was only 1.2 years. Thus, systemic failure remained the predominant pattern of failure independent of type of locoregional treatment.

Radiotherapy or Mastectomy Following Neoadjuvant Chemotherapy

As discussed later in this chapter, neoadjuvant chemotherapy (NAC) has become the mainstay of treatment for IBC to reduce the rate of metastatic spread. It also plays a pivotal role in optimizing locoregional control. Among responders, rates of locoregional tumor control with NAC followed by RT were improved compared to RT alone; LRF, however, remained substantial (84,85). In a report comparing outcomes in 60 patients treated with RT only compared to 91 patients and 79 patients treated with successive induction chemotherapy regimens followed by RT at the Institut Gustave Roussy, Rouesse et al. reported 4-year rates of LRF of 53% with RT alone versus 32% and 31% with induction chemotherapy and RT (p = .01) (85).

The question of whether RT or mastectomy (M) alone after NAC resulted in better outcomes was tested in a small randomized trial from Tunisia (86). In this study in which 83 patients with IBC received induction CMF (cyclophosphamide, methotrexate, 5-flurouracil), only 57 patients completed therapy with a significant improvement in stage-specific DFS compared to patients treated in an earlier study without NAC. However, no significant difference in disease-free interval was observed between patients treated with M or RT.

The Effectiveness of Mastectomy Combined with Radiotherapy

From results acquired over a 30-year period, Perez et al. reported improved rates of locoregional control with trimodality therapy, with LRF as isolated failure or component of failure occurring in 70% treated with RT alone, 63% with chemotherapy and RT, 24% with RT and surgery, and 21% with triple therapy (82). Fleming et al. from MD Anderson Cancer Center analyzed outcomes in 178 women with IBC treated with anthracycline-based NAC followed by local therapy (87). The addition of M to RT significantly improved local control compared to RT only, with rates of LRF of 16.3% with M+RT compared to 35.7% with RT only after chemotherapy (p = .015). A benefit in both DFS and OS was observed by the addition of M only among patients achieving either a complete or partial clinical response to induction chemotherapy.

As shown in Tables 59-1 and 59-2, the outcomes from various retrospective series differ greatly by regimens used but improved rates of local control, 5-year DFS and OS appear to be associated with the addition of M to RT. However, selection biases confound interpretation of the results. There are no randomized comparisons between RT only and M+RT following NAC. However, a recent population-based analysis of curative treatment strategies for IBC in British Columbia found that M was increasingly utilized (with chemotherapy and RT) from 1980 through 2000, with only 33% of patients undergoing M from 1980–1985 compared with 78% from 1996–2000 (88). On multivariate analysis, incorporating M into locoregional therapy was associated with significantly improved locoregional relapse-free survival (RFS). Ten-year locoregional RFS for patients undergoing M after chemotherapy, M before chemotherapy, and no M were 62.8%, 58.6%, and 34.4%, respectively (p = .0001). In a recent consensus statement from an international expert panel on IBC, primary systemic chemotherapy, surgery (i.e., modified radical mastectomy) and RT was felt to be the standard treatment plan (10).

To optimize locoregional control with M, chemotherapy should be delivered until areas of skin inflammation have resolved prior to proceeding with surgery and any breast and nodal masses which were fixed at presentation are operable. If breast or nodal disease remains inoperable after systemic therapy, preoperative RT is strongly recommended to convert fixed lesions to technically operable disease. Extended RT fields can also help to achieve microscopically negative margins, an important factor in optimal locoregional control. A series by Curcio et al. of 28 patients with IBC identified margin status as a prognostic indicator for local control, DFS and OS (89). Three-year results for OS, DFS, and local control were 47%, 38%, and 60% with negative margins and 0%, 17%, and 32% with positive margins (p < .05). In a separate review of multiple factors predictive of LRF in 256 patients with IBC, surgical margin status remained an independent predictor of outcome on multivariate analysis, with negative margins associated with a 91% rate of locoregional control compared to 68% with positive or unknown surgical margins, p = .0005 (90). If the extent of disease and surgical operability is unclear based upon physical findings, radiologic studies such as CT or PET/CT should be strongly considered.

The sequencing of RT, that is, preoperative or postoperative RT, does not appear to affect locoregional outcome in patients with technically operable disease after NAC (88,91).

TABLE 59-1

Outcomes in Patients with Inflammatory Breast Cancer Treated with Chemotherapy and Radiotherapy

Author	*Number of Patients*	*Regimen*	*Locoregional Control %*	*Disease-free Survival % (5 yr)*	*Overall Survival % (5 yr)*
Buzdar et al. 1981 (143)	32	FAC+BCG+RT	75	32[a]	34[a]
Lamb et al. 1991 (84)	47	AC/CMF+RT	51	NA	30
Chevallier et al. 1993 (144)	64	CMF/AVCF+RT	NA	18	29
Perez et al. 1994 (82)	35	CAF/CMF+RT	37	6	NA
Arthur et al. 1999 (95)	28	CAF/CMF+RT	68	NA	NA
De Boer et al. 2000 (145)	35	Anthracycline-based/CMF+RT	69	24	38
Bourgier et al. (2012) (146)	124	AVCMF+RT	75 (10 yr)	39 (10 yr)	39 (10 yr)

[a]Extrapolated from actuarial curves.
F, 5-fluorouracil; A, doxorubicin; C, cyclophosphamide; BCG, bacille Calmette-Guérin; RT, radiotherapy; M, methotrexate; V, vincristine; NA, not available.

TABLE 59-2

Outcomes in Patients with Inflammatory Breast Cancer Treated with Chemotherapy, Mastectomy, and Radiotherapy

Author	*Number of Patients*	*Regimen*	*Locoregional Control %*	*Disease-free Survival % (5 yr)*	*Overall Survival % (5 yr)*
Maloisel et al. 1990 (147)	38	FAC+M+RT	NA	48	75
Pisansky et al. 1992 (96)	36	CFP+M+RT	81	24	34
Perez et al. 1994 (82)	86	CAF/CMF+M+RT	79	40	NA
De Boer et al. 2000 (145)	19	Anthracycline-based/CMF+M+RT	68	9	15
Harris et al. 2003 (91)	52	CMF/CAF+RT+M	92	49	56
Bristol et al. 2008 (90)	192	FAC/VP/MV_b/T+M+RT	84	47	51
Damast et al. 2010 (94)	107	ACT/CMF+M+RT	87	40	61

F, 5-fluorouracil; A, doxorubicin; C, cyclophosphamide; M, mastectomy; RT, radiotherapy; P, prednisone; NA, not available; V, vincristine; V_b, vinblastine; T, taxane.

In the population-based study from British Columbia, the timing of RT (early vs. late) resulted in 10-year locoregional RFS of 52.2% and 49.7% (p = .72) with no difference in BCSS (88). In the absence of benefit with preoperative RT, postoperative treatment is recommended so RT dose can be tailored, as necessary, to operative findings.

Radiation Therapy Following Mastectomy

Patterns of disease failure have largely dictated the locoregional target volumes to be irradiated in IBC (82,92,93). In a series of 10 patients with IBC whose disease progressed after M but prior to receiving or completing RT, 6 progressed at the chest wall and in regional lymphatics other than the dissected axilla (92). In a review of the sites of LRF in 20 of 61 patients with IBC who experienced a LRF, including those previously irradiated, 85% of the recurrences included the chest wall and 20% included the regional lymphatics but excluded the axilla. Other series have also demonstrated LRF predominantly outside of the axillary bed in IBC patients treated with axillary dissection (82,93). Therefore, the chest wall (including the mastectomy scar), supraclavicular and infraclavicular nodes, and the internal mammary nodes (IMN) should be irradiated. The decision whether to irradiate the axillary bed should be based upon the results of the axillary dissection and the extent of axillary involvement.

The skin is an important target in IBC and tissue equivalent bolus should be placed daily on the skin of the chest wall to lessen the skin-sparing of megavoltage beams. The goal should be to achieve a brisk erythematous skin reaction at the chest wall. Prior studies have suggested a trend for higher rates of local recurrence when brisk erythema has not been achieved (92). In a recent study from Memorial Sloan-Kettering Cancer Center, high rates of locoregional control were, in part, attributed to the aggressive use of daily bolus (94).

The rates of locoregional tumor control in IBC have significantly differed by initial response to chemotherapy, with significant improvements among patients with a complete clinical response (cCR) or partial clinical response (cPR) compared to patients with less than a partial disease response (88,90,92,95). In a large review of IBC patients treated from 1977 through 2002, the strongest predictor for locoregional control was clinical response to NAC, with a 5-year locoregional control rate of 95% for patients with a cCR, 86% for those with a cPR, and 51% with less than a partial response (90). Dose and choice of fractionation also impact rates of locoregional control particularly in disease not responsive to chemotherapy. Standard fractionation at 2 Gy/day to 50 Gy to the chest wall and regional nodes generally followed by a 10 Gy boost in 2 Gy fractions to the mastectomy scar is commonly used and has resulted in 5-year locoregional rates of 72% to 87% (82,90,94,96). Hyperfractionated RT, where the total dose is divided into smaller fractions delivering more than 1 dose daily, offers the theoretical benefit of preventing tumor repopulation between radiation fractions and is appealing in rapidly proliferating disease. Experiences with hyperfractionated regimens (such as 66 Gy in 1.5 Gy bid fractions over 4.5 weeks) or a more accelerated hyperfractionation regimen (44.2 Gy in 1.7 Gy bid fractions over 2.5 weeks) have suggested a trend toward improved locoregional control when compared to once daily fractionation, particularly 1.8 Gy daily (92,96). There has never been a prospective trial comparing dose or fractionation in IBC but a recent analysis by Bristol et al. from MD Anderson Cancer Center demonstrated no difference in rates of control between 60 Gy in 2 Gy fractions and 66 Gy in 1.5 Gy bid fractions in patients with a cCR or a cPR. Control rates were improved with hyperfractionated therapy in patients with less than a partial response and patients with positive, close, or unknown margins. Grade 3 and 4 late complications were greater in patients treated to the higher dose using hyperfractionated RT. Based upon this analysis and others, 50 Gy in 2 Gy fractions to locoregional targets followed by a 10 Gy boost to the mastectomy scar is recommended as standard therapy with consideration of higher doses and possible hyperfractionation in the presence of risk factors strongly predictive for LRF.

Controversies in Local Disease Management

Management of the axilla is an important component of the locoregional treatment of IBC. While the use of sentinel node surgery following NAC in early stage disease or non-IBC LABC is somewhat controversial (see Chapter 58 on Locally Advanced Breast Cancer) (96a), there is little controversy in IBC. Detection rates of sentinel nodes in IBC have ranged from 75% to 80% with false negative rates of 18% to 33% following isosulfan blue dye injection only (97,98). Concerns of technical difficulties due to blockage of the lymphatics by tumor emboli and inability of blue dye to reach the sentinel node(s) appear warranted. As systemic therapies improve

for IBC, sentinel node surgery should be further studied; however, at this time, axillary dissection remains the standard of care in IBC.

Another area of controversy is whether immediate reconstruction is appropriate with IBC. Primary concerns with immediate reconstruction relate to the delay in initiating postoperative RT due to wound healing and the difficulties sometimes experienced in delivering comprehensive RT in the presence of a reconstructed breast mound. Other concerns include poor cosmesis following immediate RT, particularly if tissue-equivalent bolus is used to decrease the skin-sparing effect of megavoltage radiation. Although some institutions offer immediate breast reconstruction to patients with IBC, it is the authors' preference to delay reconstruction until all therapy has been completed.

Unlike the data presented in Chapter 58 on Locally Advanced Breast Cancer, breast preservation for IBC following NAC with or without preoperative RT remains a subject for further investigation (96a). In a prospective study from the National Cancer Institute of 107 patients with LABC including IBC, chemohormonal neoadjuvant therapy was given to maximal response followed by local therapy (99,100). For patients with less than a cCR, local therapy consisted of M+RT while patients with a cCR underwent multiple incisional biopsies throughout the breast. If no residual disease was identified, patients were offered breast conserving surgery (BCS) and if disease was present, M+RT was performed. Of the 46 patients with IBC, 33% (15/46) had a pathologic complete response (pCR) as defined by multiple negative incisional biopsies and were treated with BCS. With a median follow-up of 16.8 years for live patients, 40% of patients with IBC treated with BCS had LRF compared to 23% treated with M+RT (p = .52) (99). Of note, a cosmetic analysis was performed among 25 patients treated with breast conservation in an earlier report (100). Forty-four percent (11/25) had a fair cosmetic result and 12% (3/25) had a poor result, with marked fibrosis, retraction, and severe volume loss, with one patient requiring mastectomy due to severe breast pain. The 3 patients with poor cosmesis had IBC with results attributed, in part, to use of bolus on the skin of the intact breast.

Others have attempted to use not only response to NAC but also response to RT as a means to select those patients amenable to breast preservation (95,101). In a report from Medical College of Virginia, patients with IBC received NAC followed by accelerated hyperfractionated RT for a total dose of 63 to 66 Gy over 4 to 5 weeks (95). An evaluation to assess persistent or residual disease was performed at 1 month using physical examination, mammography, and multiple needle aspirates, and those with residual operable disease underwent M. Using this algorithm, 50% of patients were treated with BCT and locally controlled with 2-year median follow-up.

In a report of alternating chemotherapy and RT where 3 2-week courses of RT were delivered between successive courses of chemotherapy ("sandwich" therapy) in 124 women with IBC, 82% of patients achieved a cCR by the end of treatment, and local relapse rates were 26% at 10 years and 33% at 20 years (101). Complications were considerable, with 54% of patients developing severe (grade 3) breast fibrosis with markedly retracted breast tissue. Nine percent had symptomatic pneumonitis requiring intervention, 4% developed a brachial plexopathy, and 11% developed rib fractures.

Other series have included brachytherapy implants to improve rates of local control while others have used lumpectomy to excise gross disease remaining after NAC (102,103). There are clearly many variables when considering a conservative approach for IBC to optimize tumor control and cosmesis while minimizing late complications. For these reasons, at this time, it is recommended that BCS for IBC only be offered within the context of a clinical trial.

Future Directions in Local Therapy

With NAC, M, and RT, rates of locoregional control for IBC have dramatically improved and yet for those whose disease is not rendered operable by chemotherapy (or preoperative RT) and for the 15%–30% of patients who recur locally following tri-modality therapy and are at risk for uncontrolled locoregional disease, quality of life can be significantly compromised. The rates of recurrence or persistent disease following NAC and RT for IBC suggest not only chemoresistance but also radioresistance. Laboratory investigations suggest an inherent radioresistance in IBC cell lines (104). These cell lines provide pre-clinical models for study of new agents to improve radiation sensitivity.

Investigation of radiation sensitizers, agents that can increase the biologic effectiveness of a given dose of radiation, are desirable in IBC. In a Phase II trial of 28 patients with inoperable disease including 5 with IBC, concomitant administration of capecitabine and standard dose RT (50 Gy) resulted in an 82% rate of operability (105). These results compared favorably to the 60% operability observed in historical controls treated at the same institution with RT alone. In another study of 14 patients (8 with IBC) with inoperable anthracycline- and taxane-resistant disease, concurrent RT and 5-FU or capecitabine with vinorelbine resulted in 100% operability (106). While these results are preliminary, they are encouraging and emphasize the importance of exploiting mechanisms of radiosensitization in clinical trials.

In addition to investigating use of chemotherapy drugs as radiosensitizers, new agents are also being studied for potential sensitizing effects with RT for IBC. One such class of drugs currently under study is PARP (poly [adenosine diphosphate-ribose] polymerase) inhibitors. PARP enzymes play a critical role in DNA repair such that inhibition of function results in DNA single strand break and secondarily double-strand break accumulation. Radiation also causes DNA damage; thus, treatment with PARP inhibitors could potentiate radiation effect. Radiosensitization with PARP inhibition has been demonstrated in multiple *in-vitro* and *in-vivo* studies and is now being tested in a multi-institution, Phase I study including patients with IBC in which patients are treated with concurrent post-mastectomy RT and escalating doses of PARP inhibitor (Pierce L, Jagsi R, personal communication). The degree of clinical radiosensitization and toxicities observed will be carefully documented in preparation for the next generation of PARP inhibitor and RT trials.

SYSTEMIC THERAPY FOR INFLAMMATORY BREAST CANCER

Conventional Neoadjuvant Chemotherapy: Anthracyclines, Taxanes, Dose-Intensity

The benefit of neoadjuvant systemic therapy (NST) in the treatment of IBC includes facilitating the rapid control of locoregional disease while concurrently reducing the risk of developing systemic metastasis. The acceptance of NST as the primary treatment for IBC transformed its previously dismal outcome and tri-modality therapy (systemic treatment followed by local therapy, i.e., mastectomy/radiation therapy) has become the current standard treatment approach for IBC (Table 59-2) (107,108). Because of the rarity of this disease, the majority of clinical trials investigating the efficacy of NAC include not only patients with IBC but

also patients with non-IBC LABC which confounds the interpretation of therapeutic efficacy specifically for IBC. A consistent surrogate for DFS and OS utilized among these studies is the incidence of pCR noted at the time of mastectomy. The definition of pCR varies among the clinical trials, which also confounds the interpretation of efficacy across published studies. One of the initial retrospective analyses which confirmed the benefit of using primary NAC for IBC was performed by Perez et al. who evaluated 179 patients with IBC treated with 4 different regimens administered between 1958 and 1989; 86 patients received tri-modality therapy with cyclophosphamide, doxorubicin, and 5-FU (CAF) as its NAC base (82). Tri-modality therapy resulted in an improved 5-year DFS equaling 40% compared with that seen with radiation and surgery (24%) or with radiation with or without chemotherapy (6%).

Subsequent studies attempted to determine the optimal combination of NAC for the treatment of IBC. Several studies confirmed the importance of anthracycline-based NAC for IBC (109–111). Bauer et al. compared the outcomes of 2 cohorts of patients with IBC: 28 patients treated between 1973 and 1988 received CMF with or without vincristine and prednisone (VP) and 10 patients treated after 1988 received FAC (110). The median OS was significantly improved when anthracyclines were added, compared with CMF/VP (30 months vs. 18 months, respectively, p = .02), as was the 3-year OS (41% vs. 14%, respectively) and 3-year DFS (46% vs. 0%, respectively). The introduction of taxanes into the NAC armamentarium also resulted in improved outcomes. A retrospective review of 6 sequential clinical trials involving 240 patients with IBC treated at MD Anderson Cancer Center from 1973 and 2000, compared disease outcomes among patients treated with anthracycline-based NAC with or without paclitaxel (T) (112). The median PFS was improved with the addition of T (33 weeks with T vs. 26 weeks, p = .18), as was the median OS (52 weeks with T vs. 41 weeks, p = .11). Statistical significance was demonstrated in the ER negative sub-population. Horvath et al. also retrospectively compared their experience of anthracycline-based NAC versus docetaxel (D) with epirubicin (E) and found an improved 3-year OS with the taxane-based NAC; however, statistical significance was not achieved (75% with DE vs. 61%) (Table 59-3) (113).

Currently, the standard NAC for IBC includes an anthracycline- and taxane-based regimen, although the optimal combination or sequence of these agents has not been established. In early stage breast cancer, increased dose-intensity of chemotherapy has shown improved efficacy, and several single arm studies suggested the possibility of benefit in IBC; however, randomized trials have not been as encouraging, possibly because of the overall poor prognosis associated with IBC (85,114–116). The neoadjuvant AGO-1 study evaluated 6 cycles of combination ET every two weeks (dose-dense chemotherapy = DD-CT) or every 3 weeks (conventionally-dosed chemotherapy = CD-CT) administered to a total of 668 patients with LABC, then subsequently analyzed the outcome specifically among the 101 patients with IBC (117,118). Overall, the pCR rate was superior in the DD-CT group compared with CD-CT (18% vs. 10%, respectively) which translated into a superior estimated 5-year DFS (70% vs. 59%) and estimated 5-year OS (83% vs. 77%). However, after a median 6 year follow-up, the benefit of the DD-CT was not seen among the IBC subgroup compared with the CD-CT group; neither with respect to pCR rate (11% DD-CT vs. 10% CD-CT), recurrence rate (55% vs. 51%), or OS (41% died vs. 33%).

The continued high rate of relapse seen in IBC following conventional NAC stimulated greater investigation into higher doses of chemotherapy, such as those used in conjunction with autologous stem cell transplant (HDCT/ASCT). The few studies that focused on IBC utilized conventional anthracycline-based NAC followed by HDCT/ASCT (119–122). As seen in non-IBC treatment, the overall efficacy of this intensive treatment approach does not outweigh the associated toxicity and currently remains highly investigational.

Neoadjuvant Targeted Therapies: HER2-directed, Anti-angiogenic

The prevalence of HER2 positive IBC lends itself to the incorporation of NST that specifically target HER2. The majority of the published literature evaluating HER2 directed therapy with NAC, combines the outcome of both non-IBC LABC and IBC into a single analysis of efficacy (123–126). In addition, most of these trials included less than 20 patients with IBC among their LABC cohort. However, the overall benefits of adding two humanized-monoclonal antibodies against HER2, trastuzumab and pertuzumab, to NAC in LABC, support the current recommendation of using these therapies as primary treatment for HER2 positive IBC.

Trastuzumab, the humanized-monoclonal antibody against HER2, has been evaluated in several NST trials that

TABLE 59-3

Representative Studies Using Anthracyclines with or without Taxanes as Neoadjuvant Chemotherapy in Patients with Inflammatory Breast Cancer

Author	*Number of Patients*	*Regimen*	*Clinical (c) or Pathologic (p) Complete Response %*	*Disease-free Survival % (yr)*	*Overall Survival % (yr)*
Ueno et al. 1997 (109)	178	FAC/FACVP(MV_b)	12 (c)	28 (15)	29 (15)
Bauer et al. 1995 (110)	36	CMF(VP) vs. FAC	17 vs. 40 (c)	0 vs. 46 (3)	14 vs. 41 (3)
Veyret et al. 2006 (116)	120	FEC-HD	15 (p)	36 (10)	41 (10)
Harris et al. 2003 (91)	52	CMF vs. CAF	18 vs. 12 (p)	49 (5)	56 (5)
Ellis et al. 2011 (111)	115	AC®T	20 (p)	53 (5)	39 (5)
Cristofanilli et al. 2004 (112)	240	FAC/FACVP(MV_b) vs. FAC®T	10 vs. 25 (p)	26 vs. 33 (mo)	41 vs. 52 (mo)
Horvath et al. 2011 (113)	74	FAC/FEC/AC vs. TE	10 vs. 0 (p)	47 vs. 36 (3)	75 vs. 61 (3)

F, 5-fluorouracil; A, doxorubicin; C, cyclophosphamide; P, prednisone; V, vincristine; V_b, vinblastine; HD, higher dose; T, taxane; NA, not available; E, epirubicin.

include IBC patients. One of the earliest studies that evaluated the added efficacy from trastuzumab added to NAC for HER2 positive LABC, the NOAH (NeOAdjuvant Herceptin) trial, included an appreciable number of IBC patients (n = 63) and performed a subset analysis of their outcome (127,128). All patients received an intensive schedule of NAC including doxorubicin, paclitaxel, and CMF, with the HER2 positive patients (n = 135) randomized to receive additional trastuzumab. A third component of the study included HER2 negative patients receiving the same NAC. Treatment with NAC concurrent with trastuzumab was associated with a significant benefit in event-free survival (EFS) among the IBC patients, with a hazard ratio of 0.27 (95% CI = 0.11–0.65). The pCR rate was 48% (no invasive disease in breast or lymph nodes) with the addition of trastuzumab compared with 13% treated with NAC alone (p = .002). A recent retrospective review from the Cleveland Clinic Foundation found that among 34 patients with HER2 positive IBC, 23 (68%) received trastuzumab and NAC resulting in fewer patients developing distant metastasis (8/23 = 35%) compared with 5/11 (45%) who were treated with NAC alone (93).

The majority of studies focusing on the oral small molecule tyrosine kinase inhibitor against HER2 and EGFR, lapatinib, have involved patients with metastatic IBC. Forty-nine of 126 (39%) highly pre-treated patients with HER2 positive recurrent or refractory IBC experienced a partial disease response with single agent lapatinib (129). Prior treatment with trastuzumab was not related to disease response with lapatinib; objective response rate of 35% (33/94) with prior exposure compared with 48% (15/31) without prior trastuzumab. Correlative studies established an association between response to lapatinib and co-expression of HER-2 and HER-3 along with lack of p53 expression (130). Based on these encouraging results with a single targeting agent given to a highly pre-treated patient population, combination lapatinib and paclitaxel was investigated as NST for 49 patients with HER2 positive IBC (131). Central pathologic review confirmed HER2 positivity in 32 patients, 17 of whom achieved a clinical response permitting surgical resection (mastectomy). Among these 17 patients, 3 patients (18%) attained a pCR (no invasive disease in the breast or axilla, DCIS permitted).

The phase 3 trial GeparQuinto, compared the impact on pCR using trastuzumab or lapatinib combined with 4 cycles of epirubicin and cyclophosphamide (EC) followed by 4 cycles of docetaxel (T), (ECH-TH vs. ECL-TL, respectively). (R1) Among the 620 patients, 13% had IBC, with 42 IBC patients randomized to ECH-TH and 41 randomized to ECL-TL. The results overall demonstrated an inferior pCR rate with lapatinib vs. trastuzumab (30.3% vs. 22.7%, p = .04). This trend was also seen among the IBC patients, though the difference did not reach statistical significance (odds ratio for achieving a pCR ECH-TH vs ECL-TL = 0.72). These less than auspicious results with single agent lapatinib combined with chemotherapy are also demonstrated in other NST trials for non-IBC patients, supporting the recommendation that lapatinb should not be used as a single HER2 targeting agent combined with NAC for HER2-positive IBC.

Pertuzumab is another humanized monoclonal antibody that blocks heterodimer formation of HER2, most importantly with HER3, and binds to a different domain on HER2 than trastuzumab. NeoSphere is a multicenter randomized phase II trial examining the efficacy of adding pertuzumab to trastuzumab and docetaxel for NST for patients with operable breast cancer, non-IBC LABC, or IBC (132). Given the diversity of prognosis associated with these different stages of breast cancer, the specific efficacy of this regimen for IBC is difficult to assess. Twenty-nine IBC patients out of a total of 198 (15%) were randomized in this 4-arm trial. Most importantly, the overall pCR rate was superior with the dual HER2-targeting regimen of pertuzumab, trastuzumab, and docetaxel (29%), and although the specific effects on IBC were not reported, this combination is likely to be effective in the IBC population. An ongoing clinical trial for HER2 positive IBC using dual HER2 blockade with pertuzumab, trastuzumab, and paclitaxel is evaluating this premise (Overmoyer B, *Personal communication*) (132a). Although recent reports of effective therapy using dual HER2 blockade without chemotherapy are exciting, this approach as NST for IBC remains highly investigational (133).

The important contribution of angiogenesis to the pathophysiology of IBC has prompted investigation into utilizing this biologic component as a therapeutic target. Clinical trials in IBC with anti-angiogenic agents have also incorporated correlative studies which facilitate a greater understanding of this disease and apply this knowledge to the future development of more successful therapies. One of the early phase IB studies involved 18 patients with stage III or IV IBC treated with SU5416 (NSC 696819) a small molecule tyrosine kinase inhibitor against the VEGF receptor Flk/KDR (VEGFR-2) in combination with single agent doxorubicin (134). Seventeen patients were able to proceed to mastectomy (89%); however, there were no pCRs. Among patients with stage III disease (10/18), the median OS was 47 months. DCE-MRI (dynamic contrast-enhanced magnetic resonance imaging) demonstrated a decrease in tumor blood flow with treatment and there was a reduction in tumor microvessel density, yet plasma levels of VEGF increased with treatment. Changes in soluble endothelial adhesion molecules also occurred with this combination of anti-angiogenic therapy and chemotherapy; ICAM-1 (intracellular adhesion molecule-1) levels increased and E-selectin levels decreased. Only the baseline ICAM-1 levels were correlated with the event free survival (EFS). SU5416 was associated with 22% cardiac toxicity when combined with doxorubicin and is no longer being produced.

The effect of angiogenesis inhibition by SU5416 on tumor blood flow as demonstrated by changes in DCE-MRI was confirmed by a study of 21 patients with either stage III or IV IBC (1 patient had non-IBC LABC) treated with a humanized monoclonal antibody against all isoforms of VEGF, bevacizumab (135). The reduction in DCE-MRI parameters continued when bevacizumab was combined with docetaxel and doxorubicin. One patient achieved a pCR and with a median potential follow-up of 27 months, the median OS had not been reached. VEGFR-2 activation at two tyrosine phosphorylation sites (951 and 996, i.e., pVEGFR-2) was assessed prior to and after treatment with bevacizumab. A 67% median decrease in pVEGFR-2 occurred with bevacizumab administration, and persisted with the addition of chemotherapy. CD31 encodes an endothelial cell adhesion molecule involved in cellular signaling and motility, and its expression on IBC vascular endothelium was down-regulated with bevacizumab and corresponded to disease response (136). Tumor VEGF-A levels also corresponded with disease response, with higher baseline levels associated with a more favorable response.

Early data from a phase II trial (PACS 09/Beverly 1) of bevacizumab combined with more extensive chemotherapy (FEC followed by docetaxel) among 100 patients with IBC demonstrated an overall pCR rate of 27%, which was primarily attributed to the HR negative subgroup; 38% (21/55 HR negative) versus 13% (6/45 HR positive) (137). Although these trials and others involving bevacizumab in NST for IBC, have not demonstrated the anticipated enhanced disease response, the correlative studies have provided confirmation that targeting the angiogenesis pathway is still potentially effective and deserves further investigation (126,138,139).

Based upon the interaction of HER2 activation and subsequent downstream signaling of VEGF expression, trastuzumab and bevacizumab were combined with chemotherapy (FEC followed by docetaxel) and used as NST for 52 patients with HER2 positive IBC (Beverly-2) (140). The pCR rate of this combination of dual targeted therapy with NAC was 68% (35/52); however, the impact upon clinical endpoints (DFS, OS) is not yet mature. A note of caution from this study pertains to potential cardiac toxicity in that the incidence of cardiac failure was 8%.

Future Directions: Neoadjuvant Targeted Therapies

Although the advent of NAC for the treatment of IBC brought about significant improvements in OS compared with primary local therapy alone, a greater understanding of the unique molecular mechanisms involved in the biology of IBC has led to the pursuit of novel agents targeting these specific pathways. The improvement in clinical outcomes that occur when HER2 targeting agents are combined with chemotherapy support this approach in the treatment of IBC, i.e., chemotherapy alone is not sufficient treatment for this disease; specific molecular targeting agents must be included. Several clinical trials are either ongoing or have recently been completed (results pending) that have used novel agents targeting VEGFR, PDGF (pazopanib, sunitinib), FGFR3 (TK128/dovitinib), EGR1, HER2 (afatinib), CK2 (CX-4945) and RAS pathways (tipifarnib) (141). To advance this approach even further, many laboratories are involved in investigating novel therapies involving IBC cell-lines and xenograph models (72,126). There are too many exciting advances to thoroughly discuss in this chapter; however, ongoing studies are addressing targeting Notch signaling, inactivating RhoC, JAK2/STAT3 inhibition, suppressing the Akt/mTOR pathway, and suppressing ALK (anaplastic lymphoma kinase) expression, to name a few (62,70–73,75,142). The goal of this work is to unravel the specific details of the unique biology of IBC in order to identify the optimal treatment and continue to improve the prognosis of this virulent disease.

MANAGEMENT SUMMARY FOR THE TREATMENT OF INFLAMMATORY BREAST CANCER

- IBC is rare and presents with a rapid onset of symptoms, usually occurring within three months, and characterized by the following clinical features: erythema usually involving one-third or more of the breast; edema of the skin of the breast (peau d'orange); breast enlargement, often without a palpable mass; and the breast may be warm or tender.
- Breast imaging should be performed, including mammogram and ultrasound, to detect sites within the breast that could be biopsied to confirm adenocarcinoma of the breast. Breast MRI is often more successful in determining extent of disease with IBC. (See Chapter 58 on Locally Advanced Breast Cancer.) (96a)
- A biopsy confirmation of adenocarcinoma of the breast is necessary. Skin biopsy is optional and should not be used to confirm the diagnosis of IBC. Diagnosis is based upon the presence of the clinical signs (noted above) in the setting of adenocarcinoma of the breast.
- IBC is highly metastatic, therefore complete staging is necessary, including: CT chest, abdomen, pelvis; bone scan (not necessary if PET is used). FDG PET/CT may be considered to identify unsuspected nodal involvement or distant metastasis, but should not replace standard staging studies. CNS imaging should be performed if symptoms exist. Biopsy confirmation of distant metastasis is recommended.
- A multi-modality evaluation should occur, including medical oncology, radiation oncology, and surgery prior to initiating therapy.
- Neoadjuvant chemotherapy is given, usually containing an anthracycline- and taxane-based regimen. Standard adjuvant chemotherapy regimens should be used off clinical trial (4–6 months duration). If HER2 positive disease is present, trastuzumab and pertuzumab should be added to the NAC as outlined in standard regimens. Systemic therapy should continue until all signs of skin inflammation (edema and erythema) have resolved and the breast and axillary masses are operable.
- A complete mastectomy with axillary lymph node dissection should follow completion of NST. Reconstruction of the breast should be delayed.
- If the breast or nodal disease remains inoperable after NST, then radiation therapy should be given prior to surgery as described above. Otherwise, radiation therapy is given following mastectomy using standard radiation therapy fields determined by CT planning, with a tissue equivalent bolus placed daily on the skin of the chest wall to induce a brisk erythematous skin reaction. The chest wall (including mastectomy incision), supraclavicular, infraclavicular, and internal mammary lymph nodes should be irradiated. The decision to irradiate the axillary bed following axillary dissection should be individualized.
- Standard adjuvant endocrine therapy should be given if the disease is ER and/or PR positive. This should begin following surgery and is based upon accepted guidelines. Adjuvant trastuzumab should be given to complete one year of treatment for HER2 positive disease.

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CHAPTER 60

Preoperative Systemic Therapy for Breast Cancer

Marc E. Lippman

Preoperative (or neoadjuvant) systemic therapy for breast cancer is a rapidly changing field with complex issues surrounding appropriate patient selection, management, and research considerations. Unquestionably, patients require coordinated multidisciplinary care with input from radiologists, surgeons, radiation oncologists, and medical oncologists for optimal outcomes.

Substantial data do not exist suggesting that preoperative therapy has superior survival to postoperative systemic therapy, but there are other potential benefits for the patient. Preoperative systemic therapy is indicated for patients with locally advanced breast cancer—T4 tumors or N2 or N3 nodal disease—to convert them to operable. While not formally demonstrated in randomized clinical trials, survival rates for locally advanced breast cancer have increased substantially with preoperative systemic therapy. For patients with unicentric cancers, which are too large relative to the size of the breast to allow cosmetically acceptable breast-conserving surgery (BCS), preoperative chemotherapy will allow BCS in at least one-third of these patients. The lack of reliable methods for evaluating the extent of residual disease in the breast after preoperative chemotherapy remains an obstacle to increasing rates of BCS, even as pathologic complete responses to newer drug combinations and targeted therapy become more frequent. In patients with clinically negative nodes at presentation, sentinel node biopsy after chemotherapy accurately stages the axilla, and this approach has been shown in randomized trials to decrease the need for axillary dissection. There is more controversy regarding the management of patients who present with clinical nodal metastases that appear to resolve with preoperative chemotherapy. Two recent prospective trials investigating the accuracy of sentinel node biopsy in this setting (1,2) reported false negative rates of 18% to 21% with the removal of 2 sentinel nodes. False negative rates decreased below the 10% threshold if 3 or more nodes were removed, but the median number of sentinel nodes identified in large multicenter trials of sentinel node biopsy prior to chemotherapy is 2. At the present time, axillary dissection remains the standard management for patients presenting with clinically involved (and histologically confirmed) nodal metastases, pending the results of additional trials discussed below. Outside of clinical trials, there is little justification for preoperative systemic therapy for tumors suitable for management by established means of breast conservation with appropriately administered systemic adjuvant therapy or in patients who require mastectomy due to multicentric disease. In fact, optimal guidelines for postoperative radiation therapy, which are reasonably well established for breast cancers managed by surgery first, are far less clear for patients staged after the completion of preoperative systemic therapy and are the subject of intense investigation. Particularly unclear at this time are optimal recommendations for treatment of clinically or pathologically positive nodes that become either clinically negative or pathologically negative after preoperative systemic therapy. In general, there is wide agreement that radiation therapy is required for essentially all patients rendered operable and downstaged by systemic therapy; however, there remains a substantial lack of clarity of how best to treat formerly involved lymph node areas. A major potential advantage of using neoadjuvant systemic treatments would be to permit the tailoring of local-regional treatment recommendations based on disease response. Specifically, based on the data available to date, it is reasonable to ask whether patients with a very favorable response could potentially avoid the toxicities of more aggressive local-regional therapies. Two recently activated phase III trials investigate this concept; one with respect to axillary management and one with respect to avoidance of postmastectomy or regional lymph node radiation.

The recently approved axillary management trial is being led by the Alliance Group (A11202 trial). This trial will study patients who present with node-positive disease and who continue to have positive sentinel lymph nodes (SLNs) after chemotherapy (plus anti-HER2 therapy if HER2-positive) despite no longer having clinical evidence of gross residual lymph node disease. Patients will be randomized to the current standard of care of performing axillary lymph node dissection plus breast/chest wall and nodal irradiation versus avoidance of axillary lymph node dissection and use of breast/chest wall and nodal irradiation to eradicate potential residual microscopic disease within the undissected lymph nodes. If this trial is able to achieve balanced results, the avoidance of an axillary dissection for patients will likely result in less patient morbidity and lower costs.

The radiation trial for initial node-positive patients being treated with neoadjuvant chemotherapy (plus anti-HER2 therapy if HER2-positive) is being led by NSABP and RTOG (NRG 9353 trial). This study will enroll patients with initial node-positive disease who convert to node-negative with chemotherapy (determined by SLN surgery or axillary lymph node dissection [ALND]). Eligible patients for this study will include those with clinical T1–3N1 disease who have pathologically negative lymph nodes after neoadjuvant chemotherapy. All patients treated with breast conservation will receive radiation to the breast, and the study will randomize these patients to the addition or omission of regional lymph node radiation. For patients treated with mastectomy, randomization will be between radiation to the chest wall and draining lymphatics versus no radiation.

Within the confines of prospective clinical trials—with the potential availability of tissue sampling prior to, during, and after therapy—the efficacy of novel targeted therapies can be explored in detail. It is certainly clear that responses to novel treatments can be assessed objectively in this setting along with critical information that may more accurately predict which patients will benefit from therapy.

It has been proposed that the ability to induce a pathologic complete response (pCR) may be a surrogate for long-term event-free and overall survival and that, plausibly, preoperative systemic therapy could be used as a means of validating therapy efficacy sooner and on fewer patients than in the adjuvant setting. Clearly, this approach could lead to a vastly less expensive and time-consuming approval process for new agents. However, it is important to state that in the randomized preoperative systemic therapy trials that have been reported to date, differences achieved in rates of pCR have not uniformly translated into improved event-free survival rates for the group with a higher pCR rate. This is a dismaying and somewhat unexpected result given the clear association between pCR and improved outcome for any individual patient. This may or may not change when (hopefully) more effective therapies are explored in the future.

Multiple reports have plainly established that preoperative therapy that results in a pathologic pCR is associated with a substantially better survival for the individual patient. However, the most appropriate way to diagnose a pCR is not completely agreed upon. Whether or not residual ductal carcinoma in situ (DCIS) should be an exclusion criterion for a pCR is unsettled, as is residual microscopic axillary lymph node (ALN) disease. We believe that while "almost" pCR may well be a gratifying pathologic response for patients and physicians alike, validated systems are needed to assess the degree of response to preoperative systemic therapy and its prognostic value. These systems are covered in Chapter 56, Pathologic Assessment of Treatment Response after Neoadjuvant Therapy. The two most widely used systems are Miller-Payne (3) and the Residual Cancer Burden (4).

There are significant differences in successful induction of pCR's based in part on the breast cancer subtype. TNBC and HER2-positive cancers have substantially higher pCR rates than Luminal A (ER-positive, PR-positive, HER2-negative breast cancers). There is general consensus that essentially all systemic chemotherapy regimens should include a taxane and most regimens employ an anthracycline as well. There have been few, if any, studies suggesting that there are important differences in efficacy between established adjuvant therapy regimens and those which are efficacious in the preoperative setting so any well-validated adjuvant regimen is appropriate absent data tying a specific combination to a specific molecular subtype.

To date, HER2-targeted therapy is the only adjunct to chemotherapy that has been proven to improve outcomes. Multiple studies are underway exploring agents additional to trastuzumab, and this area should be followed closely to assure ideal therapy for HER2-positive patients. (The NEOSPHERE and NEOALTTO randomized neoadjuvant trials looking at pertuzumab plus trastuzumab or lapatinib plus trastuzumab together with taxol showed a doubling of the pCR rate compared to the single agent targeted therapy.) Recently reported results using dual HER2 blockade without any cytotoxic drugs has suggested similar pCR rates to those achieved with intensive chemotherapy plus trastuzumab, which, if validated, will be a very exciting development.

Multiple trials are underway exploring a variety of other potential targets, including trials investigating novel drugs such as PI3K inhibitors (NeoPHOEBE / NCT01816594), PARP inhibitors (NeoPARP / NCT01204125), multikinase inhibitors such as sunitinib and pazopanib (NCT00849472, NCT00887575), and IAP (Inhibitor of Apoptosis Protein) antagonists such as LCL161 (NCT01617668).

In Luminal A patients, rates of pCR are very low while responses to endocrine therapy, particularly aromatase inhibitors, are reasonable, and a high proportion of patients will downstage. Thus, very serious consideration should be given to preoperative endocrine therapy. This is a particularly attractive approach in elderly patients with advanced breast cancers that appear to be more a result of neglect than aggressiveness. Such patients are often not ideal for aggressive chemotherapy treatment. Responses can be slow and gradual, and careful assessment over a period as long as 6–12 months may be needed.

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SECTION IX

Special Therapeutic Problems

CHAPTER 61

Male Breast Cancer

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CHAPTER CONTENTS

EPIDEMIOLOGY

Male breast cancer (MBC) is a rare disease worldwide. As a result of its rarity, it is treated similarly to female breast cancer but important differences exist. In the United States, it is estimated that 2,190 men will be diagnosed with breast cancer and 410 will have died from this disease in 2012. MBC accounts for less than 1% of all breast cancers and less than 0.5% of all male cancer deaths in the United States (1). Globally, the highest male incidence rate was observed in Israel at 1.24 per 100,000 man-years followed closely by the Philippines, Italy, and France. The lowest male incidence rate was recorded in Thailand at 0.16 per 100,000 man-years followed by Japan, Singapore, and Colombia (2).

The worldwide female-to-male incidence rate ratio of breast cancer is 122:1 (2). MBC compared to female breast cancers occur later in life with higher stage, higher grade, and more estrogen receptor–positive tumors. The median age of onset of MBC is 72 years of age, compared to 61 years in women (3). According to the United States Surveillance, Epidemiology, and End Results (SEER) registry database, the incidence rate of MBC was slightly increasing from 1975 to 2004 (from 0.9 to 1.2 cases per 100,000 men at risk). A rapid increase in female breast cancer incidence was observed in the mid 1970s to mid 1990s in the United States and Europe largely due to the greater use of mammographic screening. Mortality rates in the late 1980s and 1990s tended to be lower than three decades earlier, likely owing to advances in diagnostics and therapeutics (4). The most recent SEER database analysis shows a decrease in breast cancer incidence and mortality in both men and women, but the trends were greater for women. Comparing patients diagnosed from 1996 to 2005 versus 1976 to 1985 and adjusting for age, stage, and grade, MBC death declined by 28% among men and 42% among women (5).

Racial/ethnic differences also exist. In the United States, the ratio of female-to-male breast cancer is approximately 100:1 in whites and 70:1 in blacks. Age-adjusted incidence rates per 100,000 men are highest in blacks (1.65), intermediate in whites (1.31), and lowest in Hispanics (0.68) and Asian/Pacific Islanders (0.66). Blacks are also diagnosed at an earlier age and at a more advanced stage compared to other ethnicities (6). Similar to black women, black men have an increased breast cancer-specific mortality even after adjustment for clinical, demographic, and treatment factors (7).

The distribution of tumor subtypes is also different across racial/ethnic groups. In the largest population-based study evaluating breast tumor subtypes in 606 patients with MBC, 82.8% of white men (95% CI, 79.3%–86.4%) had hormone receptor positive tumors, 14.6% had HER2-positive tumors (95% CI, 11.3%–18%), and 2.6% had triple negative breast cancer (95% CI, 1.1%–4%). In contrast, among blacks, 73.3% had hormone-receptor positive tumors (95% CI, 60.4%–86.3%), 17.8% had HER2-positive tumors (95% CI, 6.6%–29%), and 8.9% had triple negative tumors (95% CI, 0.6%–17.2%); whereas, among Hispanics, 77.6% had hormone-receptor positive tumors (95% CI, 67.6%–87.6%), 16.4% had HER2-positive tumors (95% CI, 7.6%–27.5%), and 6% had triple negative tumors (95% CI, 0.3%–11.6%). Among the patients with hormone receptor-positive tumors, black and Hispanic men were more likely to have PR-negative tumors than white men. No statistically significant differences in survival were observed according to tumor subtype (p = .08). Among hormone receptor-positive patients, blacks experienced the worst survival (8).

RISK FACTORS

Several risk factors are associated with the development of MBC, including endocrine, nutritional, and genetic factors (Table 61-1). In a large retrospective review of a United States Veterans Affairs database assessing 642 cases of MBC, conditions associated with increased risk of MBC included diabetes, orchitis/epididymitis, Klinefelter syndrome, and gynecomastia. Among blacks, cholelithiasis emerged as a significant risk predictor (9). A large prospective study found family history,

TABLE 61-1

Risk Factors Associated with Male Breast Cancer (MBC)

Endocrine
Gynecomastia
Testicular conditions
Liver disease
Diabetes mellitus
Nutritional/lifestyle
Obesity
Low physical activity
Alcohol use
Genetic
Family history
Klinefelter syndrome
BRCA carrier (*BRCA2* > *BRCA1*)
Cowden syndrome
Li-Fraumeni syndrome
HNPCC (Lynch) syndrome

history of bone fracture, obesity, and low physical activity to be positively associated with MBC. Some of these identified risk factors are common to female breast cancer and suggest an importance of hormonal mechanisms (10).

The strongest risk factor for MBC is Klinefelter syndrome (9). This rare condition results from the inheritance of an additional X chromosome (XXY). Men with this condition have atrophic testes, gynecomastia, high serum levels of gonadotropins (follicle-stimulating hormone, luteinizing hormone), and low plasma levels of testosterone. It is hypothesized that the increased estrogen-to-testosterone ratio could in turn lead to abnormal hormonal stimulation of cell proliferation in mammary ductal epithelium. Of the few epidemiologic studies conducted in this area, the largest cohort study of 3,518 men with cytogenetically diagnosed Klinefelter syndrome found 19- and 58-fold increases in incidence of, and mortality from, MBC, respectively, compared to the general population. Alteration of hormone levels, particularly the elevated ratio of estrogen-to-testosterone, administration of exogenous androgens, gynecomastia, and genetic factors are possible explanations for the high risk. Additional studies are needed to delineate which patients with Klinefelter syndrome are at increased risk for MBC, and the importance of patient education, self-examination, and regular examinations should be enforced (11).

Chronic liver diseases such as cirrhosis, chronic alcohol injury, and schistosomiasis have been associated with an increased risk of MBC. Cirrhosis limits the ability of the liver to metabolize endogenously produced estrogen, leading to a relative hyperestrogenic state with an imbalance in the estrogen-to-testosterone ratio (12). Similarly, ethanol, which has been associated with an increased risk of breast cancer in females, is a metabolic modifier for mammary epithelium and may promote the most carcinogenic pathway of estradiol metabolism to catechol estrogen. Very few cases of MBC have been documented in patients with chronic liver diseases, possibly due to the shortened lifespan associated with these disorders. Results from some studies have not found an association between liver cirrhosis and MBC (9).

Gynecomastia, when related to states of estrogen excess, has been associated with MBC. Gynecomastia is most often drug-related, and several medications that cause gynecomastia have been associated with an increased risk of MBC. Breast cancer has been described in three men who were prescribed finasteride, a drug approved for the treatment of benign prostatic hyperplasia. Cases of MBC have also been reported with digoxin, thioridazine, and spironolactone, and in male-to-female transsexuals who were castrated and given high doses of estrogen (13).

Testicular conditions have also been associated with an increased risk of MBC. These include orchitis, undescended testis (cryptorchidism), and testicular injury. Other conditions associated with an increased estrogen-to-testosterone ratio such as thyroid disease and marijuana use have not firmly established a link to MBC.

Experimental evidence suggests that prolactin may promote tumorigenesis in animal models; however, physiologic states of prolactin excess in humans (e.g., multiple pregnancies) do not confer an increased risk of breast cancer and may be protective. Several case reports have described the development of MBC in association with a prolactinoma, a setting in which low plasma testosterone levels are often observed (14). The association between prolactin excess and MBC remains unclear.

Androgens may convey a protective effect by inhibiting cell proliferation in breast tissue. In some reports, mutations in the DNA-binding domain of the androgen receptor (AR) gene have been implicated in the development of MBC. Conversely, a pathologic case study that analyzed tumor material from two series of patients with MBC without clinical evidence of androgen insensitivity reported no AR gene mutations. In a study of 43 MBC patients, AR expression by immunohistochemistry inversely correlated with survival (15).

Approximately 5% to 10% of female breast cancer cases are thought to be hereditary, with the majority of these cases associated with mutations in two genes: breast cancer type 1 and 2 susceptibility genes (*BRCA1* and *BRCA2*). These genes are inherited in an autosomal dominant pattern and confer a lifetime risk of female breast cancer ranging from 50% to 85%. Approximately 15% to 20% of MBC is associated with a positive family history for the disease compared to only 7% of the general male population (16).

BRCA2 mutations are more frequent than *BRCA1* mutations. In an Italian series of 50 *BRCA* carriers, 92% harbored the *BRCA2* mutation compared to 8% with the *BRCA1* mutation (17). Inherited mutations in *BRCA* do not increase the risk of breast cancer to the same degree in males as in females. The breast cancer risk also appears to be higher with *BRCA2* mutations as opposed to *BRCA1*. Men who carry a *BRCA2* mutation have an approximate 6.5% cumulative risk for breast cancer by age 70, which is 100-fold higher than the general male population. A paucity of data exists correlating the risk for MBC in *BRCA1* carriers. One Dutch and one American family have been described that carried the *BRCA1* mutation; each had one case of MBC as well as multiple associated female breast cancer cases. A report from the National Cancer Institute Cancer Genetics Network suggests that the cumulative risk of breast cancer by age 70 in men harboring a *BRCA1* mutation is 1.2% (95% CI, 0.22%–2.8%) (16).

The classification of molecular subtypes based on immunohistochemical profiles as proposed in female breast cancer, is still controversial in MBC. In one report of 382 MBCs including 50 *BRCA* carriers, the immunophenotypic profiles differed between 4 *BRCA1*- and 19 *BRCA2*-asssociated patients, in whom complete ER, PR, and HER2 status was available. Of the 4 *BRCA1*-related MBC cases, 3 showed a luminal A subtype and 1 a triple negative tumor. Of the 19 *BRCA2*-related MBCs, 7 were luminal A, 9 luminal B, and 3

HER2-positive. Notably, all 7 triple negative tumor cases were *BRCA2* mutation negative. In a multivariate logistic model, *BRCA2*-associated MBCs showed positive association with high tumor grade (OR 4.9, 95% CI, 1.0–23.9) and inverse association with PR expression (OR 0.19, 95% CI, 0.04–0.92), suggesting that the *BRCA2* subgroup is characterized by a more aggressive phenotype (17).

Genetic mutations other than *BRCA* may predispose males to developing breast cancer. Cowden syndrome, an autosomal dominant cancer susceptibility syndrome, is associated with germline mutations in the tumor suppressor gene *PTEN* located on chromosome 10. This syndrome is characterized by multiple hamartomas and an increased risk for both male and female breast cancer and thyroid malignancies. Two cases of MBC have been reported with germline *PTEN* mutations and the Cowden syndrome phenotype. Other hereditary syndromes associated with MBC include Li-Fraumeni syndrome, caused by the *TP53* mutation, and hereditary nonpolyposis colorectal cancer (Lynch) syndrome, caused by mutations in the mismatch repair genes (18).

Recent genome-wide association studies (GWAS) identified common single nucleotide polymorphisms (SNPs) that influence female breast cancer risk. A GWA study of MBC compromising 823 cases and 2,795 controls were genotyped and validated in an independent sample set, and the SNP RAD51B was found to be significantly associated with MBC risk (19). Other studies have found genetic variants that influence susceptibility to breast cancer, which differ between male and female breast cancer.

Guidelines from the National Comprehensive Cancer Network (NCCN) recommend that genetic testing be offered to men who develop breast cancer as well as to families with a known *BRCA* mutation, a case of MBC, or the presence of female relatives with a history of breast or ovarian cancer that suggests the presence of an inherited breast or ovarian cancer syndrome. Furthermore, adherence to recommended screening guidelines for prostate cancer is advised, as males with *BRCA2* mutations have an elevated risk of prostate cancer.

CLINICAL FEATURES

Similar to cancer in women, MBC typically presents as a painless lump. The mass is usually subareolar and less often in the upper outer quadrant. A slight predilection exists for the left breast. Nipple involvement is a fairly early event, occurring in 40% to 50%, with retraction in 9%, discharge in 6%, and ulceration in 6%. Bilateral MBC is very rare with a reported incidence of 1.5% to 2% of all MBCs (20). Infrequently, MBC presents as an axillary nodal metastasis without a palpable breast lump. Other findings on examination for malignancy include fixation to skin or muscle and breast tenderness (21).

The majority of breast lesions in males are benign, with gynecomastia as the most common etiology. Other pathologic lesions in the male breast are related to the cutaneous and subcutaneous tissue and can include lipoma, breast abscess, metastatic lesion to the breast, and other primary malignancies such as sarcoma (22). Gynecomastia has been found in up to 55% of male breasts in a series of autopsy specimens (21). As opposed to MBC, gynecomastia usually presents as bilateral, symmetrical breast enlargement with irregular borders in the absence of axillary lymphadenopathy or fixation to the chest wall. On mammography, MBC is usually subareolar and eccentric to the nipple. In contrast, gynecomastia appears as a round or triangular area of increased density positioned symmetrically in the retroareolar region. Calcifications are rarer and coarser than those occurring in female breast cancer. Because of the low incidence of MBC in the general population, there is no role for screening mammograms in men. One report described a male *BRCA2* carrier who was diagnosed with breast cancer by screening mammography; clear guidelines have not been established for this population (23).

DIAGNOSIS

The first step in the evaluation of a suspicious breast mass in a male is mammography. A mammogram can usually distinguish between malignancy and gynecomastia and is abnormal in 80% to 90% of MBCs. Mammographic features of malignancy include a dense mass generally without calcifications and often with spiculated, indistinct, or microlobulated margins. Sonography usually reveals an irregularly-shaped hypoechoic mass, as seen in female breast cancers. Any cysts that are discovered on imaging should be sampled, as simple cysts are rare in men and are associated with neoplastic papillary lesions. Likewise, radiologic features such as a well-defined lesion that would suggest a benign finding in a female are unreliable in men and require biopsy. In one series, MBC was manifested as a well-defined mass in 15% of cases using mammography and in 23% using sonography (24).

Several studies have suggested that mammography added no diagnostic information to the combination of physical examination and pathologic evaluation. In one retrospective analysis of 134 male patients with a history of a breast lump between 2001 and 2003 and undergoing mammographic imaging, only four cases of breast cancer were diagnosed. All four patients presented with a painless lump, for a mean duration of 7 months, and breast cancer was suspected due to clinical examination and confirmed by biopsy (25). The use of breast MRI has not been widely studied in MBC, and no prospective data exists for its use in screening or diagnosis of MBC.

Once a suspicious breast mass is identified, biopsy is required to confirm the diagnosis and to assay for ER, PR, and HER2 status. Fine needle aspiration (FNA) is a reliable procedure, and has been shown to avoid surgical biopsy in 59% of cases. However, in one report of 153 FNAs of the male breast, 13% did not provide sufficient tissue for diagnosis (26). Compared to FNA, core needle biopsy offers a more definitive histologic diagnosis, avoids inadequate samples, and usually distinguishes between invasive and *in situ* cancer.

PATHOLOGY

The most common histopathologic type of MBC is invasive ductal carcinoma, similar to female breast cancer, and accounts for 85% of all MBC cases. Conversely, invasive lobular carcinoma is much less frequent in males compared to females, constituting only 1.7% of MBCs (27). The rarity of lobular carcinoma in males may be due to the lack of acini and lobules in normal male breast tissue. Ductal carcinoma *in situ* (DCIS) accounts for 20% to 25% of all cases of female breast cancer. In contrast, the frequency of DCIS in men ranges from 0% to 17%, with an average of 7%. Few case reports of lobular carcinoma *in situ* (LCIS) exist in the published literature. Paget's disease of the breast has a higher incidence in males (5%) compared to females (1% to 4%) and appears to have a worse 5-year survival in men (28).

Likewise, invasive papillary carcinoma is more common in males (2% to 4%) than in females (1%). All other subtypes of breast cancer, including inflammatory breast cancer, have been reported in men (29).

Immunohistochemical and molecular characteristics of MBC have shown a greater incidence of hormone receptor positivity and significantly less frequent overexpression of HER2/neu. In females with breast cancer, tumors are ER-positive in 77% of patients compared to 92% of ER-positive tumors in males. The incidence of HER2 overexpression is only 2% to 15% in MBC; approximately 18% to 20% of all female breast cancers overexpress HER2 (30).

More information has become available regarding molecular markers in MBC. In a series of 134 cases of MBC, tumor samples were analyzed for ER, PR, HER2, AR, the protooncogene p53, the cell cycle regulatory protein cyclin D1, and a marker of apoptosis bcl-2, among others. According to immunohistochemically-defined molecular subtypes, the vast majority of cases were classified as luminal A (75%), whereas 21% of tumors were luminal B. No HER2-driven cases were identified, as all HER2-positive cases (3%) showed ER positivity and were classified as luminal B. The remaining 4% of cases were basal-like (31). Expression of AR (81%), bcl-2 (75%), and cyclin D1 (77%) were very common, in line with previous studies. Approximately half of the tumors were positive for p21 (48%) and BRST2 (56%). The most important downstream effector of p53, p21, is a universal cyclin/cyclin-dependent kinase inhibitor which inhibits proliferation and has been associated with worse disease-free survival. Overexpression of p21 has been seen more frequently in MBC than in female breast cancer. In contrast, p53 accumulation (15%) was rare, somewhat lower than other reports in which up to 54% of samples were p53-positive. Expression of the basal markers CK5/6 (9%), CK14 (1%), and EGFR (12%) were encountered infrequently. This study also elucidated the clinical relevance of several biomarkers in MBC. PR-positive and bcl-2-positive tumors showed favorable histologic features, while HER2-positive, Ki-67-positive, and p21-positive tumors correlated with higher grade and mitotic count. p53 and BRST2 significantly predicted the presence of lymph node metastases, and PR-negativity and p53 accumulation emerged as independent predictors of decreased survival (32).

TREATMENT OF LOCALIZED AND LOCALLY ADVANCED DISEASE

Surgical Management

The treatment of localized invasive early stage breast cancer in men follows the same general principles as in women. The current operative procedure of choice in MBC is a total mastectomy with sentinel lymph node (SLN) biopsy. Traditionally, the preferred approach was a modified radical mastectomy (MRM). Although randomized studies have not been conducted in men, retrospective data suggest the equivalence of radical mastectomy and MRM in terms of local recurrence and survival, and studies in women also support the equivalence of these two procedures. The only exception is extensive chest wall muscle involvement in which radical mastectomy may be of benefit if neoadjuvant chemotherapy does not sufficiently reduce the tumor burden. Breast conserving therapy (lumpectomy followed by breast irradiation) is a possible option for men with breast cancer. However, the lack of adequate surrounding breast tissue and the central location of tumors precludes this approach in some.

The literature suggests that MRM is used in approximately 70% of male patients, followed by radical mastectomy (8% to 30%), total mastectomy (5% to 14%), and lumpectomy with or without radiation (1% to 13%). Radical mastectomy was more commonly used in older series, likely reflecting practice patterns as well as later stage at diagnosis (30). In a review of more recent data from the SEER database, of 1,541 cases of MBC, almost 20% were treated with breast conservation. Though these SEER data do not include information on local recurrence rates, in one retrospective study of seven patients treated with breast conserving therapy with a median follow-up of 67 months, there were no local recurrences (33).

Axillary nodal involvement is a strong predictor of both local recurrence and metastatic risk and is present in approximately 50% of men with breast cancer. As such, surgical assessment of the axillary nodes is an essential component of primary treatment. In early-stage breast cancer in women, SLN biopsy has emerged as a less morbid alternative to a full axillary lymph node dissection (34). In an experienced center, the SLN accurately predicts the status of the remaining regional nodes, and a negative SLN eliminates the need for a complete axillary node dissection. In an effort to understand the predictive value of SLN biopsy in men, several retrospectives studies have been carried out. The European Institute of Oncology (IEO) investigated 32 MBC patients with clinically negative axillary lymph nodes who underwent a SLN biopsy. Preoperative lymphoscintigraphy and subsequent imaging successfully identified the SLN in all patients, with a mean number of 1.5 SLN removed per patient. A total of 26 patients (81%) had negative SLN; lymph node metastases were found in 4 patients and micrometastases in the remaining 2 patients. After a median follow-up of 30 months, no axillary recurrence events occurred (35). Memorial Sloan-Kettering Cancer Center reported their experience in 78 patients with MBC. SLN biopsy was successful in 76 (97%), yielding a similar failure rate as in female breast cancer. Negative SLNs were found in 39 of 76 (51%) patients. Of these, three (8%) were found to have a positive non-SLN during intraoperative palpation. Positive SLNs were found in 37 of 76 (49%) patients. The two patients who failed SLN biopsy underwent a complete axillary node dissection. At a median follow-up of 28 months, there were no axillary recurrences (36). Recent data from the American College of Surgeons Oncology Group Z0011 study suggest that patients with clinically staged T1N0 or T2N0 breast cancer with less than 3 positive sentinel lymph nodes can forgo completion axillary node dissection, as long as adjuvant therapy and whole breast irradiation are part of the treatment plan. Although this study did not include men, there are case reports of men utilizing this technique (37).

These retrospective and single institution experiences with SLN biopsy in men are comparable to those in women. A joint expert panel of the Breast International Group and the North American Breast Cancer Group concluded that total mastectomy with SLN biopsy is the established standard of care (30). An expert panel convened by the American Society of Clinical Oncology (ASCO) concluded that the use of SLN biopsy in MBC was "acceptable."

Adjuvant Radiation Therapy

There are limited data assessing the role for, and clinical impact of, adjuvant radiation therapy in men. In several series, postoperative radiation therapy was administered to some patients but the technical aspects of radiotherapy varied between series and over time, making any assessment of clinical impact difficult. Men are more likely to

be offered postmastectomy chest wall radiation therapy (PMRT) due to concern of adequate surgical margins even in small tumors and the higher incidence of nipple or skin involvement. Prospective studies of PMRT have demonstrated a survival advantage in women with node-positive breast cancer, though their generalizability to MBC is unclear. In one series with 75 MBC cases, 29 (39%) did not undergo PMRT and 46 (61%) completed PMRT. Patients who received PMRT demonstrated no benefit in overall survival but significantly better local recurrence-free survival compared with those who did not receive radiation therapy (38). A retrospective study from Johns Hopkins suggests that similar indications for PMRT should be applied to both men and women with breast cancer (39). As with female breast cancer, PMRT is recommended for men with four or more positive lymph nodes (N2/N3) or locally advanced (T3/T4) primary tumors.

There is less agreement on radiation treatment for fewer positive nodes. Data from a combined analysis of two Danish trials and the NCIC CTG MA.20 trial demonstrated a survival benefit from PMRT in patients with fewer than four positive nodes. Therefore, radiation therapy should also be considered in men with one to three positive lymph nodes.

Adjuvant Systemic Therapy

Recommendations for adjuvant endocrine therapy, chemotherapy, or biologic therapy following surgical resection of the primary tumor in MBC are based largely on the benefits derived from these interventions in women with early-stage breast cancer. The low incidence of MBC precludes robust clinical trial development and timely completion to assess the efficacy of adjuvant therapy.

Because most MBCs are hormone receptor-positive, adjuvant tamoxifen for five years is often recommended. Prospective trials to confirm this approach are not available, however retrospective studies support a survival benefit from tamoxifen in MBC. In one report, 39 patients who received tamoxifen demonstrated improved 5-year actuarial survival and disease-free survival compared to a historical control group who underwent mastectomy alone (61% vs. 44% and 56% vs. 28%, respectively) (40).

Tamoxifen is generally well-tolerated but several studies indicate that a large proportion of men discontinue treatment before five years. A recent retrospective review from MD Anderson Cancer Center evaluating 64 MBC patients treated with adjuvant tamoxifen demonstrated a high rate of adverse events. At a median follow-up of 3.9 years, 34 (53%) patients experienced one or more toxicities, most commonly weight gain (22%) and sexual dysfunction (22%). Thirteen (20.3%) patients discontinued tamoxifen due to toxicity, including ocular complaints (1 patient), leg cramps (1 patient), neurodegenerative deficits (2 patients), bone pain (2 patients), sexual dysfunction (3 patients), and thromboembolic events (4 patients) (41). In a study of 116 men, adherence to tamoxifen decreased from 65% at year 1% to 18% at year 5. Factors associated with low adherence were lack of social support, age ≤ 60 years, and side effects. Compared to men who were adherent to tamoxifen, those with low adherence had significantly diminished overall survival (98% vs. 80%, respectively, $p = .008$) and disease-free survival (95% vs. 73%, respectively, $p = .007$). Sixty-four patients experienced side effects, including fatigue, anxiety, sleep disorders, decreased libido, and weight gain (42). Conversely, in a recent, large, population-based study of 158 cases of MBC, adjuvant tamoxifen was prescribed to 109 patients, and only 14 (11.7%) patients discontinued therapy due to toxicity, similar to a matched female control group (43).

Aromatase inhibitors are an established adjuvant treatment for postmenopausal female breast cancer and have been shown to be more effective than tamoxifen in preventing recurrence. In a retrospective study of 257 men with hormone-receptor-positive breast cancer, overall survival was significantly better with tamoxifen compared to an aromatase inhibitor at a median follow-up of 42.4 months. After adjusting for patient and tumor characteristics, aromatase inhibitor treatment was linked to a 1.5-fold increase in risk of mortality compared to tamoxifen (HR 1.55; 95% CI 1.13–2.13, $p = .007$). These findings may be related to insufficient suppression of estrogen levels in men by aromatase inhibitors, as 20% of estrogen is produced by the testes. Moreover, aromatase inhibitors lead to an increase in FSH and testosterone level, which may in turn increase the rate of aromatization (44). As such, tamoxifen remains the preferred agent in MBC when hormone therapy is indicated.

Studies concerning adjuvant chemotherapy are similarly limited in MBC. One report of 11 patients with stage 2 or 3 MBC treated with adjuvant cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) showed favorable outcomes compared with historical controls. At the National Cancer Institute (NCI), 31 patients with axillary node-positive, stage 2 MBC were treated with adjuvant CMF chemotherapy for up to 12 cycles. At a follow-up of 20 years, the overall survival was shown to be 65% at 10 years, 52% at 15 years, and 42% at 20 years (45).

There are no data on the benefit of anthracyclines or taxanes in men with breast cancer.

The Oncotype DX breast cancer 21-gene assay using standardized quantitative RT-PCR was validated in women with early stage, node-negative hormone receptor positive breast cancer to estimate the likelihood of chemotherapy benefit. In a genomic study of 347 male and 82,434 female breast cancer patients with estrogen receptor positive tumors, the patterns of expression of the Oncotype DX genes were more similar than different between males and females. The proportion of tumors with low risk of recurrence based on the Recurrence Score was 53.6% in males versus 53.4% in females, intermediate risk of recurrence was 35.2% in males versus 36.3% in females, and high risk of recurrence was 11.2% in males versus 10.3% in females. Of note, mean expression of ER, PR, and proliferation genes (Ki-67, MYBL2, Survivin, Cyclin B1, and STK15) were higher in males. In conclusion, current recommendations for adjuvant chemotherapy options in women with early-stage breast cancer should be considered for men.

Trastuzumab, a humanized monoclonal antibody directed against the HER2 protein, was associated with a significant survival benefit in women with HER2-positive breast cancer, when combined with chemotherapy. The incidence of HER2 overexpression/amplification in MBC appears to be low, and there are no prospective data evaluating survival outcomes with adjuvant trastuzumab in MBC. In a study with 147 stage 1 to 3 MBC cases, 9 patients were known to overexpress HER2, and only 5 of these patients received trastuzumab with chemotherapy (43). Nonetheless, its use should be considered in men with HER2-positive breast cancer.

TREATMENT OF METASTATIC DISEASE

Hormonal manipulation has played a central role in the initial management of metastatic MBC due to the high incidence of hormone receptor positivity. Multiple reports of orchiectomy as treatment of metastatic MBC indicate response rates between 32% and 67%, with a median survival of 56 months in responding patients versus 38 months

in nonresponding patients. Other ablative surgical procedures have been evaluated in metastatic MBC, either as primary treatment or at the time of disease progression after orchiectomy. Adrenalectomy and hypophysectomy are associated with response rates of 76% and 58%, respectively. These surgical procedures are rarely used today due to the associated morbidity and the introduction of medical management of metastatic disease.

Tamoxifen is the endocrine treatment of choice in metastatic disease. Objective response rates as high as 81% have been reported in ER-positive MBC with tamoxifen treatment (46). Other agents, including aminoglutethimide, megestrol acetate, androgens, antiandrogens, steroids, and luteinizing hormone-releasing hormone (LHRH) analogs are associated with 50% to 70% response rates in ER-positive MBC.

Aromatase inhibitors are very active in women with hormone receptor-positive metastatic breast cancer, but their roles for men are less clear. One study of 15 patients treated with an aromatase inhibitor reported a complete response in 2 patients, partial response in 4 patients, and stable disease in 2 patients (response rate of 40%); activity correlated with significant reductions in estradiol levels (47). Current data suggest that aromatase inhibitors may be considered following progression on tamoxifen. The German Breast Group will conduct a prospective, randomized multicenter phase II study (GBG-54 MALE) evaluating tamoxifen with and without an LHRH analog versus an aromatase inhibitor with an LHRH analog in MBC. The role of fulvestrant, a selective estrogen receptor downregulator, is less clear. One case series described 14 men treated with fulvestrant in the second to fourth-line setting. In all cases, fulvestrant was well tolerated. Partial response was noted in 3 (21%) patients, stable disease in 7 (50%) patients, with a median overall survival of 62 months (48).

Treatment with chemotherapy should be considered for patients with ER-negative tumors, for those with rapidly progressing disease, and for patients refractory to hormone therapy, similar to principles for initiating chemotherapy in women. HER2-directed therapies including trastuzumab, pertuzumab and lapatinib, have not been formally studied in metastatic MBC. Using these agents in HER2-positive metastatic MBC is reasonable considering the significant survival benefit seen in women with metastatic breast cancer.

PROGNOSTIC FACTORS

Male and female breast cancers are staged according to the American Joint Committee on Cancer (AJCC) Staging System. Similar to women with breast cancer, stage, tumor size, and axillary lymph node status are important factors influencing outcome. This was illustrated in a report derived from the SEER database of 1,541 men with breast cancer. The breast cancer-specific mortality increased by stage: 1% *in situ,* 5% stage 1, 15% stage 2, 38% stage 3, and 57% stage 4 (49).

Molecular subtyping of breast cancer has emerged as a significant predictor of outcome in women. Because MBC is rare, large series elucidating the significance of molecular subtyping is lacking. Some studies have found the distribution of tumor subtypes in MBC to be different compared with female breast cancer, which may point to important differences in biology and outcomes (31). Furthermore, in one study of 197 patients, HER2 positivity was not associated with poorer outcome, even though the majority of patients had not received adjuvant chemotherapy or trastuzumab. Larger studies are required to validate these findings.

The risk of a contralateral breast cancer and second primary non-breast cancers appears to be increased in men with breast cancer. In a review of 4,873 MBCs from the SEER database, 93 (2%) were identified with a second MBC and 1,001 (21%) with a second primary cancer. This underlines the importance of continued long-term surveillance for a second breast cancer and appropriate screening for non-breast cancers in men.

Some reports have suggested that MBC has a worse prognosis than female breast cancer. From the SEER database, 6,157 cases of MBC were compared to 877,885 cases of female breast cancer from 1973 to 2008. Survival was significantly higher in female breast cancer compared to MBC but improved over time in MBC (1 year, 96% vs. 91%; 3 years, 85% vs. 80%; 5 years, 77% vs. 68%, respectively) (3). Conversely, in a case-control study of 144 patients (72 female, 72 male) with early-stage breast cancer, male patients received systemic therapy comparable to that received by their female counterparts. Disease-free and overall survival were similar, suggesting that male sex is not a poor prognostic factor for treatment outcomes (50).

Race/ethnicity may also influence breast cancer prognosis and treatment. It is known that black women have poorer survival when compared to white women. From the SEER data, one report illustrated that black and Asian men had lower 1 to 5 year survival compared to white men, despite similar treatment modalities. Notably, black and Asian men had a higher incidence of poorly differentiated histology compared to white men (19%, 20%, and 13%, respectively) (3). In an analysis of 510 MBC cases (456 white, 34 black), black men were approximately 50% less likely to undergo consultation with an oncologist and subsequently receive chemotherapy, however results did not reach statistical significance. After multivariate analysis, breast cancer-specific mortality hazard ratio was shown to be more than tripled for black versus white men (7).

MANAGEMENT SUMMARY

- A suspicious breast mass in a man must be evaluated by tissue sampling. Needle biopsy is the preferred method of diagnosis.
- Total mastectomy with SLN biopsy is the established surgical approach for most male cancers.
- Chest wall and regional lymph node irradiation should be given using the same criteria developed for use in women.
- Adjuvant systemic therapy recommendations are similar to those for women with the same stage of disease. For hormone receptor-positive tumors, adjuvant tamoxifen with or without chemotherapy should be recommended. Current recommendations for adjuvant chemotherapy options for women with early-stage breast cancer should be considered for men. Trastuzumab is indicated for HER2-positive MBC.
- In patients with metastatic disease, tamoxifen should be utilized as first-line treatment in hormone receptor-positive metastatic disease. The role for aromatase inhibitors and fulvestrant remains unclear. Chemotherapy should be recommended for rapidly progressing disease, hormone receptor-negative, or hormone-refractory disease. HER2-directed therapy should be used in HER2-positive advanced breast cancer.

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CHAPTER 62

Phyllodes Tumors

Kristine E. Calhoun, Kimberly H. Allison, Janice N. Kim, Habib Rahbar, and Benjamin O. Anderson

CHAPTER CONTENTS

PHYLLODES NOMENCLATURE

Phyllodes tumors are fibroepithelial breast tumors capable of a diverse range of biological behavior. Also termed "phylloides tumors" or "cystosarcoma phyllodes," these lesions are similar to benign fibroadenomas in their least aggressive form, but with an increased propensity for local recurrence following excision. Although the original term, "cystosarcoma phylloides," coined by Johannes Müller in 1838 was used to describe the tumor's grossly fleshy physical appearance, it was not intended to indicate metastatic potential as is typically implied by the term "sarcoma" (1). Phyllodes tumors in their most aggressive form, however, can recur locally and distantly, typically degenerating into a sarcomatous lesion lacking an epithelial component (2). Fortunately, this malignant form of phyllodes is uncommon, with fewer than 5% of lesions ever developing distant metastases (3). Various histologic classification schemes have been used to subtype phyllodes based on histologic features that have been associated with clinical behavior. The World Health Organization (WHO) recommends classification of phyllodes into three subtypes as follows: benign phyllodes, borderline phyllodes (also known as "low grade malignant") and malignant phyllodes (also known as "high grade malignant") (4).

PATHOLOGIC CHARACTERISTICS

Macroscopic Appearance

Nonmalignant phyllodes tumors typically have a gross appearance similar to fibroadenomas, presenting as a circumscribed, round or oval mass that lacks a true histologic capsule but which generally can be easily shelled out from surrounding tissues. Malignant forms have less circumscription and often gross infiltration of surrounding breast tissue. In contrast to the classic stellate, depressed gross appearance of an invasive carcinoma of the breast, phyllodes tumors typically bulge from the surrounding tissue when cut and have a multi-nodular, fleshy appearance. Most phyllodes tumors are detected in the 1 to 2 cm range but there are reports in the literature of lesions ranging from less than 1 cm up to 40 cm (5).

Microscopic Appearance

Histologically, phyllodes tumors have a broad range of appearances, from those that resemble fibroadenomas to others that appear as outright sarcomatous lesions. Like fibroadenoma, phyllodes tumors are fibroepithelial lesions composed of both stromal and epithelial components, with both layers capable of manifesting a range of histopathologic

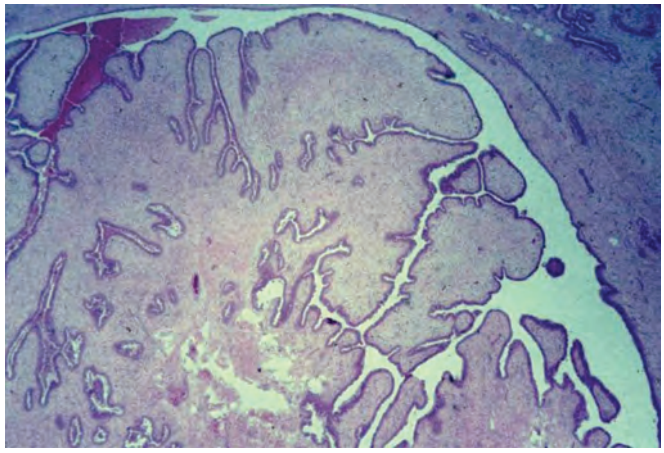


FIGURE 62-1 Phyllodes tumor illustrating characteristic "leaf-like" architecture. This histopathology image is from the borderline phyllodes tumor surgical case shown in Figure 62-5.

changes. The characteristic "leaf-like" architecture of phyllodes tumors is the result of a stromal proliferation with formation of elongated cleft-like spaces lined by epithelium that extend into cystic spaces (Fig. 62-1). This leaf-like, or intracanalicular, growth pattern may not be present in all tumors, particularly those toward the malignant end of the spectrum, where the epithelial component is typically minimal or absent (Fig. 62-2). The epithelium is generally single layered, but hyperplasia, atypical hyperplasia, *in situ* carcinoma, and/or epithelial metaplasia may be seen as well (6–7). It is the stromal characteristics rather than the epithelial features, however, which determine WHO subclassification and clinical behavior of phyllodes tumors.

Histologic Classification

Numerous studies have attempted to determine which histologic features of phyllodes tumors are useful in predicting clinical behavior (8–12). The WHO classification of phyllodes tumors is based on characterization of multiple features of the stromal component of the lesion including degree of stromal cellular atypia, mitotic activity per 10 high-power fields (hpfs), presence or absence of stromal overgrowth, defined as a single 40X field of pure stroma devoid of epithelium, and infiltrative versus circumscribed tumor margins (Table 62-1). Benign phyllodes tumors (low-grade lesions) are characterized by increased stromal cellularity with no more than mild to moderate cellular atypia, circumscribed tumor margins, low mitotic rates (generally less than 4/10 hpf), and a lack of stromal overgrowth. Borderline phyllodes tumors are characterized by a greater degree of stromal cellularity and atypia, microscopically circumscribed or infiltrative borders, and mitotic rates in the 4–9/10 hpf range, but a lack of stromal overgrowth (Fig. 62-3). Malignant phyllodes tumors (high-grade lesions) are characterized by marked stromal cellularity and atypia, infiltrative borders, high mitotic rates (generally greater than 10/10 hpf), and areas of stromal overgrowth (Fig. 62-2). Over 50% of lesions are classified as benign in most large series. Alternatively, some authors continue to refer to tumors as low-, intermediate-, or high-grade lesions as advocated by Azzopardi and Salvadori (13,14). Unfortunately, some tumors do not fit neatly into one of these three categories and tumors can have a range of behaviors within each category.

Immunohistochemistry

There has been interest in identifying immunohistochemical markers that can predict outcome. However, most of the markers identified to date are associated with grade of phyllodes lesions and have not proven to have clinical utility in predicting outcome. Increased MIB1 (Ki-67), p53, c-kit (CD117), and EGFR expression have all been associated with higher grade lesions (15–22). To date, no marker has been found to conclusively and reproducibly classify lesions or predict recurrence and metastasis.

Molecular Characteristics of Phyllodes Tumors

Due to their similarity to fibroadenomas, and the heterogeneity that can exist in any given phyllodes tumor, many theorize that phyllodes tumors arise from preexisting fibroadenomas. Studies have suggested phyllodes tumors can progress from fibroadenomas based on clonal analysis of the stroma and loss of heterozygosity analyses (23,24). Whether all phyllodes tumors originate as fibroadenomas or conversely start *de novo* is still a matter of debate.

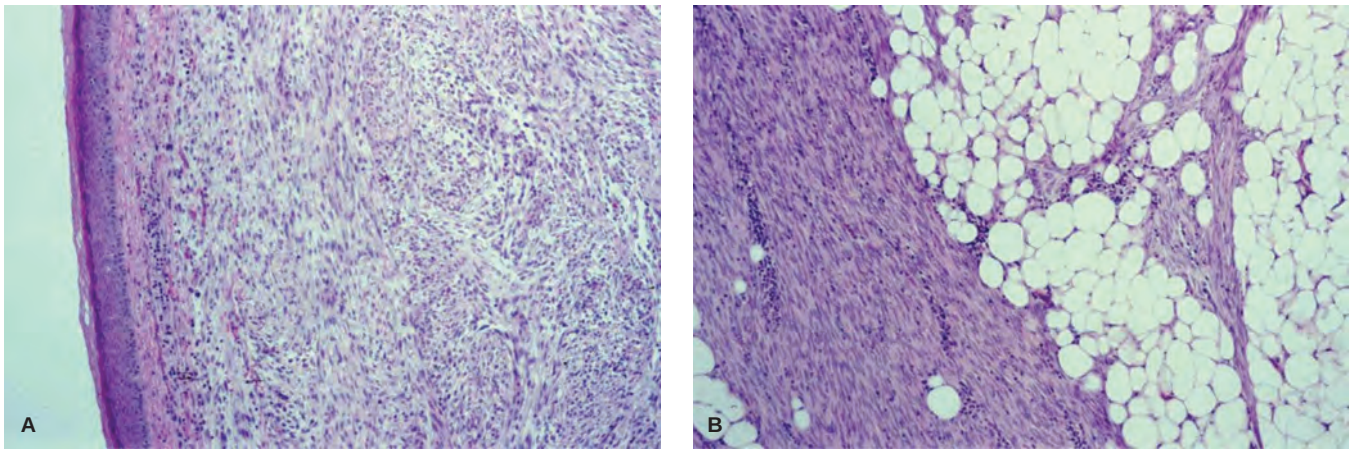


FIGURE 62-2 Recurrent malignant phyllodes tumor showing **(A)** dermal infiltration and **(B)** stromal overgrowth with infiltration of surrounding fatty breast tissue. Note the loss of epithelial elements from this recurrent tumor. These histopathology images are from the surgical case illustrated in Figure 62-8.

TABLE 62-1

Histologic Features Used in the WHO Classification of Phyllodes Tumor Subtypes

Histologic Features	*Benign*	*Borderline*	*Malignant*
Stromal cellular atypia	Mild	Marked	Marked
Mitotic activity	<4 10 hpf	4–9 10 hpf	≥10 10 hpf
Stromal overgrowth	Absent	Absent	Present
Tumor margins	Circumscribed	Circumscribed or infiltrative	Infiltrative

More recent gene expression profiling data looking at the spectrum of phyllodes tumors supports the categorization of phyllodes tumors into benign, borderline, and malignant categories (25). Genes important in differentiating these categories are related to matrix production, cell adhesion, epidermis formation, and cell proliferation. Chromosomal changes associated with malignant phenotypes of phyllodes tumors have also been identified, with 1q gains being more common in the borderline and malignant categories and in general increasing numbers of chromosomal alterations with increasing malignancy. However, because these changes are often unique, characteristic genetic changes that could be useful in classification and prognosis have not yet been reproducibly identified.

Differential Diagnosis

The differential diagnosis for benign phyllodes tumors includes cellular fibroadenoma and juvenile fibroadenoma. Distinction of benign phyllodes tumors from fibroadenoma variants can be challenging. Cellular fibroadenomas have increased stromal cellularity, generally lack the prominent intracanalicular (leaf-like) growth pattern of phyllodes tumors and have a negligible mitotic rate (although some authors allow for rare mitotic figures up to 3/10 hpfs). Juvenile fibroadenomas are similar but are characterized by pronounced epithelial hyperplasia. Phyllodes tumors can also be quite heterogeneous, with areas indistinguishable from classic fibroadenoma and other areas of more clearly atypical stromal elements.

On the malignant end of the spectrum, the main differential diagnosis includes metaplastic carcinoma. This differential can be especially challenging when a malignant spindle cell lesion is present without identifiable epithelial elements. Usually, identification of a typical infiltrating ductal carcinoma or residual phyllodes tumor architecture can help distinguish between metaplastic carcinoma and phyllodes tumor. For cases in which only malignant stroma is present, a panel of immunostains including cytokeratins can also assist in this differential diagnosis.

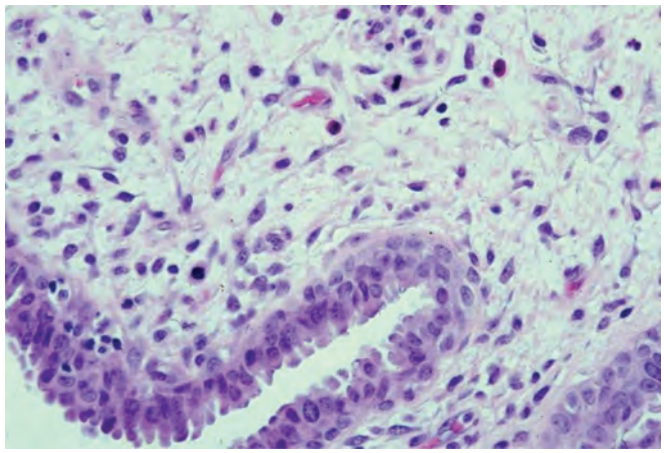


FIGURE 62-3 Borderline phyllodes tumor demonstrating intermediate level of mitotic activity and lacking stromal overgrowth. This histopathology image is from the surgical case illustrated in Figure 62-5.

CLINICAL CHARACTERISTICS

Incidence

Phyllodes tumors are uncommon breast masses, accounting for 0.3% to 1% of breast tumors in females. In one review of 8,567 breast cancer cases treated between 1969 and 1993, only 32 cases of phyllodes tumors (0.37%) were identified among 31 patients (26). More recent series have reported numbers ranging from 33 to 821 patients (27–29). A population-based study from California noted a higher risk in Latino than in white or Asian women (30), while another study found a propensity for higher grade tumors among Hispanic patients (31). Phyllodes tumors have been reported in males but are extremely rare, occurring in conjunction with gynecomastia and lobular development in male breast tissue (32).

Most patients with phyllodes tumors tend to be in their 40s, a decade or so older than women diagnosed with palpable fibroadenomas. While those with benign phyllodes lesions are typically up to a decade younger than those with malignant tumors, these tumors have been reported in prepubertal females as well as elderly patients (Fig. 62-4).

Clinical Presentation

Typically, phyllodes tumors present as painless, palpable masses in the breast that demonstrate continuous growth, although some individuals may report rapid growth in a previously stable, long-standing nodule (3). Often, the history will be that of a breast mass with rapid clinical progression, growing to a relatively large size in a matter of a few months.

The mass may produce visible bulging when tumors expand quickly (Fig. 62-5A). Although tumors may grow quickly, rapid growth does not necessarily indicate malignancy. Shiny, stretched, and attenuated skin with varicose veins can overlie a phyllodes tumor as it pushes against the skin. In neglected cases, skin ulceration may develop from ischemia secondary to stretching and pressure. Such skin changes can occur with all types of lesions, so while ulceration associated with carcinoma is an indication of malignant behavior (T4 lesion), it is not necessarily an indication of a malignant phyllodes tumors. The nipple may be effaced, but invasion and/or retraction is unusual (3), as is bloody nipple discharge.

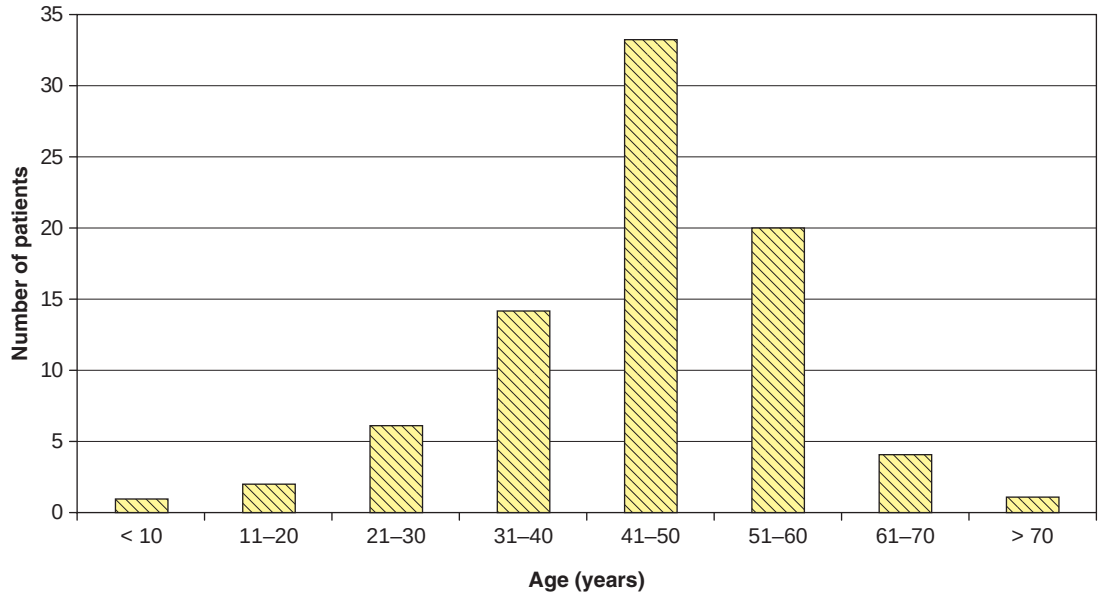


FIGURE 62-4 Age distribution of women diagnosed with phyllodes tumors. (Modified from Salvadori B, Cusumano F, Del Bo R, et al. Surgical treatment of phyllodes tumors of the breast. *Cancer* 1989;63(12):2532–2536.)

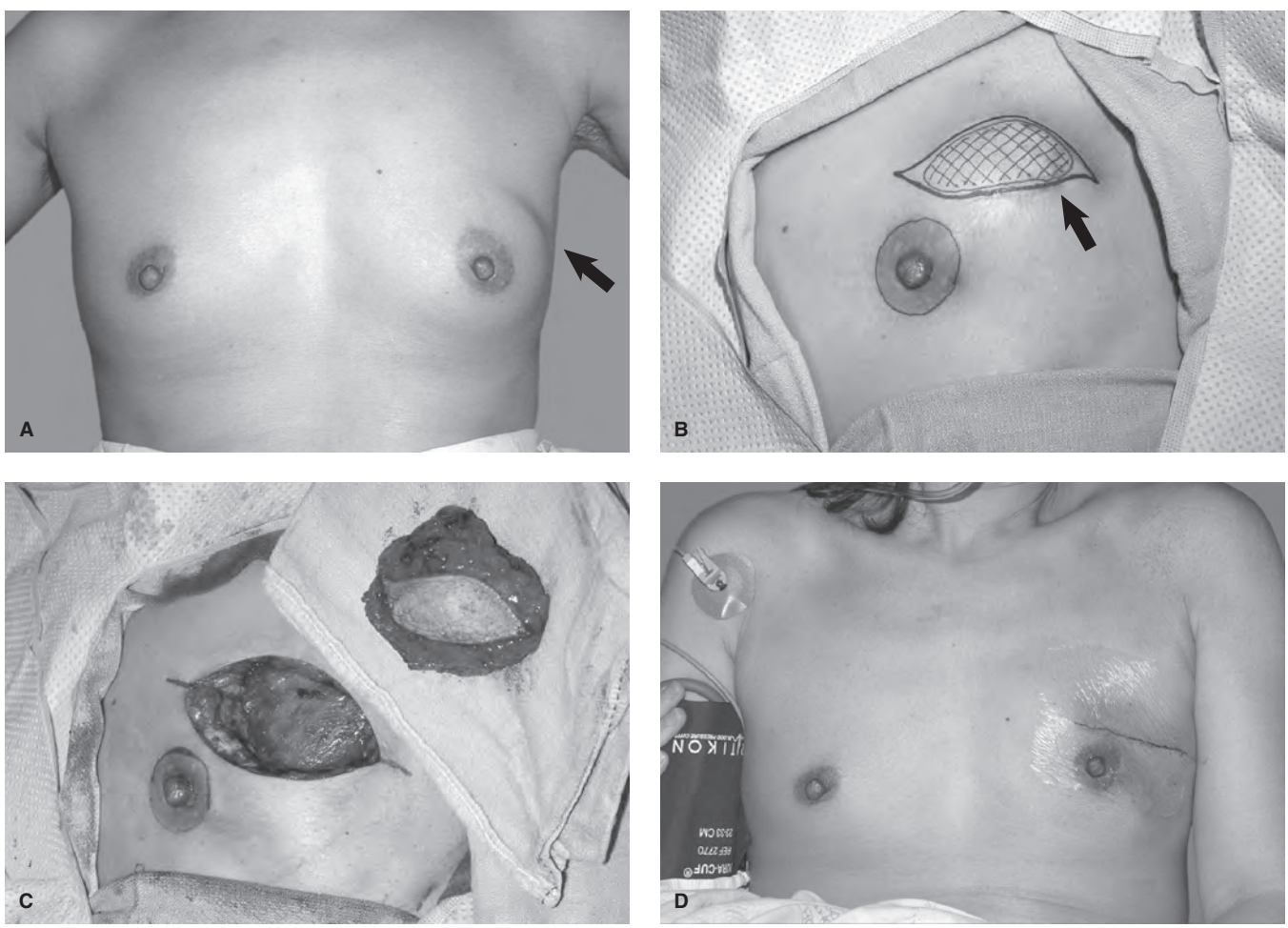


FIGURE 62-5 Presentation and excision of a primary phyllodes tumor. A 44-year-old female presented with a palpable mass in the left upper outer quadrant, which had grown from 2.4 to 5.2 cm over 6 months. Imaging and core needle sampling at first presentation were interpreted as "fibroadenoma." The final pathology on excision was a borderline phyllodes tumor. **(A)** Preoperative presentation with bulging mass apparent on inspection. The mass is located in the upper outer quadrant (*arrow*). **(B)** Operative preparation showing the borders of palpable tumor (*hatch marks*) and planned skin excision (*outer line*), which is located immediately superficial to the mass. **(C)** Operative excision down to level of pectoral fascia. **(D)** Postoperative closure with flap advancement mastopexy closure.

Risk Factors

No clear risk factors for the development of phyllodes tumors have been identified in the general risk population. Patients with germline p53 mutations (Li-Fraumeni syndrome) are at increased risk for developing these lesions, but this represents only a small portion of diagnosed tumors (33).

Associated Tumors and Bilaterality

Bilateral phyllodes tumors (synchronous or metachronous) have been reported but are uncommon. An Memorial Sloan Kettering Cancer Center (MSKCC) series of 293 patients found only 10 individuals (3.4%) with bilateral lesions (34). Typically, concurrent tumors have similar histology, but in one documented case, a patient presented with a benign phyllodes tumor in one breast and a synchronous malignant phyllodes tumor in the other (35).

Patients can present with phyllodes tumors as well as separate noninvasive (36) or invasive breast carcinoma lesions (37). Occasionally, foci of intraductal and/or invasive carcinoma may also be found in association with a malignant phyllodes tumor (38). Because phyllodes tumors are so uncommon, it is unclear if there is any physiologic connection between these and other breast tumors when they occur in the same patient, such as a familial genetic abnormality predisposing to both lesions. Finally, pregnancy associated phyllodes tumors are rare, with fewer than 10 reported in the literature (39).

DIAGNOSIS

Clinical Features

Preoperative clinical suspicion of a phyllodes tumor is helpful but, because the lesions resemble fibroadenomas both on imaging and tissue sampling, this can be challenging. Short of being suspicious due to the large size of the mass or rapid growth of a pre-existing lesion, the majority of phyllodes tumors will be diagnosed postoperatively. In an individual series of 21 cases, only 6 (29%) were successfully identified before surgery on the basis of clinical features and/or preoperative diagnostic investigations (40). Most phyllodes tumors, therefore, are surgically "shelled out" (enucleated) at initial intervention, resulting in the inadequate surgical margins associated with an increased risk of local recurrence in the absence of additional surgery.

Imaging Features

On imaging, phyllodes tumors commonly resemble large fibroadenomas (Fig. 62-6A), and there are no distinct imaging characteristics that can reliably distinguish benign from malignant phyllodes tumors (41). Like fibroadenomas, phyllodes tend to present mammographically as round, oval, or lobular-shaped masses with circumscribed margins (Fig. 62-6B), and occasionally contain calcifications (41,42). Sonographically, phyllodes tumors present as oval or round-shaped, hypoechoic, well-circumscribed, solid masses (Fig. 62-6C) that may contain scattered cystic regions (41–43). Although large size (>3 cm) and presence of intramural cystic regions or clefts make the diagnosis of phyllodes tumor more likely, these features can also be present in fibroadenomas. Thus, any circumscribed mass presenting on imaging with large initial size or significant interval growth warrants excision to rule out phyllodes tumor.

On magnetic resonance imaging (MRI), phyllodes tumors typically present as oval, round, or lobular shaped masses with smooth margins and intrinsic high signal intensity on T2- weighted images (Fig. 62-7). On dynamic contrast-enhanced images, both phyllodes and fibroadenomas most commonly exhibit slow initial phase enhancement with persistent and progressive delayed phase enhancement, a pattern typical of a benign process (Fig. 62-7B,C) (44). Although MRI may more accurately delineate the true extent of disease prior to surgery, there is little data to support the routine use of MRI for imaging phyllodes tumors. MRI may be most helpful when mastectomy is being considered and the full extent of the tumor is difficult to determine from standard imaging. Because a pathologic hallmark distinguishing phyllodes from fibroadenomas is greater cellularity, an emerging MRI technique sensitive to cell density, called diffusion-weighted imaging, could prove useful in the future for predicting phyllodes tumor risk on imaging (45).

Fine Needle Aspiration (FNA) and Core Needle Biopsy

Image-guided needle sampling of phyllodes tumors often yields histologic features that can be ambiguous. In the case of FNA, cytologic features suggestive of phyllodes, such as hypercellular stromal fragments and multinucleated giant cells, are not specific enough to be used as the sole diagnostic criteria in making this distinction (46,47). In addition, because cytology of tumors with cystic degeneration shows foamy macrophages, apocrine cells, and thick fluid in the background, aspirates from some phyllodes tumors may erroneously be labeled "fibrocystic change" resulting in diagnostic error on FNA (48). Ultimately, the final pathologic assessment frequently hinges on examination of the complete surgical excision specimen. Perhaps the greatest role of image-guided biopsy in cases of suspected phyllodes is to provide the surgeon a preoperative pathologic index of suspicion that will guide surgical technique. Lesions that definitively can be diagnosed as phyllodes tumors on image-guided sampling can be excised with wide margins, whereas more equivocal lesions on pathology may be enucleated for definitive diagnosis (if clinical suspicion is also low) as is typically performed for fibroadenomas.

TREATMENT

Surgical Excision and Margins

The core principle of local therapy for all classifications of phyllodes tumors is local excision to negative margins to achieve definitive local control. Most studies advocate at least a 1-cm margin, which has traditionally been accepted as an adequate resection. Mangi and colleagues found that recurrence correlated with excision margin, showing that among 40 patients, local recurrence occurred in 5, each of whom had margins less than 1 cm following definitive resection. These 5 patients remained free of disease after reexcision to a 1-cm margin (49). The desired 1-cm margin width is based on retrospective analysis. Because these lesions are rare, any trial to study optimal margin width is impractical. A pseudocapsule of dense, compressed, normal tissue containing microscopic projections of the lesion commonly surrounds phyllodes tumors. As a result, more tissue typically needs to be removed in order to achieve the desired histologic margin than might be predicted on the basis of preoperative physical examination or imaging findings (50). Some authors actually argue that 2-cm should be considered the standard of care for desired surgical margin for excision of phyllodes tumors, with a goal of a 2–3-cm margin if a phyllodes tumor locally recurs (Table 62-2) (3). An investigation from Germany identified 8 of 33 patients with local recurrence, with 7 of the 8 having less than a 2-cm margin at initial resection (28). In practice, margins of 2 to 3 cm can be difficult

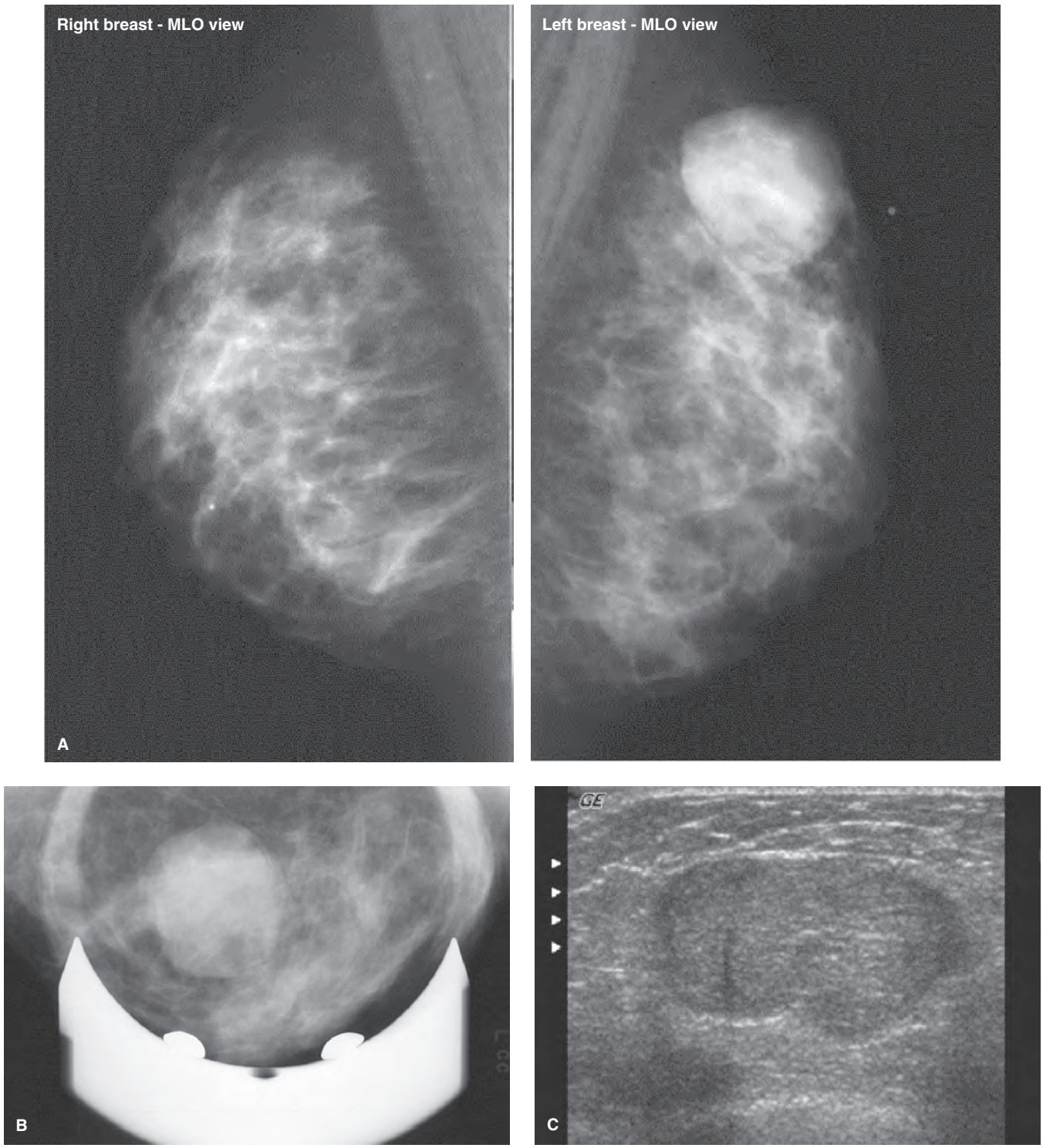
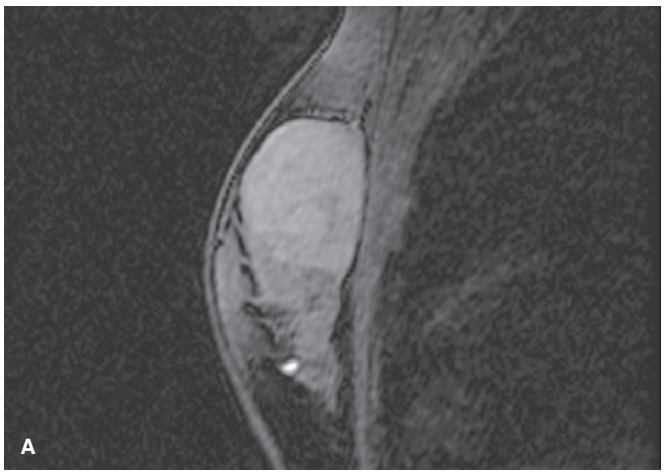
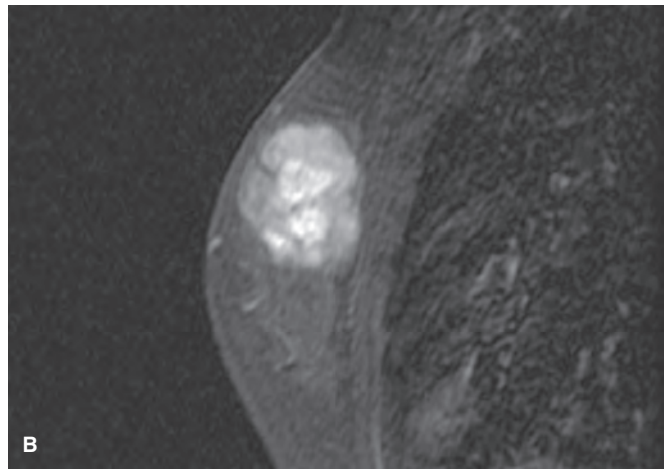


FIGURE 62-6 Standard imaging studies of a phyllodes tumor. **(A)** Bilateral mammogram, MLO view, demonstrating circumscribed round mass at 12 o'clock in left breast, biopsy proven phyllodes tumor. **(B)** Spot compression mammographic view of phyllodes tumor from (A). **(C)** Ultrasound image of a 2.4-cm phyllodes tumor, showing typical sonographic features including oval shaped solid mass with circumscribed margins.

to achieve with good cosmesis, except when the breast is quite large and the tumor favorably located.

Although not the current standard of care, at least one series has reported the use of ultrasound-guided, vacuum assisted breast biopsy for management of benign phyllodes tumors. Benign tumors that were excised completely in this manner were followed, and only 1 out of 31 tumors had recurred after a mean of 6 years (51).





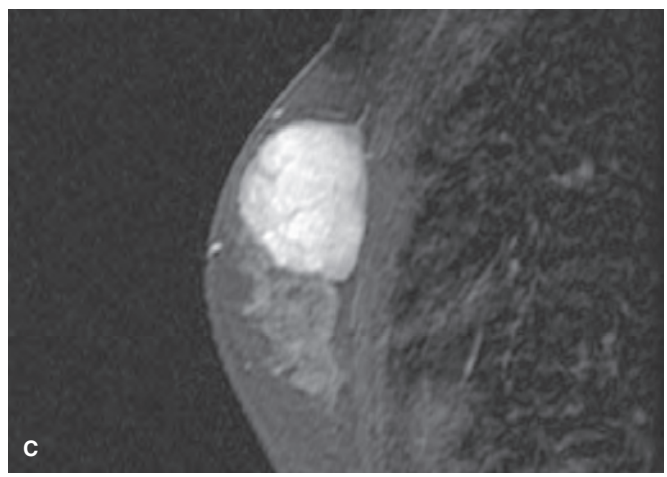


FIGURE 62-7 Sagittally-oriented MRI images of a phyllodes tumor. **(A)** Pre-contrast, **(B)** 2 minutes post-contrast, **(C)** 5 minutes post-contrast. Note the persistent and progressive enhancement of the phyllodes tumor on the delayed post-contrast images. These MRI images are from the surgical case illustrated in Figure 62-5.

Reexcision Following Narrow Margin Excision

Approximately 20% of phyllodes tumors recur locally if excised with inadequate margins. The proportion of recurrences appears to be somewhat higher with borderline or malignant varieties and lower with benign phyllodes tumors (52), with most authors demonstrating a benefit to negative margin resection for all histologic types secondary to all lesions having a propensity to recur with anything short of wide local excision (Table 62-2).

Technical Considerations in Lumpectomy

In order to achieve 1 cm or greater surgical margins with lumpectomy, special approaches may be necessary, particularly when a phyllodes tumor develops in a smaller breast. Tunneling through the fibroglandular tissue from a periareolar incision is contraindicated with phyllodes tumor excisions because of the potential for tumor seeding. Even a curvilinear incision directly over the mass without removal of skin may be too small to obtain adequate surgical margins,

TABLE 62-2

Factors Associated with Risk of Local Recurrence

Study	*Stromal Atypia*	*Positive Margins (Definition of Positive Margin)*	*Necrosis*	*Fibroproliferation*	*Other*
Asoglu, 2004 (67)	No	Yes (<1 cm)	No	—	Size
Chen, 2005 (68)	No	Yes (<1 cm)	No	—	Age >40 Mitosis
Fou, 2006 (69)	Yes	No (None given)	No	—	N/A
Barrio, 2007 (34)	No	Yes (<1 mm)	Yes	Yes	N/A
Lenhard, 2007 (27)	No	Yes (<2 cm)	No	—	N/A
Telli, 2007 (74)	Yes	Yes (<1 cm)	No	—	N/A
Belkacemi, 2008 (28)	Yes	Yes (<1 cm)	Yes	—	N/A

or may leave excessive redundant skin behind when a large section of fibroglandular tissue is removed (Fig. 62-5A). Full thickness excisions from skin to chest wall muscle can be very helpful in achieving the 1 cm desired surgical margins. This approach allows *en bloc* removal of skin, tumor, and surrounding fibroglandular tissue in an oncoplastic fashion (Fig. 62-5B). The excision is then carried out full thickness from the skin island, widely around the mass, and down to and including the pectoral muscle fascia (Fig. 62-5C).

Breast Conservation versus Mastectomy

In the M. D. Anderson experience of 101 patients with phyllodes tumors (2), surgery included local excision with breast conservation (47%) or mastectomy (53%). Local recurrence occurred in 4 patients, with an actuarial 10-year rate of 8%. The investigators concluded that local failure was uncommon, showing that breast-conserving surgery with negative margins is the preferred primary therapy. Kleer and colleagues found that malignant phyllodes tumors have a favorable prognosis if widely excised without mastectomy (18). Multiple additional series have also failed to show a benefit to mastectomy over lumpectomy in patients who are otherwise good breast conserving therapy candidates, regardless of tumor histology, provided negative surgical margins can be achieved with lumpectomy (34).

Axillary Staging

Routine axillary dissection is unnecessary in patients with phyllodes tumors (26,53). While axillary nodes are palpable in 20% of cases, fewer than 5% will actually have histological nodal involvement (49), with one SEER study demonstrating a 3.4% incidence of node positivity among 1,035 phyllodes tumors over a 16 year period (54). In another series of 45 patients with phyllodes tumors who underwent axillary staging, none were found to have axillary metastases (55). If suspicious lymph nodes are identified clinically or on imaging studies, directed axillary ultrasound with fine needle aspiration (56) or, preferably, core needle sampling can be performed. If this work-up is negative, sentinel lymph node biopsy can be considered if there is still reason to believe that the axillary nodes are involved. In the absence of such suspicion, neither sentinel node biopsy nor axillary node dissection are considered standard care in the surgical management of the clinically node-negative patient with phyllodes tumors.

Adjuvant Radiation Therapy

Overall, the role of radiation therapy for phyllodes tumors remains unclear, with the majority of data derived from single-institution retrospective studies (57). For benign phyllodes tumors managed conservatively with surgery alone, adjuvant radiotherapy appears unnecessary when adequate margins are achieved. Similarly, most authors show that treatment of borderline and malignant phyllodes tumors with mastectomy alone yields excellent local control rates (2,58). Unfortunately, with lumpectomy alone, local control rates appear worse for borderline and malignant phyllodes patients (58). One study endorsed the use of adjuvant radiotherapy after breast conserving surgery for borderline or malignant phyllodes tumors larger than 3 cm, with local recurrence rates of 45% with conservative surgery alone (28), while another demonstrated the benefits of post lumpectomy radiotherapy in the treatment of malignant phyllodes tumors with a local failure rate as low as 12% (59). A prospective, multi-institutional study of borderline and malignant phyllodes tumors evaluated 46 patients who underwent breast conserving surgery with negative surgical margins, revealing that adjuvant radiotherapy improved local control with no recurrences reported at 56 months of median follow-up (60).

Adjuvant radiation therapy may be considered appropriate treatment for selected locally recurrent phyllodes tumors, such as following mastectomy (Fig. 62-8). Unfortunately, recurrent phyllodes tumors arise so infrequently and the biologic profiles of recurrent phyllodes tumors are so heterogeneous that no large series of locally recurrent phyllodes tumors is ever likely to be collected.

If adjuvant radiotherapy is utilized, it would be reasonable to use the guidelines for soft tissue sarcomas, which entail treating the entire breast tissue or chest wall in the radiation fields to deliver 50 to 50.4 Gy in standard daily fractions. After completion of the primary fields, treatment would proceed with a generous tumor bed or mastectomy scar boost with an additional 10 to 20 Gy.

Combined Therapy

Some reports have supported the use of combined chemoradiation following phyllodes tumor recurrence. In one case study of a locally recurrent malignant phyllodes tumor, neoadjuvant hyperfractionated radiotherapy, superficial hyperthermia, and ifosfamide were administered after the second local recurrence of this tumor. Resection of the tumor bed revealed a pathologically complete response with an actual disease free follow-up of 48 months (61).

Adjuvant Endocrine Therapy

Phyllodes tumors variably express steroid receptors, but there is no known value to adjuvant endocrine therapy with tamoxifen or aromatase inhibitors (62). There would be little rationale for using these drugs because steroid receptor protein expression decreases with increasing malignancy, they are primarily expressed by the epithelial component of phyllodes tumors, and only the stromal component of phyllodes tumors metastasizes. Overall, the systemic treatment principles of phyllodes tumors are driven by similar principles to those governing the management of soft tissue sarcoma.

Systemic Therapy

Chaney and colleagues observed that some patients, especially those with stromal overgrowth, particularly when the tumor size was more than 5 cm, had higher rates of distant failure. These authors suggested that such patients merit consideration of a trial that examines the efficacy of systemic therapy, even in the absence of metastatic involvement (2). Burton and colleagues found that two of three patients with metastases achieved effective palliation when treated with cisplatin and etoposide combination chemotherapy (62). The current National Comprehensive Cancer Network (NCCN) guidelines suggest that patients with metastases be managed according to the Soft Tissue Sarcoma Clinical Practice Guidelines in Oncology (63).

RECURRENCE AND PROGNOSIS

Local Recurrence Following Resection

Recurrence of phyllodes tumors is possible for all lesions (27,34), with recurrence rates as high as 46%. A 13-year institutional review found 27 women diagnosed with 19 (73%) benign, 3 (12%) borderline, and 4 (15%) malignant lesions. Of the 26 cases followed for a mean period of 37 months, 4 (16%) recurred at a mean time of 9 months following surgery, occurring among all histologic subtypes (1 benign, 1 borderline, and 2 malignant lesions) (64). In another series,

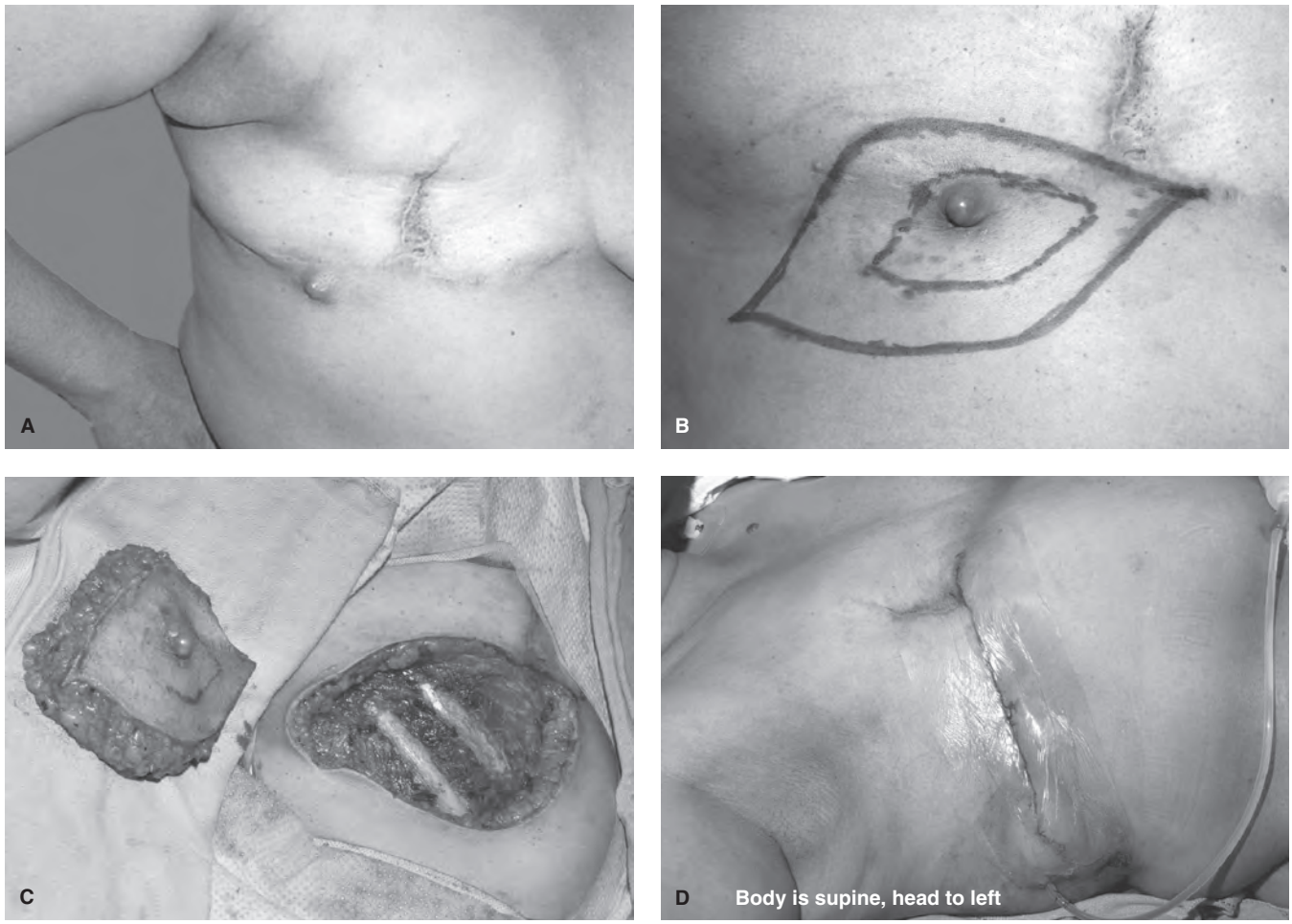


FIGURE 62-8 Presentation and excision of a malignant phyllodes tumor that recurred locally following mastectomy. At age 37, this patient had a palpable breast mass surgically shelled out. The mass proved to be a malignant phyllodes tumor and was re-excised with a partial mastectomy. The mass recurred in the lumpectomy site 15 months later. A subsequent mastectomy was performed using a three-sided incision to facilitate wide excision down to the level of skeletal muscle. Despite this second reexcision, the mass recurred again within 23 months, this time adjacent to the mastectomy incision. **(A)** Recurrent nipple-like mass growing inferior to lateral limb of mastectomy incision. In addition to the protuberant mass, the tumor extends under the skin into the surrounding soft tissue and fat. **(B)** Operative preparation showing palpable edge of subcutaneous tumor (inner ring) and planned skin excision (outer ring). **(C)** Full thickness operative excision including skin, soft tissue, and skeletal muscle excised down to the level of the ribs. **(D)** Soft-tissue advancement flap closure with subcutaneous drain.

local recurrence developed in three of 21 cases (15%) and was not associated with patient age, tumor size, or histological subtype (40). Time to recurrence corresponds to the degree of histologic differentiation. In a Milan series of 216 patients operated on between 1970 and 1989, the average disease-free interval was 32 months for benign phyllodes tumors, 22 months for malignant, and 18 months for borderline phyllodes tumors (65).

Although surgical margins remain the best predictor of local recurrence, two studies suggest that tumor necrosis is also linked to an increased local recurrence risk. "Fibroproliferation" has been defined as the presence of coexisting fibroadenoma or fibroadenomatoid change in the breast tissue surrounding a phyllodes tumor (34). In the large phyllodes series of 293 patients from Memorial Sloan-Kettering with median follow-up of 42 months, fibroproliferation was found to be significantly associated with a higher actuarial local recurrence rate. While no other series have described fibroproliferation as a local recurrence risk factor, this histologic feature was not specifically analyzed or referenced in prior studies (Table 62-2). In addition, Geisler and colleagues observed that there was a trend toward a higher rate of locoregional recurrences and metastases with high-grade lesions, but neither high grade nor large tumor size was a statistically significant predictor of recurrence or survival (26).

When phyllodes tumors recur after lumpectomy, wide reexcision is performed if possible, although management sometimes requires mastectomy. When phyllodes tumors recur after mastectomy, full thickness soft tissue excision from skin to rib cage may be necessary to achieve 1 cm

TABLE 62-3

Factors Associated with Risk of Metastatic Recurrence

Study	*Mitotic Index*	*Stromal Overgrowth*	*Tumor Size*	*Other*
Asoglu, 2004 (67)	No	Yes	No	N/A
Chen, 2005 (68)	Yes	Yes	No	Margins
Fou, 2006 (69)	Yes	Yes	Yes	N/A
Barrio, 2007 (34)	Yes	Yes	Yes	Necrosis Cellularity
Telli, 2007 (74)	No	Yes	Yes	N/A

margins (Fig. 62-8). Soft tissue advancement flap closure is typically necessary to close the defect (Fig. 62-8D) and, in some cases, skin grafting or more complex reconstructive approaches are needed.

Distant Metastases

In the M. D. Anderson series of 101 patients, 8 patients developed distant metastases, with an actuarial 10-year rate of 13% (2). Overall survival in the series was 88%, 79%, and 62% at 5, 10, and 15 years, respectively. For patients with nonmalignant (benign or borderline) and malignant phyllodes tumors, the overall survival was 91% and 82%, respectively, at 5 years, and 79% and 42%, respectively, at 10 years.

Prognosis is uniformly poor if metastatic disease develops. In a review of 67 reported cases of metastatic phyllodes tumors, Kessinger and colleagues reported that the average survival time after diagnosis of metastasis was 30 months. Metastatic lesions have been reported as early as initial presentation of the primary tumor and as late as 12 years after diagnosis. The longest reported survival time after development of metastatic disease is 14.5 years (66).

Stromal overgrowth, which is a required feature for malignant phyllodes tumors, is the most consistent histologic predictor of metastatic behavior (Table 62-3) (2,28,67–70). In the M.D. Anderson series, large tumor size, infiltrative borders, necrosis, and increased mitotic index were associated with increased metastatic risk, but only stromal overgrowth was an independent predictor of distant failure in multivariate analysis.

The lung is the most common site of phyllodes tumor metastases. As with sarcomas, distant pulmonary metastases may be resectable for cure in selected cases (71).

Other metastatic sites can include bone, liver, heart, distant lymph nodes, distant soft tissue locations such as the forearm, the thyroid, and the pancreas (66,70,72). Although these lesions rarely metastasize to the brain or central nervous system (CNS), such occurrences are refractory to therapy, and carry a dismal prognosis (73).

Predictive Recurrence Models

While several have been studied, no individual, or combination of, immunohistochemical tumor markers has been found to be more predictive of metastasis than standard histologic analysis. Multifactor scoring systems have been proposed to better predict recurrence risk for phyllodes tumors. Meneses and colleagues developed a system for assessing degree of histological aggressiveness based on specific histological parameters, including stromal-to-gland ratio, tumor margins, mitotic index, and degree of stromal pleomorphism (55). The relative risk for recurrence was 6.0 for intermediate (borderline) lesions and 11.4 for malignant lesions when compared with the benign category. It is unclear to what degree this system actually changes clinical management, where the principles remain those of wide surgical excision without axillary sampling or dissection.

Patient Follow-Up

After resection of a phyllodes tumor, patients should be followed for local recurrence in the original tumor bed, which generally will be apparent on clinical examination. August and Kearney recommend clinical breast examinations and breast imaging studies twice per year for the first 5 years, then on an annual basis (50). Routine breast ultrasound examination of the lumpectomy site can be considered, or can be reserved for diagnostic work-up of clinical findings. If the breast is dense and ample in volume such that ultrasound might not be able to identify a mass, our institutional preference is to consider breast MRI imaging. We have not found CT useful for imaging the breast.

MANAGEMENT SUMMARY

- Suspicion of phyllodes tumor is typically based upon clinical criteria including older patient age, rapid growth, or large tumor size.
- Mammogram and ultrasound evaluation are advised, although imaging studies often fail to distinguish phyllodes tumors from fibroadenomas.
- When preoperative tissue sampling is warranted, core needle sampling is the preferred modality.
- Surgical management consists of excision to achieve widely negative surgical margins to decrease the likelihood of local breast recurrence. The majority of studies indicate a margin of more than 1 cm is preferable, with some actually advocating for more than 2 cm.
- When phyllodes tumors are excised with positive or close margins, reexcision should be performed.
- The role of adjuvant radiation is controversial, with some studies indicating improved local control but no increased survival when used in patients with borderline or malignant tumors.
- Locally recurrent tumors may warrant adjuvant chest wall radiation following reexcision.

  Routine adjuvant systemic therapy following initial excision is not recommended. Chemotherapy for locally recurrent tumors remains questionable. When used for treatment of metastatic disease, guidelines for treating sarcoma, rather than breast carcinoma, should be followed.

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CHAPTER 63

Paget's Disease

Nora M. Hansen

CHAPTER CONTENTS

Paget's disease, a rare presentation of breast cancer accounts for 1% to 3% of all breast cancers (1,2). The majority of cases are associated with an underlying malignancy and prognosis is dependent upon the stage of the underlying cancer (3). In a recent review of the Surveillance, Epidemiology, and End Results (SEER) data by Chen et al. (4), it was reported that the incidence of Paget's disease has decreased between 1988 and 2002. The age-adjusted incidence rates decreased by 49% for Paget's associated with invasive ductal cancer and by 44% for Paget's associated with ductal carcinoma *in situ* (DCIS).

The first description of Paget-like features was in 1307 by John of Arderne who recorded the several-year evolution of nipple ulceration in a male priest, with the subsequent development of a breast cancer. Velpeau is typically credited with the first clinical description of Paget's disease when, in 1840, he described the visual surface lesion of Paget's disease in two patients. It was in 1874 that Sir James Paget recorded the association of the clinical findings with an underlying breast cancer in 15 patients, although he speculated that the chronic skin condition was benign. It was Thin, in 1881, who concluded that the nipple lesion was not a benign entity, but a malignant one. He postulated that the nipple lesion contained cells that were related to the underlying cancer which had extended to the nipple through the major lactiferous sinuses which we refer to today as Pagetoid spread.

PATHOGENESIS

The pathogenesis of Paget's disease is an interesting one because there are two main theories for the origin of Paget's disease. The most widely accepted one is the epidermotropic theory, first described by Jacobeus, who suggested that the Paget cells arise in breast ducts and spread through the lactiferous sinuses to the nipple epidermis. This view is supported by several observations. First of all, it is well documented that most patients with Paget's disease have an underlying breast carcinoma which is ductal in origin and that the immunohistochemical profile and pattern of gene expression in the Paget cell and the underlying cancer are similar (5). In addition, heregulin alpha, a motility factor released by normal epidermal keratinocytes can induce chemotaxis of the Paget cells to migrate into the overlying nipple epidermis (6).

Because not all Paget's disease is associated with an underlying carcinoma, another theory, the intraepidermal transformation theory (*in situ* transformation theory) proposes that the Paget cells arise either in the terminal portion of the lactiferous duct at its junction with the epidermis or from multipotential cells in the epidermal basal layer. This *in situ* transformation theory is thought to occur in pre-existing benign intraepidermal clear cells of the nipple areolar complex, or Toker cells, which are thought to have migrated from nonneoplastic ducts (7). Support for this theory is found in the rare cases of Paget's disease without an underlying breast carcinoma or cases in which the Paget's disease and the underlying carcinoma appear to be separate tumors (8). Other studies have identified desmosomal attachments between the Paget cells and adjacent keratinocytes supporting the *in situ* development of the Paget cell (9).

Histologically, Paget's disease is characterized by the infiltration of the nipple epidermis by Paget cells, described as large pale-staining cells with round or oval nuclei and prominent nucleoli. The cells are between the normal keratinocytes of the nipple epidermis, occurring singly in the superficial layers and in clusters toward the basement membrane. Serous fluid can seep through the disrupted keratinocyte layer, resulting in the crusting and scaling of the nipple skin. Paget cells can traverse the epithelium and, thus, sometimes are found in the superficial layers. The basement membrane of the lactiferous sinuses is in continuity with the basement membrane of the skin. Paget cells do not invade through the dermal basement membrane and therefore are a form of carcinoma *in situ*. Paget's disease is often associated with a chronic inflammatory infiltrate in the dermis (Figs. 63-1 and 63-2).

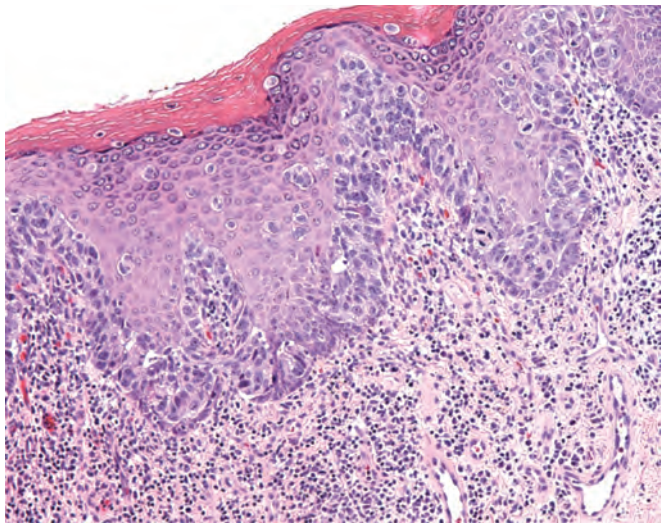

FIGURE 63-1 Section through the nipple epidermis demonstrating Paget's cells. Hematoxylin-eosin stain. Large, pale staining Paget's cells are more densely concentrated toward the basement membrane. (Courtesy of Barbara Susnik, MD, Department of Pathology, Northwestern Memorial Hospital, Feinberg School of Medicine, Northwestern University.)

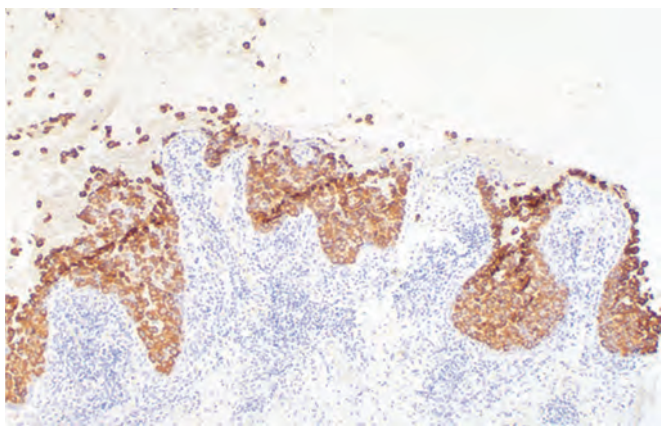

FIGURE 63-2 Cytokeratin 7 (CK7) stain demonstrating cytoplasmic staining pattern which differentiates Paget's from melanoma or squamous cell carcinoma. (Courtesy of Barbara Susnik, MD, Department of Pathology, Northwestern Memorial Hospital, Feinberg School of Medicine, Northwestern University.)

INCIDENCE

The incidence of Paget's disease varies whether one refers to the pathologic or clinical entity. Paget's disease is a more common pathologic than clinical entity (1,10). Its clinical incidence ranges from 0.5% to 2.8% with a mean of 1.3% in more than 50,900 patients combined from nine studies (1,10,11). Histological evidence of Paget cells is present in 0.5% to 4.7% of nipples from breast cancer specimens (1). In a series by Lagios et. al. (10) of 3,000 consecutive breast cancer mastectomy specimens, 21 (0.7%) had clinical evidence of Paget's disease and 147 (4.9%) had Paget cells histologically, thus yielding a sevenfold difference.

Of the 158,621 microscopically confirmed female and male breast cancer registrants from the SEER registry of the National Cancer Institute, 1,775 (1.1%) had histologic Paget's disease (12). Of patients with breast cancer from this database, Paget's disease was histologically identified in 1.1% of white female patients, 1.3% of African American female patients, 1.1% of white male patients, and no African American male patients. Clinical Paget's disease has been reported in patients ranging in age from 23 to 90 years, with mean ranging from 53 to 65 years (13–17). In a further analysis of the SEER data, the mean age of women with Paget's disease was 62 years and that of the men was 69 years. This was not significantly different from female (61 years) and male (67 years) patients with ductal breast cancer. In an update of the SEER data, Paget's disease associated with both invasive and DCIS has decreased from 1988 to 2002 by 49% and 44%, respectively (4). However the number of cases of Paget's diagnosed without underlying invasive disease may be increasing. This may be accounted for the increased use of mammography and finding cancers at an earlier stage before they develop Pagetoid features.

Paget's disease is not confined to women and can occur in men but it is extremely rare. There are probably less than 50 cases described in the world medical literature and most are case reports. There was one report of bilateral Paget's disease of the male nipple with the patient being treated with bilateral mastectomies.

CLINICAL PRESENTATION AND DIAGNOSIS

The majority of patients with Paget's disease present with eczema or ulceration of the nipple and many have a prolonged period of symptoms before diagnosis. It is, therefore, important to have a high index of suspicion for Paget's when a patient presents with nipple complaints. The most common initial presentation is erythema and mild eczematous scaling which progresses to crusting, skin erosion, and ulceration, with exudation or frank discharge (Figs. 63-3 through 63-5).

The clinical differential diagnosis of scaling skin and erythema of the nipple-areola complex in addition to Paget's includes eczema, contact dermatitis, and post radiation dermatitis. Although bilateral Paget's has been reported, bilateral symptoms are most consistent with eczema or contact dermatitis. Skin changes that are confined to the areola and spare the nipple are typically attributed to eczema, although they can occur rarely in Paget's disease. The clinical

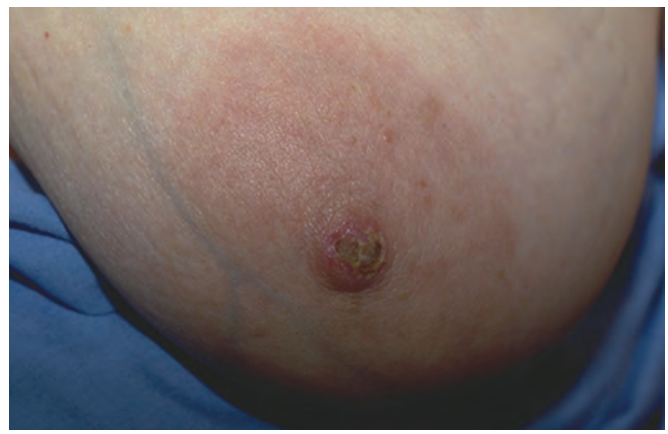

FIGURE 63-3 Paget's nipple. Erythema and crusting of nipple occupying the majority of the nipple surface.

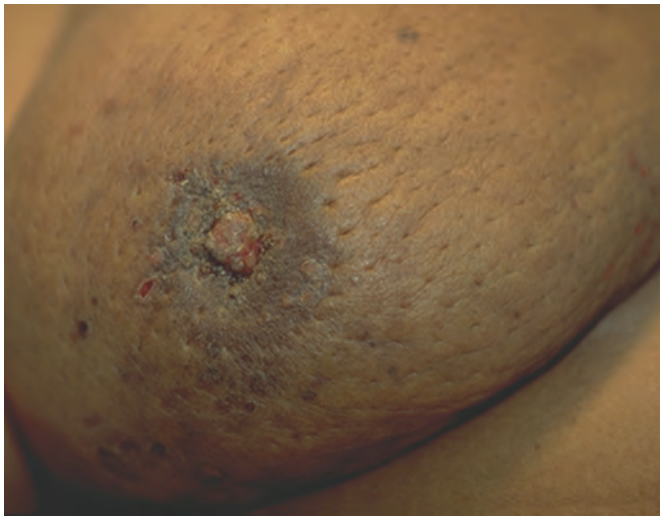

FIGURE 63-4 Paget's nipple. Ulceration of nipple with progression onto areola.

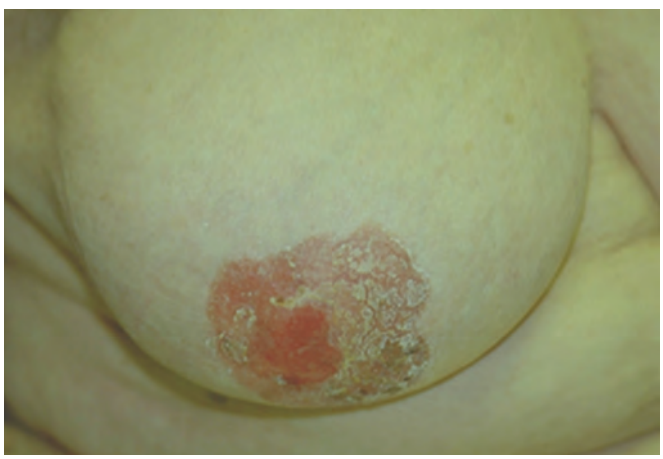

FIGURE 63-5 Paget's nipple. Advanced Paget's with crusting and ulceration extending from nipple and encompassing areola.

differential diagnosis has prompted initial topical steroid treatment, often with transient improvement of symptoms (3). Other patients have been treated with antibiotics. In patients who have been previously treated with breast conservation, Paget's disease may mimic post radiation scaling. Given the infrequency of Paget's disease in this setting, the diagnosis of Paget's disease may be delayed. Symptom duration preceding the diagnosis of Paget's disease is variable and averages 9½ weeks to 27 months, with a range of 1 week to 20 years (18). In a study from the MAYO clinic, the median duration of symptoms was 6 days with a range of 1 to 80 days, clearly a unique patient population (14).

Less common diagnoses in the clinical differential of mammary Paget's disease include nipple adenoma, papillomatosis, melanoma, Bowen's disease, and, rarely, basal cell carcinoma, squamous carcinoma, sebaceous carcinoma, Merkel cell carcinoma, infiltrating lobular carcinoma, cutaneous T-cell lymphoma, Spitz nevus, epidermotropic metastases, alteration of keratinocytes present in 10% of normal nipples. Toker cells can be distinguished from Paget cells by their lack of nuclear pleomorphism or cytologic atypia and their absence of mucin (19).

Although most patients with Paget's present with nipple changes, up to 50% will present with a palpable mass. The majority of patients who present with a palpable mass have an underlying invasive cancer and thus have a worse prognosis. Patients who present with a palpable mass also have a higher rate of nodal positivity (3,20). It has also been shown that HER2-neu overexpression has been found in both DCIS and invasive disease associated with Paget's and this may, in part, account for the poorer prognosis associated with Paget's.

The diagnosis can be obtained by scrape cytology, a superficial epidermal shave biopsy, a punch biopsy, a wedge incision biopsy, or nipple excision (19). The ideal specimen contains adequate epidermis to provide Paget cells and a lactiferous duct. Paget cells may be distributed in a patchy fashion throughout the nipple, so additional specimen sampling may be required to secure the diagnosis.

The histologic differential diagnosis of Paget's disease includes superficial spreading melanoma, squamous cell carcinoma *in situ* (Bowen's disease) and clear-cell changes of squamous cells of the epidermis (Toker cells). The cell type can be determined by immunohistochemical studies including low-molecular-weight keratins (CK7, cellular adhesion molecule 5.2[CAM-5.2]), broad-spectrum keratins, melanoma antibodies, and mucin stains (19).

Paget cells are immunoreactive for keratins (CK7, CAM-5.2, and AE1/AE3), occasionally are immunoreactive to S100 (21), and are not immunoreactive for HMB45 or high-molecular-weight keratins (22). In one study, mucin was present in 55% of 20 patients and, thus, was not informative in 45% of patients (22). Paget cells can phagocytose melanin from adjacent epidermal melanocytes and may be mistaken for melanoma if immunohistochemistry is not performed (22). Melanomas are immunoreactive for S100, are often immunoreactive for HMB45 and are only very rarely immunoreactive for low-molecular-weight (CAM-5.2), broad-spectrum keratins (AE1/AE3), or mucin stains (22). Squamous cells are immunoreactive for low-molecular-weight keratins and broad-spectrum keratins (AE1/AE3) are infrequently immunoreactive for S100 and are not immunoreactive for CAM-5.2, HMB45, or mucin stains (50). Toker cells, or clear-cell changes of the epidermal squamous cells, are a non-neoplastic DCIS, and 1% had Paget's disease only. Toker cells are concentrated within the basal layer or arranged into glandular structures growing up to the spinous layer. These clear cells of the nipple were first described by Cyril Toker in 1970 (7). On occasion these cells can be numerous and atypical and can be difficult to distinguish from malignant cells of Paget's disease. In a study by Di Tommaso et al. (7), Toker cells were identified in 10.2% of patients who underwent mastectomy. In the majority of cases the Toker cells were cytologically bland and benign, while in 27.5% of cases the Toker cells were more numerous and persistent on serial sections and referred to as hyperplastic Toker cells. In 12.5% of cases the Toker cells were hyperplastic and atypical. On immunohistochemistry Toker cells were positive for estrogen receptor and progesterone receptor and negative for CD138 and p53. In comparison Paget's cells were negative for ER and PR and positive for HER2/neu. Both Toker and Paget's cells stained positive for cytokeratin 7 and epithelial membrane antigen and negative for p63 (7).

RADIOGRAPHIC EVALUATION

In patients with clinical Paget's disease, the reported incidence of mammographic findings varies in the literature. For those patients with Paget's without a palpable breast mass,

mammography has been reported as normal in 2.5% to 100% of patients. Of the 324 patients in the 11 series, 174 (54%) had normal mammograms (2,13,15,16,23). In nine series, breast histology was evaluated for 144 patients with clinical Paget's disease and normal mammograms, with 29 patients (20%) found to have an associated invasive breast cancer, 111 patients (77%) found to have DCIS, and 4 patients (3%) found to have Paget's disease of the nipple without an associated invasive cancer or DCIS (15,23). These retrospective studies included patients accrued in the late 1970s, when xeromammography was still in use and retroareolar spot compression views were not routine.

Mammographic findings include skin, nipple, and areolar thickening, nipple retraction, subareolar or more diffuse malignant microcalcifications, and a discrete mass or architectural distortion (24). Mammography inadequately determines the existence of underlying disease in patients with Paget's. In addition, it cannot map the true distribution of the underlying pathology and, therefore, has limited value in determining the appropriate surgical procedure (24). In a more recent series from Memorial Sloan Kettering in 23 patients who had a negative mammogram, 65% had an underlying malignancy confined to the central quadrant of the breast implying that perhaps a negative mammogram may indicate suitability for breast conservation. Although the data is encouraging, the overall sensitivity of mammograms in this series was only 34%. However, if the mammogram was positive, it accurately predicted the extent of disease in 82% of patients, supporting the role of mammography in treatment planning (25).

Ultrasound may be a useful tool in evaluating the patient with Paget's, especially if the mammogram does not demonstrate any abnormalities. Using ultrasound in their study, Günhan-Bilgen (24) and colleagues confirmed the presence of tumor in 67% of patients with Paget's; of which 2% had a normal mammogram. However, in 13% of patients the mammogram did not demonstrate the mass seen on ultrasound and only documented microcalcifications. Because Paget's has been associated with multifocal and multicentric cancers in 42% to 63% of patients, it is important to evaluate the entire breast (2,23).

Breast magnetic resonance imaging (MRI) is an effective diagnostic tool to identify clinically and mammographically occult tumors and there is some evidence to suggest that it may be beneficial in the evaluation of patients with Paget's disease. There is emerging evidence that MRI can identify *in situ* disease and nipple involvement even when clinically occult (26). Recent studies have demonstrated the sensitivity of MRI in detecting breast cancer ranging from 88% to 100% (27). In cases of DCIS, contrast enhanced MRI has a sensitivity of 95% compared to 70% on mammography alone (28). There have been several small series and case reports which have evaluated the use of MRI in patients with Paget's disease. The combined series evaluated 27 patients and MRI detected the cancer in 20 of these patients of which 15 were mammographically occult (29,30). MRI failed to identify 1 invasive cancer and 4 cases of DCIS. MRI was able to accurately determine the extent of disease and, therefore, may be able to help determine which patients are best suited for breast conservation, particularly in the subset of patients with mammographically occult cancers. In another MRI study, the MRIs of 8 patients with Paget's disease were reviewed and comparative analysis of bilateral nipples were made in each patient. There was clear asymmetry with regard to both morphology and enhancement when pathologic nipples were compared to their healthy counterpart. The linear or triangular enhancement of the involved nipple was seen in all 8 patients. Nipple morphologic change consisting of flattening, areolar thickening, or asymmetry was seen in 7 of 8 patients. An associated malignancy was identified in all 8 patients undergoing MRI (31). In a recent study from the Brigham and Women's Hospital, 23 of 51 patients with Paget's had a breast MRI and 78% of those had abnormal findings. The patients with a negative MRI were found to have disease confined to the nipple areola complex (NAC). Twelve patients with a negative mammogram had disease identified by MRI, substantiating the role of MRI in patients with Paget's disease, especially when conventional imaging such as mammogram and ultrasound (US) fail to identify any abnormalities (32).

Technetium-99 methoxyisobutylisonitrile uptake is increased in breast cancer; this is thought to be due to the increased blood flow from angiogenesis and increased cellular metabolism. Several case reports have demonstrated the usefulness of ^{99m}Tc-MIBI scans in evaluating the extent of disease in patients with Paget's disease. However, this has not been a technique that has been widely adopted to date (33).

TREATMENT OPTIONS

There are various treatment options described in the literature for the management of patients with Paget's disease. These include nipple excision alone, radiotherapy alone, central lumpectomy or quadrantectomy with or without the addition of radiation therapy, and mastectomy. For many years, the concern for underlying malignancy and the potential for multifocal or multicentric disease, which has been reported in 32% to 41% of patients, led many to believe that mastectomy should be the definitive treatment for patients with Paget's disease (13). Treatment options have followed the evolution of surgical options for patients with an invasive breast cancer. For years, mastectomy with or without axillary lymph node dissection has been the standard of care for patients with Paget's disease; however, multiple randomized trials have demonstrated that breast conservation is equal in terms of survival to mastectomy and, therefore, the role of breast conservation in Paget's patients has been evaluated (34). However, in one series, 30% of patients with Paget's and no underlying mass had a peripherally located tumor and, therefore, a central lumpectomy would not have been adequate treatment (16).

Although there are no randomized trials relating specifically to Paget's, the use of breast conservation should be acceptable as long as negative margins are achieved and the patient has an acceptable cosmetic result. Several studies have shown that 20 % to 40% of mastectomy specimens have multicentric or multifocal cancers which were underestimated in the mammogram and which potentially would mandate a mastectomy in this subgroup of patients (2). In addition, although the majority of cancers associated with Paget's are centrally located, there are multiple reports depicting the variability of tumor location despite negative mammograms. Paone and Baker (35) reported that in 12% of cases, the underlying cancer was 2cm or more from the nipple while Ikeda et al. (23) reported that in 55% of patients the DCIS was located far from the nipple and in 40% of patient's multicentric disease was identified. Others have reported a 50% incidence of peripherally located tumors, the majority of those with a negative mammogram (38). Wertheim et al. (36) reported a 22% incidence of peripherally located invasive tumors in 18 cases of Paget's patients undergoing a mastectomy. Kothari et al. (13) reported a 75% rate of tumor extension beyond the central quadrant. Failure to identify peripheral cancers when patients are treated with breast-conservation surgery without irradiation may yield

increased local failure rates. Complete removal of the nipple areolar complex is mandatory in patients undergoing breast conservation regardless of the extent of nipple involvement.

BREAST CONSERVATION WITHOUT RADIATION

Breast conservation alone leads to a high local failure rate and is not recommended. There have been several series published which have reported high local recurrence rates with central lumpectomy alone. Polgar et al. (17) reported a 33% rate of local recurrence in 33 patients with Paget's disease of the nipple undergoing conservation, 30 patients had an underlying DCIS and 3 patients had Paget's of the nipple without an underlying malignancy. With a median of 6 years of follow-up, 11 patients (33%) experienced a local recurrence, of which 10 were invasive with 6 developing metastatic disease. Dixon et al. (2) evaluated 10 patients with Paget's without any documented underlying disease on imaging. The nipple areola complex was excised with an underlying cone biopsy. All patients were found to have underlying DCIS and 1 patient had an invasive cancer. Despite negative margins on pathologic exam, at a median follow-up of 56 months, 40% of patients had a local recurrence. Zurrida et al. (37) treated 31 patients with wide excision alone and 29% developed a local recurrence with a median follow-up of 60 months. Other studies have reported low recurrence rates; however, there were limited numbers of patients and the length of follow-up was not specified (35).

RADIATION WITHOUT SURGERY

Radiation treatment alone for patients with Paget's disease without a palpable mass or abnormal mammogram has been reported; however, widespread experience with such conservative treatment remains limited. Although the numbers are small, the local recurrence rates range from 0% to 17%. Bulens et al. (18) treated 13 patients with radiotherapy alone and reported no recurrence with a median follow-up of 52 months. Christiaens et al. (38) reported a 14.8% local recurrence rate in 27 patients at a median follow up of 79 months, while Fourquet (39), with the longest follow-up of 90 months, reported a 17.6% local recurrence rate. Stockdale et al. (40) treated 19 patients and 3 patients recurred, 1 with invasive cancer and 2 with microinvasive cancer. Clearly this approach should be limited to patients with minimal disease which is difficult to evaluate without surgical intervention.

BREAST CONSERVATION WITH RADIATION

If breast conservation is to be considered, the gold standard should be a central lumpectomy with postoperative radiation therapy (Figs. 63-6 through 63-8). The addition of radiotherapy has improved the efficacy of breast-conserving surgery for patients with Paget's disease. There have been several recent, retrospective, nonrandomized studies comparing breast conservation to mastectomy in patients with Paget's disease. The studies, however, are difficult to compare due to the varying presentations of the disease and the varied treatment algorithms. Initial studies only offered breast conservation to patients without a palpable mass or mammographic finding while more recent studies included all types of disease presentation. In a prospective single-arm trial by the European Organization for Research and

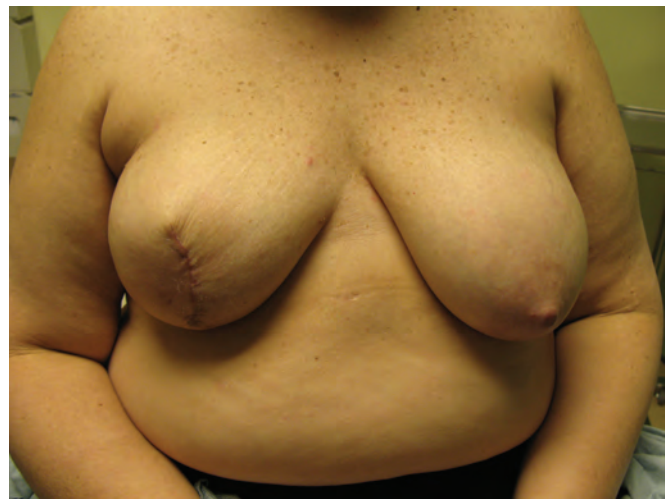

FIGURE 63-6 Patient with Paget's who underwent central lumpectomy with removal of NAC.

Treatment of Cancer, Bijker et al. (15) evaluated 61 patients with Paget's disease. The majority (93%) had an underlying DCIS and were treated with excision of the nipple-areolar complex and underlying breast tissue to tumor free margins followed by whole-breast radiation (50 Gy in 25 fractions). The majority of patients did not have an underlying mass (97%) or mammographic abnormality (84%). With 6.4 years of follow-up, the 5-year local recurrence rate was 5.2%. Marshall et al. (14), in an update of a previous study, reported the 10- and 15-year results for 36 cases of Paget's disease from seven institutions, none of whom had a palpable mass or mammographic abnormality. Of the 36 patients, 69% had a complete excision of the NAC, 25% had a partial resection, and 6% had a biopsy alone. Final margins were negative in 56% of cases. All patients received whole breast irradiation to a median dose of 50 Gy with a boost to the tumor bed in 97% of cases for a total medial dose of 61.5 Gy. Eighty-three percent of patients had a documented underlying malignancy, the majority were DCIS. At a median follow-up

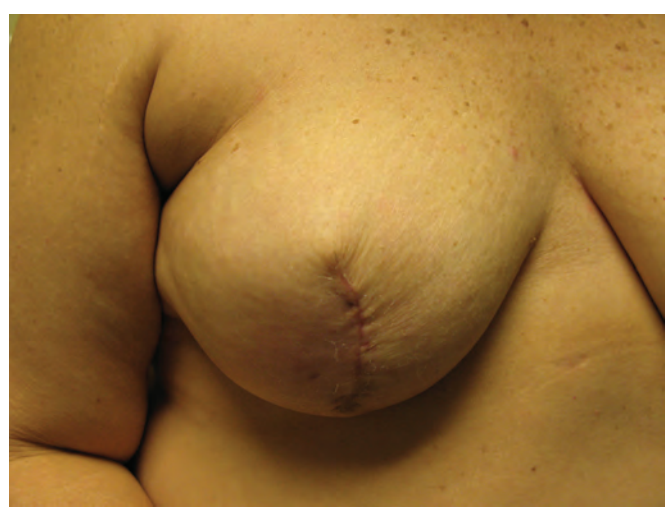

FIGURE 63-7 Closer view of central lumpectomy prior to nipple reconstruction. Closed with vertical incision as patient plans on proceeding with left mastopexy after RT and nipple reconstruction to right breast.

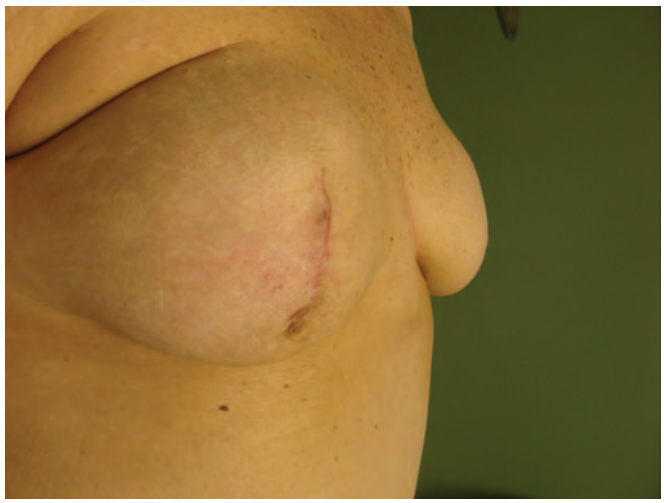

FIGURE 63-8 Patient with Paget's who underwent central lumpectomy with removal of NAC; side view demonstrating shape of breast is intact.

of 113 months, 11% were found to have a local recurrence, all of whom had a complete resection of the NAC. There were no clinical factors identified as a significant predictor of local recurrence. Actuarial local control rates for breast recurrence were 91%, 83%, and 76% at 5, 10, and 15 years, respectively. Actuarial rates for disease free survival (DFS) were 97% for 5, 10, and 15 years. Overall survival rates were 93% at 5 years and 90% at 10 and 15 years. These findings confirm that, for selected patients without a palpable mass or mammographic abnormality, breast conservation affords excellent rates of local control, disease free survival, and overall survival for patients with Paget's disease. In a study by Dalberg et al. (41), 223 patients at 13 Swedish hospitals were diagnosed with Paget's disease. The majority (79%) had an underlying malignancy diagnosed prior to surgery, 30% were invasive cancers. Nineteen percent of patients underwent breast conservation while 75% had a mastectomy and only 19% of patients were radiated. Eleven elderly patients had no surgical intervention. At 10 years, the local recurrence rate for the mastectomy patients was 8% while the conservation patients had a local recurrence rate of 16% which may, in part, be due to the low rate of postoperative radiation therapy. Risk factors associated with breast cancer recurrence and death were presence of invasive cancer and a palpable mass. Lymph node metastases was a risk factor for recurrence but not cancer death. In the largest series from the SEER data base, Chen et al. (4) reported on 1,642 patients with Paget's disease diagnosed between 1973 and 1987. Fifteen year breast cancer specific survival for conserved patients with DCIS was 92% compared to 94% for patients who had a mastectomy. For patients with invasive cancer there was an 87% 15 year breast cancer specific survival and only a 60% survival for patients who underwent a mastectomy. However, there was no difference between the groups after adjusting for tumor size and lymph node status. Only tumor size and lymph node status were significant prognostic indicators of disease specific mortality. The group from MD Anderson Cancer Center (20) reported on 104 patients with Paget's disease and demonstrated that breast conserving approaches had local control and survival rates similar to those achieved with mastectomy and a positive nodal status was the only significant predictor of disease free and relapse free survival with a disease specific survival of 47% in node positive patients and 93% in node negative patients. The local recurrence rate with breast conservation was 8% at a median follow-up of 7 years and all patients had postoperative radiation. Zakaria et al. (3) also demonstrated no difference in survival based on the surgical procedure but the presence of a palpable mass, suspicious mammogram, advanced tumor stage, invasive cancer, and axillary metastases were all associated with a worse outcome. Disease free survival decreased from 90% to 60% and 86% to 30% at 5 and 10 years respectively for patients who presented with a palpable mass and suspicious mammogram compared to those patients without a palpable mass and a benign mammogram.

The European Institute of Oncology of Milan (42) reported their experience of Paget's disease in women from May 1996 to February 2003. The majority of patients presented with typical nipple changes and 77% were associated with suspicious x-ray findings. Ninety-four percent of patients had an underlying malignancy identified. Of the 114 patients, 71 were treated with mastectomy and 43 with breast conservation. There were more locoregional recurrences in the conservation group but this did not impact on survival. Vascular invasion was the only statistically significant prognostic factor for DFS and cancer specific survival, however, tumor size greater than 2 cm and nodal involvement were associated with a worse outcome. Others have reported that younger patients were more commonly offered mastectomy compared to conservation and that the use of radiation therapy (RT) also appeared to be based on age. Similar local recurrence rates and survival rates are seen for patients treated with either breast conservation or mastectomy.

Several studies have demonstrated that patients with Paget's disease were more likely to be ER negative, PR negative with a high histologic grade and an overexpression of c-erb B2 oncoprotein was found in up to 88% of cases (4,41,42).

Breast conservation has become an alternative to mastectomy for patients with Paget's disease with acceptable local recurrence rates and similar survival rates (Table 63-1).

TABLE 63-1

Rates of Local Control after Breast Conservation in Patients with Paget's Disease

Author (Reference)	*n*	*Median F/U (Years)*	*Treatment*	*Local Recurrence (%)*	*Local Control (%)*
Bijker et al. (15)	61	6.4	Lumpectomy + RT	5.2	94.8
Marshall et al. (14)	36	9.4	Lumpectomy + RT	11	89
Dalberg et al. (41)	42	10	Lumpectomy ± RT	16	84
Kawase et al. (20)	12	7	Lumpectomy ± RT	8	92
Zakaria et al. (3)	7	6.4	Lumpectomy ± RT	0	100
Caliskan et al. (42)	43	6	Lumpectomy ± RT	14	86

TABLE 63-2

Sentinel Node Studies in Paget's Disease

Author (Reference)	*n*	*ID rate (%)*	*SN+ rate*	*+NSN (%)*
Sukumvanich (45)	39 (16 invasive, 23 DCIS)	98%	11/39 (28.2%)	45%
Laronga (46)	36 (10 invasive, 26 Paget's +/– DCIS)	97%	4/36 (11.1%) All 4 invasive cancer	25%
Caliskan (42)	30 (19 invasive, 11 DCIS)	100%	5/19 (26.3%) invasive 0/11 DCIS	Not Reported
Morrogh (25)	19	95%	2/18 (11%)	Not Reported
Dominici (32)	26	Not reported	6	Not reported

With better reconstructive options available to patients, the loss of the NAC can be corrected and patients can have an excellent cosmetic outcome. In a study by Chung et al. (43), an immediate reconstructive technique was used in 29 women with Paget's or a subareolar cancer that necessitated the removal of the NAC along with a central lumpectomy. Using a standard Wise pattern incision for reduction mammoplasty, a central lumpectomy with removal of the NAC was performed. The inferior pedicle was deepithelialized and rotated or advanced to fill the central defect. The breast and skin flaps were then mobilized to the midline and inframammary fold and closed. The nipple reconstruction was performed after the completion of the radiation. In all 29 cases, the NAC was felt to be well centered without central depression deformities and there were no local recurrences at a mean follow-up of 3.5 years. However, there are several series which demonstrate a low rate of nipple reconstruction in patients undergoing central lumpectomy. In a study by Dominici et al. (32), only 11% of patients elected to proceed with nipple reconstruction and this data was similar to findings in the study by Marshall et al. (14). This may, in part, be related to the age of the patient, the fact that those undergoing central lumpectomy in these series were older, or that these patients placed less emphasis on cosmesis. Referral to a plastic surgeon for a more thorough discussion of the reconstructive options may, in the future, impact the patients' decision to undergo nipple reconstruction.

NODAL EVALUATION: SENTINEL NODE BIOPSY (SNB) AND AXILLARY LYMPH NODE DISSECTION (ALND)

Paget's disease is associated with an underlying malignancy in the majority of cases and although many patients have an underlying ductal carcinoma *in situ*, a substantial portion of patients may have an invasive cancer. Lymph node metastases is considered the most important prognostic indicator for patients with invasive breast cancer and all patients with invasive cancer should be offered axillary staging. Sentinel node biopsy has now replaced ALND as a less invasive procedure to stage patients with invasive breast cancer. It has been shown to be effective and accurate in detecting the presence of metastases in many single and multicenter studies (44).

Several investigators have evaluated the role of SNB in patients with Paget's disease. In the three reported series, a total of 105 patients have been evaluated (42,45,46). The sentinel node (SN) identification rate ranged from 97% to 100%. An invasive cancer was identified in 45/105 patients and a positive SN was identified in 20 of the 105 patients. None of the patients with DCIS were found to have nodal disease and 44% of the invasive patients were found to have a positive SN. In a study by Sukumvanich et al. (45) from Memorial Sloan Kettering Cancer Center, of the patients with a positive SN, 45% had additional positive nonsentinel nodes while in the study by Laronga et al. (46), the SN was the only positive node in 75% of cases. In a recent study from Brigham and Women's hospital, 51 patients with Paget's disease had surgical intervention (32). The majority of patients had a mastectomy but 37.2% of patients had a central lumpectomy. A SN was performed in 26 patients and 7 patients had nodal metastases. Fifteen percent of patients undergoing central lumpectomy had to return to the OR for a SN biopsy because of invasive disease found in the surgical specimen and the sentinel node was easily identified, confirming that a sentinel node biopsy after a central lumpectomy is feasible. In an MRI study from MSKCC evaluating MRI in Paget's disease, 19 patients (56%) had a SN biopsy with 95% success rate and 11% of patients were found to have a positive SN-(25) (Table 63-2).

Patients with Paget's disease and a known invasive cancer should be offered a SNB to evaluate their nodal status. For patients with Paget's without documented invasive disease who are undergoing a mastectomy, the addition of a SNB is a reasonable option as a subset of these patients will have an invasive component found on final pathology, thereby avoiding the need for a potentially unnecessary ALND. The role of SNB in DCIS is controversial and, therefore, patients undergoing breast conservation for Paget's without a known invasive cancer is unknown. Some clinicians may await the final pathologic evaluation and only proceed with a SNB if invasive disease is documented while others will offer a SNB at the time of breast conservation. The final decision should be made by the treating clinician and the patient.

PAGET'S DISEASE AS LOCAL RECURRENCE

Local recurrence after breast conservation can present as Paget's disease but has been considered a rare event with reports ranging from 2% to 13% (Fig. 63-9) (47). The emergence of nipple sparing mastectomy as a surgical option for a select group of patients has allowed for better aesthetic and psychological satisfaction with comparable oncologic outcomes. However, with preservation of the nipple areola complex, the possibility of a Paget's recurrence in the nipple is increased. In a study by Lohsiriwat et al. (48), there were 36 local recurrences in 861 patients who had a nipple sparing mastectomy, 19.4% were Paget's recurrence in the nipple with a median follow-up of 50 months. Complete NAC removal was performed in all 7 recurrences. The average latency from nipple sparing mastectomy to Paget's disease local recurrence

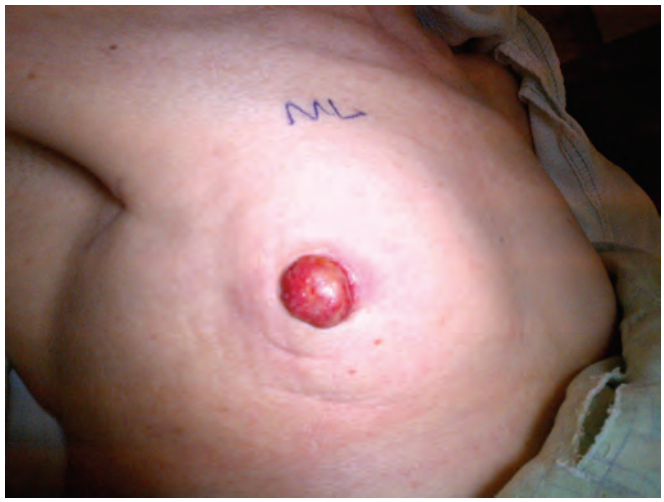

FIGURE 63-9 Patient with local recurrence of Paget's in the nipple after breast conservation.

was 32 months with a range of 12 to 49 months. At the time of the nipple sparing mastectomy, a retroareolar biopsy was performed in all cases and was negative for atypia or tumor. In all 7 cases there was no associated cancer either locally or distantly. Factors associated with a Paget's recurrence in the nipple included a primary carcinoma with ductal intraepithelial neoplasia or invasive ductal cancer with an extensive *in situ* component, negative hormonal receptor, high pathologic grade, and overexpression of HER2-neu. Therefore, in the new era of nipple sparing mastectomy (NSM), any suspicious lesion on the nipple areola complex requires prompt evaluation and Paget's should be considered and pathologic confirmation may be required. If a Paget's recurrence is identified, the NAC should be excised and any adjuvant therapy would be based on the associated pathologic findings.

PAGET'S DISEASE AND SURVIVAL

Prognosis has always been based on the underlying tumor characteristics, such as tumor size and nodal status, and has not been influenced by the presence or absence of Paget's disease. The presence of Paget's has no bearing on the staging of breast cancer as defined in the American Joint Committee on Cancer Staging (AJCC). There is limited data on whether the presence of Paget's influences prognosis. Ortiz-Pagan et al. (49) tried to address this question by comparing clinical outcomes in a contemporary cohort of age- and stage-matched patients with breast cancer with and without Paget's disease. Paget's disease in this cohort was associated with a less favorable prognostic panel with more ER negative and HER2-Neu positive cancers, was more often treated with mastectomy, and the overall survival was lower in the Paget's group compared to the control group (81% vs. 94%). When adjustments were made for local and systemic treatment, the hazard ratio (HR) was attenuated at 2.26 (95% CI, 1.74–16.27; p = .003) the 5-year DFS was similar for the two groups. Although this study was small, it does raise some interesting questions and further investigation is needed. Others have looked at survival and breast cancer associated with Paget's and found that c-molecular markers which are commonly associated with more aggressive tumor behavior and worse survival are more commonly found in patients with Paget's associated cancers (50).

MANAGEMENT SUMMARY FOR PAGET'S DISEASE

- Paget's disease is a rare presentation of breast cancer and accounts for 1% to 3% of all breast cancers.
- The majority of patients present with erythema or ulceration of the nipple.
- Diagnosis is made by either a scrape cytology or nipple biopsy.
- Radiologic workup should include mammogram with retroareolar spot compression views and ultrasound, and, if negative, MRI should be considered to evaluate occult cancer and to rule out multicentric disease.
- The majority of underlying tumors are DCIS and located centrally.
- Breast conservation in appropriately selected patients has similar outcome to mastectomy in nonrandomized trials.
- Complete removal of the nipple areolar complex is required for patients undergoing breast conservation.
- Radiation therapy is important in reducing local recurrence risk in conserved patients.
- Patients with multicentric disease or disease extending beyond the central portion of the breast should be offered mastectomy.
- Patients with known invasive cancer should be offered axillary nodal evaluation with sentinel node biopsy.
- The probability of a Paget's recurrence in the nipple is increased in patients undergoing nipple sparring mastectomy.

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CHAPTER 64

Nonepithelial Malignancies of the Breast

Francisco J. Esteva and Carolina Gutiérrez

CHAPTER CONTENTS

Nonepithelial malignancies of the breast account for less than 1% of breast tumors. The most common primary nonepithelial breast cancers are sarcomas and lymphomas. Young et al. (1) evaluated the demographic and tumor characteristics of all malignant non-carcinomas of the breast using 26 population-based registries in the United States and found that of 363,801 women diagnosed with malignant breast tumors diagnosed between 1994 and 1998, only 1,401 women (0.4%) had tumors that were nonepithelial in origin. All but nine of the nonepithelial breast cancers in that study were some form of soft-tissue sarcoma. The most common nonepithelial cancer was malignant phyllodes tumor, which accounted for 61% of these diagnoses. In addition to the 363,801 malignant cancers classified as breast tumors, another 613 tumors in Young's study arose in the breast but were classified as myelomas or lymphomas; two as solitary myelomas, two as Hodgkin lymphoma, and the remaining 609 as non-Hodgkin lymphoma (1). Cutaneous melanomas arising in the breast or the skin over the breast have been reported. Despite the infrequent presentation of these nonepithelial breast malignancies, knowledge of their unique features, clinical characteristics, pathology, molecular biology, appropriate diagnostic evaluation, proper staging, and treatment is important to provide optimal patient care. Metastasis to the breast from other organs is another presentation of a mass that can be confused with primary breast cancer. When the primary site is unknown, establishing this diagnosis requires extensive pathologic examination using conventional histology, special immunohistochemistry, flow cytometry, cytogenetics, and electron microscopy. Limited data are available regarding the molecular biology of most nonepithelial malignancies of the breast.

PRIMARY SARCOMAS OF THE BREAST

Primary sarcomas of the breast are malignant tumors arising from the connective tissue within the breast and account for less than 1% of all breast malignancies. According to the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, the annual incidence of breast sarcomas is 4.5 cases per million women (2). Sarcomas can arise *de novo* (primary) or as a consequence of treatment of an epithelial breast cancer (secondary) (3,4). Radiation therapy for breast carcinoma can lead to the development of secondary sarcomas with a latency of up to 20 years (4,5).

Malignant mesenchymal tumors of the breast are broadly composed of malignant phyllodes tumor and soft-tissue sarcoma. The stroma of phyllodes tumor develops from the hormonally sensitive periductal and intralobular stroma of the mammary gland that undergoes malignant change. Primary soft-tissue sarcomas of the breast arise from interlobular mesenchymal elements that comprise the supporting mammary stroma and exhibit histologic subtypes that do not differ from sarcomas seen in other sites in the body. In general, fibrosarcoma, angiosarcoma, malignant fibrous histiocytoma (MFH), liposarcoma, osteosarcoma, and stromal sarcoma comprise the major histological subtypes (6). The histologic distinction is still important as new molecular classification and targeted therapies are developed. Although the etiology of most soft-tissue sarcomas remains unknown, angiosarcoma of the breast has increasingly been associated with prior external beam radiation therapy of the breast and with lymphedema that occurs after radical surgery, with or without radiation, for primary breast cancer. Because of the rarity of breast angiosarcoma, only a small series of patients have been reported (7–9).

Primary breast sarcomas typically present clinically with a unilateral mass with a growth rate that often is rapid when compared to epithelial breast cancer. The size of these tumors is variable, ranging from 1 to 40 cm in most studies, with an average median size of 5 to 6 cm (10,11). The gross appearance of these tumors is influenced in part by the specific histological features, but, in general, they consist of firm, fleshy, tan to gray tissue with variable soft, cystic, and hemorrhagic areas.

Pathological grading plays a critical role in the prognosis of mammary sarcomas. The tumors vary from hypercellular,

fairly uniform spindle cell fibroblastic proliferations to atypical, highly anaplastic cells, and most tumors are intermediate to high grade. Increased mitotic activity (more than 10/10 HPF, range 0–43) and necrosis are additional findings. A diagnosis of primary breast sarcoma must be established only after a range of benign and malignant spindle cell lesions, such as fibromatosis, nodular fasciitis, fibrous histiocytoma, sarcomatoid carcinoma, and metaplastic carcinoma, have been excluded. The distinction is important for treatment and for prognosis. The pathologic evaluation of primary breast sarcomas must include extensive sampling and, in some instances, markers of differentiation, cell surface markers, immunohistochemical studies, cytogenetics, and, in some cases, electron microscopy (12,13).

Breast sarcomas differ clinically from primary breast epithelial tumors. The most common mode of spread is hematogenous, and axillary lymph node involvement is not as frequent as it is with epithelial breast tumors. The most frequent sites of initial metastases are the lungs, bone marrow, and liver (11). Breast imaging studies are nonspecific except that microcalcifications are rare, the mass is often well circumscribed, and tumors tend to be heterogeneous because of the presence of necrosis within the tumor (14,15). Diagnosis of a primary breast sarcoma requires a core biopsy, incisional or excisional. A fine needle aspiration is not adequate. Excisional biopsy is preferred, with attention to negative surgical margins. Tumor size, the presence of regional and/or distant metastases, and the tumor grade are important factors to determine the stage and prognosis (13,16).

The treatment for primary breast sarcomas is wide excision that allows adequate margins free of cancer cells (17). Axillary lymph node dissection is not recommended unless there are enlarged lymph nodes or lymph nodes that appear suspicious under ultrasound or magnetic resonance imaging (MRI). Radiation therapy and chemotherapy may be considered in patients with angiosarcomas and high-grade sarcomas because these lesions have a tendency to recur locally and can also metastasize. However, the role of adjuvant therapy in this setting is controversial. A retrospective review of 55 patients with primary breast sarcoma treated at the Mayo Clinic between 1975 and 2001 reported that adjuvant chemotherapy and radiation therapy did not improve survival although an advantage could easily be missed in such a small study (6). Responses have been reported in patients with metastatic sarcoma of the breast using anthracycline- and ifosfamide-based chemotherapy (18). The treatment regimen should be individualized and a multidisciplinary approach involving a close collaboration among the surgeon, radiation oncologist, and medical oncologist is mandatory.

Angiosarcoma of the Breast

Angiosarcoma arises in the breast more often than in any other organ, and it is also the most common soft-tissue sarcoma involving the breast (8). Angiosarcoma of the breast tends to occur in younger women at a median of 38 years. Because the disease affects younger women, an association with pregnancy has been observed; however, there is no evidence for a hormonal basis for breast angiosarcoma. A correlation has also been suggested between prior radiation therapy in the setting of breast conserving surgery and the development of angiosarcomas (11). The SEER program data compiled by the National Cancer Institute included more than 194,000 women who were treated for breast carcinoma. Among patients in the radiotherapy cohort, the relative risk of developing angiosarcoma was 15.9 (5). The median latency period between radiation for breast cancer and the diagnosis of angiosarcoma has been estimated to be about 6 years. One study failed to confirm the observation that prior radiation increased the risk of developing angiosarcoma (19). In that series, only nine cases of angiosarcoma were documented, which represents a prevalence of 5 per 10,000. Cutaneous angiosarcoma of the chest wall after mastectomy and radiation therapy may also occur (7).

Typically, patients present with a rapidly growing painless breast mass. The overlying skin may have blue or purple discoloration (20). In the largest series, containing 69 patients with breast angiosarcoma, tumor size varied between 1 and 14 cm with a median of 5.5 cm (21). In the majority of cases, the angiosarcoma forms a friable, firm, or spongy hemorrhagic tumor. In high-grade lesions, cystic hemorrhagic necrosis is usually present. Hemorrhagic discoloration in the surrounding breast tissue may indicate that the tumor extends beyond the evident mass. In some cases, the tumors have been described as poorly defined areas of thickening or induration. Microscopically, three distinct patterns of growth have been described; they reflect the degree of differentiation and were thought to correlate with prognosis although one report did not find a relationship between grade and patient outcome (9). Low-grade or type I tumors (Fig. 64-1A) are composed of open, anastomosing vascular channels that invade mammary glandular tissue and fat, producing atrophy of the terminal duct lobular units. Some prominent hyperchromatic endothelial nuclei may be found, but most often they have inconspicuous nuclei. The endothelial cells are distributed in a flat monolayer around the vascular spaces without papillary endothelial proliferation, and rare mitoses are seen. Intermediate-grade or type II angiosarcoma (Fig. 64-1B) shows scattered focal areas of more cellular proliferation consisting of well-developed papillary endothelial proliferation that may combine polygonal or spindle cells. Infrequent mitoses may be found in cellular or spindle areas. Type III or high-grade angiosarcoma (Fig. 64-1C) exhibits highly malignant features that comprise more than 50% of the tumor (22). These tumors consist of prominent epithelial tufting and solid papillary formations with cytologically malignant endothelial cells. Mitoses are readily found. Areas of necrosis and hemorrhage, so called "blood lakes," are only found in high-grade angiosarcomas. The high-grade tumors have infiltrative borders that feature low-grade vascular channels, which may lead to the erroneous diagnosis of a low-grade lesion on a core biopsy. Immunohistochemically, angiosarcomas are positive for Factor VIII related antigen, thrombomodulin, B72.3, CD31, and CD34. These reagents are useful for distinguishing angiosarcomas from carcinoma and other neoplasms. It has been reported that the level of the cell cycle protein SKp2 and the Ki-67 index as a measure of proliferation can be used to distinguish benign vascular lesions such as hemangiomas from malignant low-grade angiosarcomas (23).

Postirradiation Angiosarcomas of the Skin

The histological features of post-radiation angiosarcomas differ from primary breast angiosarcomas and mainly involve the skin with or without occasional invasion of the subjacent breast parenchyma (24,25). High-grade areas are solid, epithelioid, or spindle cell foci with slit-like spaces with intraluminal or extravasated red blood cells. In addition, regardless of the microscopic pattern, malignant cells in post-radiation angiosarcoma have poorly differentiated nuclei with prominent nucleoli and mitotic activity. Angiosarcoma in the skin and breast after radiotherapy must be distinguished from benign vascular lesions that arise in the same clinical setting and that are called *atypical vascular lesions* (AVL) (24). These lesions appear 1 to 17 years after radiotherapy as single or multiple skin nodules measuring 5 mm or less in

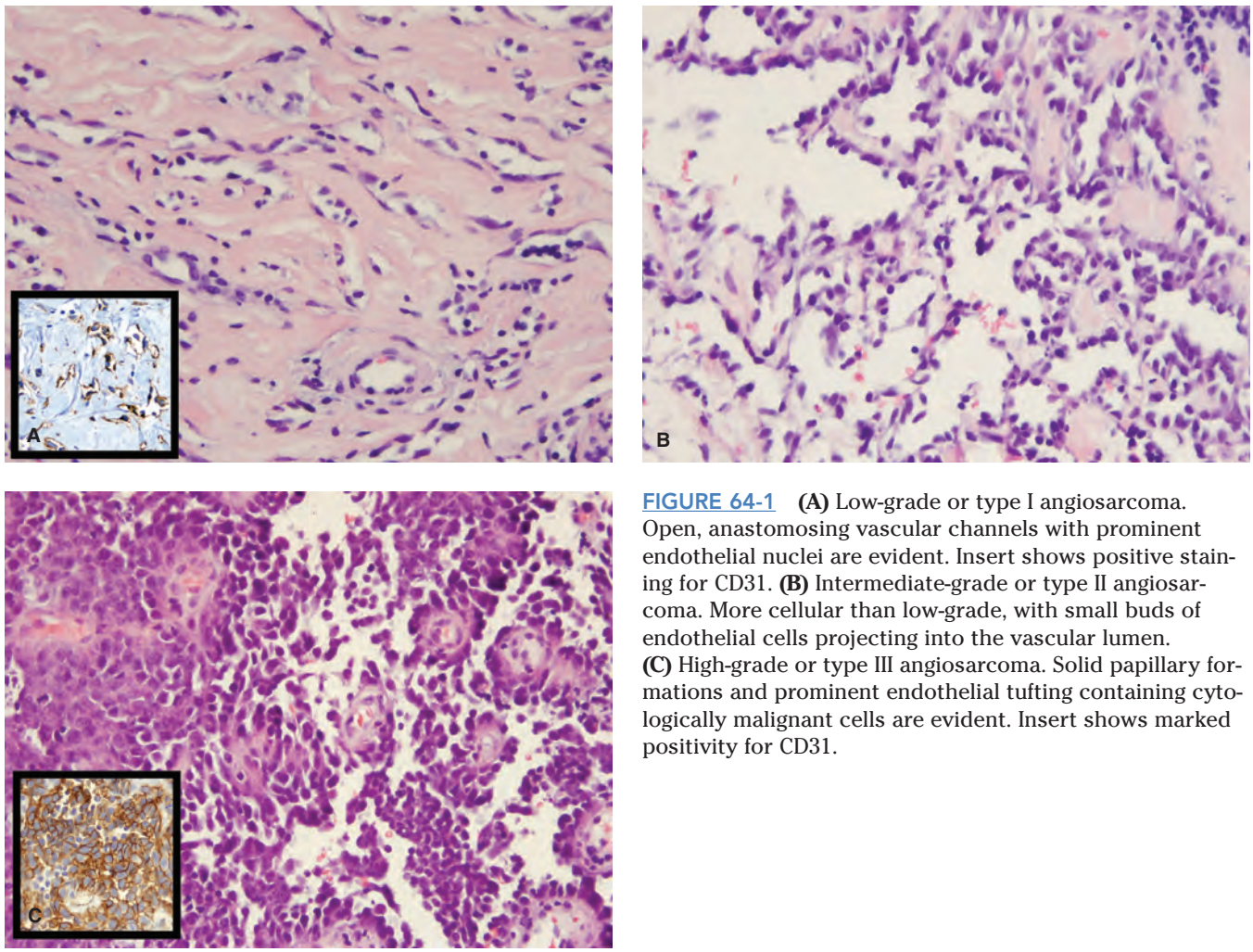

FIGURE 64-1 **(A)** Low-grade or type I angiosarcoma. Open, anastomosing vascular channels with prominent endothelial nuclei are evident. Insert shows positive staining for CD31. **(B)** Intermediate-grade or type II angiosarcoma. More cellular than low-grade, with small buds of endothelial cells projecting into the vascular lumen. **(C)** High-grade or type III angiosarcoma. Solid papillary formations and prominent endothelial tufting containing cytologically malignant cells are evident. Insert shows marked positivity for CD31.

diameter. Histologically, a focal proliferation of anastomosing vascular channels lined by a single layer of endothelial cells with occasional hyperchromatic nuclei is seen. The vascular spaces are usually empty and are limited to the superficial and mid-dermal areas. There is insufficient information to determine definitively whether AVLs can progress to sarcomas. One report suggests that AVLs may be precursors of angiosarcomas (25). Molecular analysis in a series showed that post-radiation cutaneous angiosarcoma is characterized by increased expression and amplification of MYC, whereas atypical vascular lesions do not show this alteration, questioning their role as precursors; however, cases of AVLs progressing to angiosarcoma were not studied in this report (26).

Treatment of Angiosarcomas of the Breast

The optimal surgical treatment of breast angiosarcoma is segmental mastectomy if negative margins can be achieved or total mastectomy if the former is not possible (27,28). Axillary dissection is not recommended. Patients with angiosarcomas have a worse prognosis than patients with other types of sarcoma (6). The most important prognostic markers are histologic grade (subtype) and tumor size although histologic grade was not prognostic in one study (9). However, the roles of adjuvant chemotherapy and radiation therapy are unclear. Several series suggest that adjuvant therapies do not improve disease-free or overall survival. A review of 69 patients with angiosarcoma of the breast treated at the MD Anderson Cancer Center found no improvement in survival of patients with angiosarcoma of the breast treated with neoadjuvant chemotherapy or radiation therapy. However, in this study, the response rate to anthracycline- and gemcitabine-based chemotherapy in the metastatic setting was 48%, suggesting that breast angiosarcoma is potentially a chemosensitive disease (21).

Osteogenic Sarcoma of the Breast

Extraskeletal osteosarcoma of the breast is an extremely rare tumor, accounting for 12.5% of mammary sarcomas (29). Primary breast osteosarcomas are considered highly aggressive tumors with early local recurrence and hematogenous spread (most commonly to the lungs). The most common presentation is a circumscribed and movable mass that on mammography may show osseous trabeculae or coarse calcifications. Silver et al. (30) reported a series of 50 patients with osteogenic sarcoma of the breast diagnosed at the Armed Forces Institute of Pathology (AFIP) between 1957 and 1995. The median patient age at presentation in that study was 63.2 years, and the tumor size varied from 1.4 to 13 cm at the time of diagnosis. The histological features are similar to other skeletal osteosarcomas. The most common variants observed are fibroblastic, osteoblastic, and osteoclastic. In the osteoblastic osteosarcoma, the osteoid is deposited in a fine, ramifying, lacelike, or coarsely trabecular pattern

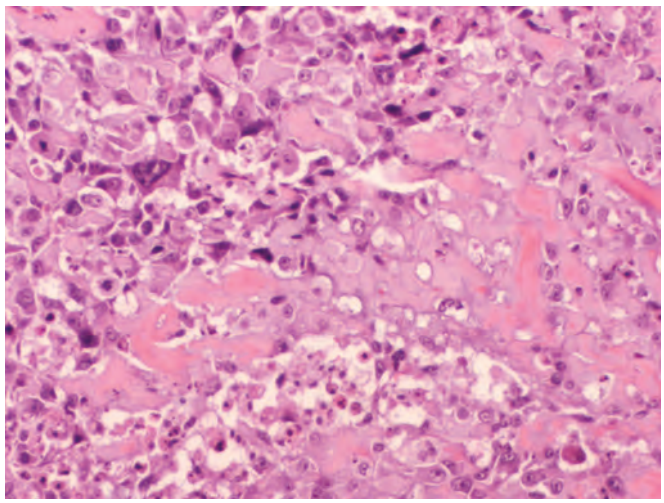

FIGURE 64-2 Primary osteosarcoma of the breast. Malignant cells with round nuclei and prominent nucleoli with lacelike osteoid are seen.

and sometimes in sheaths of osteoid or bone. Atypical cartilage has been reported in 36% of primary breast osteosarcomas. Necrotic foci can be identified in 30% of the cases. Multinucleated osteoclastic giant cells are usually present in areas of bone formation. Immunohistochemistry is helpful in ruling out a metaplastic carcinoma with heterologous elements, which expresses CAM 5.2, pancytokeratin, and high molecular weight keratin (Fig. 64-2).

The relationship between prior breast or chest wall irradiation and breast osteosarcoma is not clear. One of the patients in the AFIP series had received radiotherapy for ipsilateral breast carcinoma 9 years before presentation, but none of the other patients had been exposed to radiation therapy (30). Like other sarcomas, spread to regional lymph nodes is uncommon with breast osteosarcoma. No axillary lymph node involvement was noted in 20 patients who underwent axillary lymph node dissection in the AFIP series. Of 39 patients with follow-up, locally recurrent (n = 11) or metastatic disease (n = 15) was documented at a mean of 10.5 and 14.5 months from diagnosis, respectively, in the same study. Adjuvant radiation therapy and chemotherapy are not recommended.

A recent large international multicenter study of matrix-producing metaplastic breast carcinoma (MP-MBC) questioned the existence of primary mammary matrix-producing (MP) sarcoma, namely osteosarcoma and very rare cases of chondrosarcoma, and examined the clinicopathological features and outcomes of MP-MBC (31). In this study, the authors reviewed the published cases of MP sarcoma of the breast and the criteria to identify them, such as absence of epithelial components, the lack of over-expression of HER2 (which is frequently overexpressed in primary bone osteosarcomas), and the pattern of distant metastases (which differ from the metastatic sites of primary skeletal osteosarcoma). The conclusion of the study is that most of breast osteosarcoma and chondrosarcoma cases are in fact MP-MBC and are of epithelial origin with minimal/nondetectable residual epithelial components, once the diagnoses of phyllodes tumor and metastasis from skeletal osteosarcoma have been excluded. Complete and extensive tumor sampling, the use of a broad panel of epithelial markers, as well as discussion in a multidisciplinary team meeting are important before making the rare diagnosis of primary mammary MP sarcoma. Based on the limited data available, patients with MP sarcoma should be treated similarly to other epithelial breast carcinomas (31).

Embryonal Rhabdomyosarcoma of the Breast

Primary embryonal rhabdomyosarcomas of the breast are rare tumors that typically occur in adolescents and young women. Of the 3,500 cases of rhabdomyosarcoma registered with the Intergroup Rhabdomyosarcoma Group of the United States between 1972 and 1992, only 7 (0.2%) originated in the breast. When the data were restricted to the 423 women aged between 10 and 21 years of age, only 1.6% had rhabdomyosarcoma of breast origin. Metastatic rhabdomyosarcoma to the breast was seen in 2.6% in the same age group. The median age was 15.2 years, including primary or secondary rhabdomyosarcomas of the breast. The most common histologic subtype was alveolar rhabdomyosarcoma (32).

Histologically, alveolar rhabdomyosarcoma is composed of small, round cells that make poorly defined aggregates (Fig. 64-3). Mitoses are easily identified. The differential diagnosis, which includes malignant lymphoma and invasive lobular carcinoma, can be resolved by using immunostains for myoid, epithelial, and lymphoid markers. Cytogenetic studies may show the characteristic translocations t(2;13)(q35;q14) or t(1;13)(p36;q14) (32). The treatment of choice for embryonal rhabdomyosarcomas of the breast is surgical resection with wide tumor-free margins. Total mastectomy may provide a better outcome in some patients. There are limited data regarding the role of lymphatic mapping and sentinel lymph node (SLN) biopsy in the management of sarcomas because most sarcomas rarely metastasize to regional nodes. However rhabdomyosarcomas are usually high-grade tumors that have a propensity for regional lymph node metastases, and it has been suggested that these patients may benefit from SLN biopsy (33). Treatment of rhabdomyosarcomas is multidisciplinary and may include radiation and chemotherapy in addition to surgery. Excellent survival rates are observed in children with this disease. A five-year survival rate of 43% was reported in patients with breast rhabdomyosarcomas. These patients tend to be slightly older and have the alveolar subtype (32).

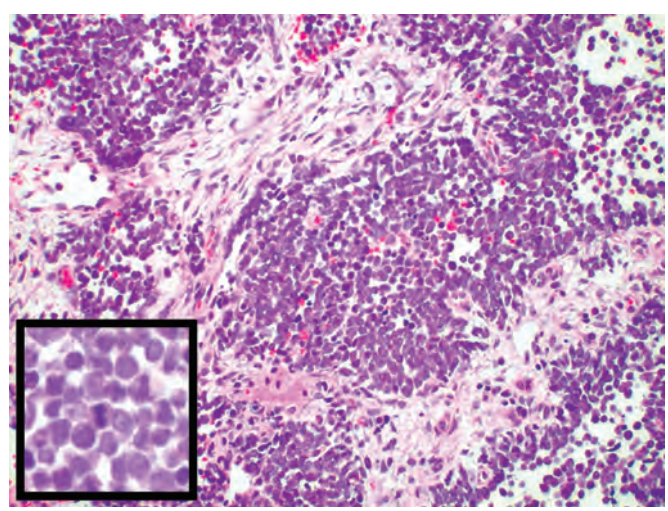

FIGURE 64-3 Alveolar rhabdomyosarcoma of the breast in a 16-year-old girl. The tumor is composed of a proliferation of small round cells mimicking a lymphoma. Molecular diagnostic pathology testing by RT-PCR showed PAX3-FKHR translocation [t(2;13)].

Miscellaneous Breast Sarcomas

A variety of other soft-tissue sarcomas can originate in the breast. They should be described, classified, and treated in a manner similar to sarcomas originating in other sites. These tumors include stromal sarcoma, leiomyosarcoma, liposarcoma, malignant fibrous histiocytoma, Ewing's sarcoma, and fibrosarcoma (11,34). These tumors are rare. Some, such as malignant fibrous histiocytoma and fibrosarcoma, are sequelae of prior postmastectomy irradiation (5,35). These tumors can occur in all age groups but tend to be more frequent in women older than 50. They present clinically as a mass although they can be found by breast imaging. Treatment of these lesions is surgical. Wide excision or total mastectomy has been performed, with the decision based on the characteristics of the tumor and the patient. The rather high local recurrence rate after wide excision in some studies suggests that total mastectomy might be preferred. Axillary dissection is not indicated because these tumors spread hematogenously (36).

Other mesenchymal tumors have been observed rarely in the breast. These include hemangiopericytoma, which has an excellent prognosis and can be treated by wide excision (37); dermatofibrosarcoma protuberans (38), which arises in the skin of the breast and can be confused with locally advanced breast cancer clinically; Kaposi's sarcoma (39); and tumors of the peripheral nerve sheath (40). These rare lesions are described in detail elsewhere (10).

Lymphedema-Associated Lymphangiosarcoma

Lymphedema-associated lymphangiosarcoma, also known as Stewart-Treves Syndrome, has been reported in women treated typically with radical mastectomy and chest wall irradiation who have chronic upper extremity edema. The incidence of lymphedema-associated lymphangiosarcoma in the United States is 1.6 per 100,000 persons (41). The pathogenic mechanism of this syndrome is unknown, but several hypotheses have been postulated. Proliferation of lymphatic vessels is often seen in areas of chronically edematous tissue. It has been suggested that the block of the lymphatics increases the expression of growth factors and cytokines, which stimulates proliferation of blood vessels and lymphatics. The association between radiotherapy and chest wall sarcomas is well known, but it is unclear whether radiation therapy contributes to this entity because most reported post-radiation sarcomas are not lymphangiosarcomas. Although postmastectomy radiation is a major predisposing factor for the development of lymphedema, other factors, such as hypertension and cardiovascular disease, have also been described as risk factors. With multimodality therapy, the 5-year survival rate for lymphedema-associated lymphangiosarcoma has been reported between 8.5% and 13.6% (42). The incidence of this complication of extensive surgery and radiation is on the decline with the increasing use of breast conservation, limited radiation, and sentinel lymph node biopsy.

PRIMARY LYMPHOMAS OF THE BREAST

Primary breast lymphomas (PBL) account for 1.7% to 2.2% of extranodal non-Hodgkin lymphomas (NHLs), 0.38% to 0.7% of all NHLs, and 0.04% to 1.0% of breast malignant neoplasms (43,44). Wiseman and Liao (45) used the following criteria to define PBL: (i) there is no prior diagnosis of extramammary lymphoma, and the breast is the primary site of disease; (ii) mammary tissue and lymphomatous infiltrate are in close association with no evidence of concurrent widespread disease; and (iii) pathology is confirmed by technically adequate specimens.

The majority of non-Hodgkin lymphomas involving the breast are B-cell neoplasms, and the most common are diffuse large B-cell lymphomas (DLBCL) (Fig. 64-4A) and extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue, but other types can also be found (Fig. 64-4B) (44,46–48). Most B-cell lymphomas of the breast present as a palpable breast mass with or without enlarged axillary lymph nodes (44,46). Typically, the mass is not painful, and it is not fixed to the chest wall or skin. Skin ulceration, erythema, or

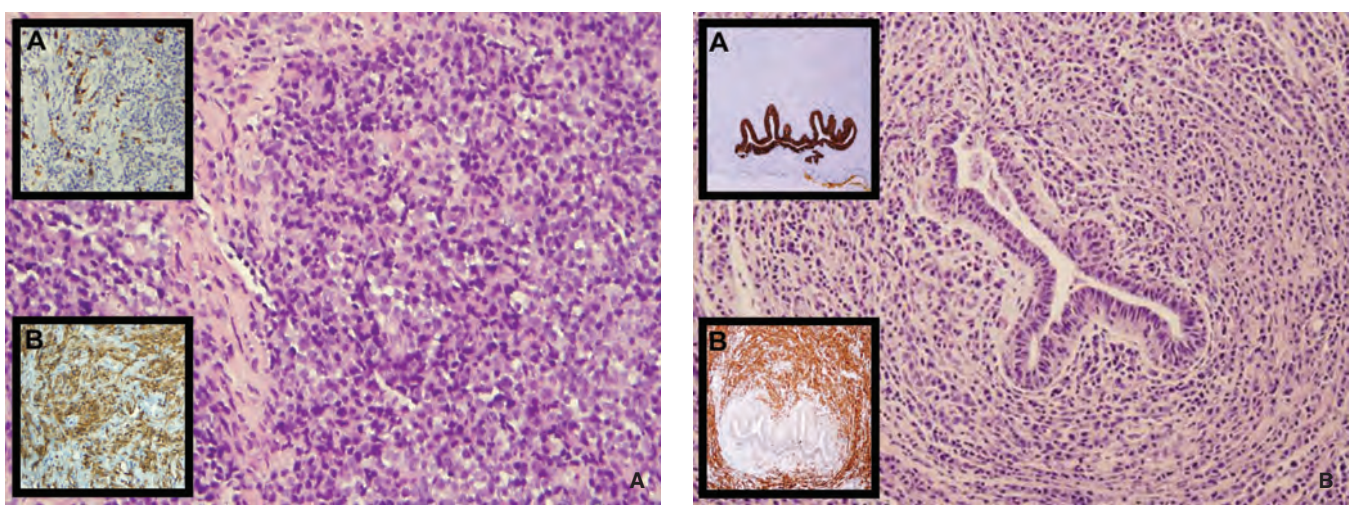

FIGURE 64-4 **(A)** Diffuse large B-cell lymphoma. The malignant cells invade the breast stroma. Insert A shows only a few cells staining with CD3. Insert B shows the majority of cells staining for CD20. **(B)** Lymphoma mimicking invasive lobular carcinoma. Insert A shows positive staining for AE1/AE3 in the normal breast duct while the neoplastic cells are negative. Insert B shows intense staining of the malignant cells with CD45, confirming the lymphoid lineage.

erosion suggests extension into the skin. When the skin is involved, a T-lymphocyte phenotype should be suspected. Other primary lymphomas that may involve the skin overlying the breasts include epidermotropic mycosis fungoides, peripheral T-cell lymphomas, or cutaneous B-cell lymphomas. Primary Hodgkin lymphoma of the breast has also been reported (44,48). Although extremely rare, a Burkitt-like lymphoma of the breast has been reported, presenting with bilateral, diffuse, and rapidly fatal disease (43,48). Cases of anaplastic large-cell lymphoma (ALCL), ALK-negative, have been reported in association with breast implants with an odds ratio of 18.2. This type of lymphoma is defined as a CD30+ peripheral T-cell neoplasm, which appears to have a better prognosis than other clinical types (49,50).

Radiographic imaging features of PBL are nonspecific, with the exception that calcifications are rare. On ultrasound, the identified lesions tend to be homogeneously hypoechoic or heterogeneously mixed hypo- to hyperechoic (51). Positron emission tomography (PET) and computed tomography (CT) scanning may be of some use in distinguishing breast lymphomas from other breast neoplasms after response to therapy and in determining remission status in the presence of minimal residual masses determined by physical examination or other imaging methods (52). Diagnosis is typically made by core biopsy of a palpable breast mass. High-grade lymphoma must be distinguished from melanoma and poorly differentiated carcinoma because curative treatment differs radically among these tumor types. Immunostaining with a broad panel of markers, including epithelial markers (cytokeratins), melanoma (S-100, human melanoma black 45 [HMB-45], and Melan A), and lymphoid markers (CD45, CD3, CD20), usually leads to the correct diagnosis. All B-cell and T-cell neoplasms express pan-B-cell (CD20, CD79a, or PAX5/BSAP) or pan-T-cell antigens (CD3, CD5, or CD45RO), respectively. B-cell and T-cell lymphomas of specific types express the appropriate markers (44). Additional molecular testing may be required to diagnose unusual entities, such as the anaplastic large-cell, ALK-negative, primary cutaneous ALCL, CD30+ T- or B-cell lymphoma with anaplastic features (49). After diagnosis, patients should be fully staged to determine extent of disease using the World Health Organization (WHO) classification of lymphoma (53). The WHO classification subdivides tumors into mature B-cell neoplasms, mature T-cell and NK-cell neoplasms, Hodgkin lymphoma, histiocytic and dendritic cell neoplasms, and posttransplantation lymphoproliferative disorders. The diagnostic evaluation should include immunophenotyping and might require cytogenetics, fluorescent in situ hybridization (FISH), antigen receptor gene rearrangement studies, and other investigations (54). Clinical staging procedures include CT scans of the chest, abdomen, and pelvis; a PET scan; and bilateral bone marrow biopsies and aspirates. Other staging studies may include CT scans of the brain, MRI scans, lumbar puncture with evaluation of cerebrospinal fluid chemistry and cytology depending on the clinical presentation and histologic subtype of lymphoma. A variety of biopsy techniques, including gastrointestinal endoscopy, bronchoscopy, mediastinoscopy, thoracoscopy, laparoscopy, thoracotomy, or laparotomy may be indicated in the process of diagnosis and staging in some patients (54).

The role of surgery in PBL should be limited to acquisition of adequate material for diagnosis, typically with a biopsy either from the breast mass or from an involved lymph node. Treatment by mastectomy offers no survival benefit or protection from recurrence (55). Rituximab plus anthracycline-based chemotherapy and involved field radiation therapy are the mainstays of treatment for PBL (48). It should be noted that most PBL reports describe patients treated in the pre-rituximab era. Systemic chemotherapy with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (RCHOP) is currently the standard of care for patients with DLBCL, and this regimen should be used in patients with PBL as well (56,57). Although some studies reported a high recurrence rate in the central nervous system (CNS), other studies reported low CNS involvement (44,57). Currently, prophylactic whole-brain irradiation is not recommended for PBL patients.

MELANOMA OF THE BREAST

Although melanoma can metastasize to the breast, primary cutaneous melanomas of the breast tissue or skin can also rarely occur (58). When melanomas occur in the nipple-areolar area, phagocytosis of melanin by Paget's cells distinguishes the melanomas from Paget's disease of the breast (59). The clinical presentation of melanoma involving the skin of the breast includes changes in size, pigmentation, ulceration, and bleeding of a pre-existing mole. The most important prognostic factors are the presence of regional lymph node metastases, the thickness of the primary tumor, tumor mitotic rate, and the presence of ulceration (60). As described earlier, melanoma and high-grade lymphoma can be confused with a poorly differentiated carcinoma. These tumors must be distinguished from one another to provide appropriate curative treatment. Staining with HMB-45, S-100, or Melan-A is helpful to confirm the diagnosis of melanoma (Fig. 64-5).

Treatment of cutaneous melanoma of the breast involves *en bloc* excision of the tumor or biopsy site, with a margin containing normal-appearing skin and underlying subcutaneous tissue (Table 64-1) (61). Randomized clinical trials have shown that a 1–2-cm margin of excision is adequate. Wider margins have not translated to improvement in survival. The recommended excision margins for primary melanoma of the breast are similar to other cutaneous melanomas (Table 64-1). Sentinel lymph node biopsy should be discussed with and offered to patients with melanoma of the breast following the protocol for other sites' primary

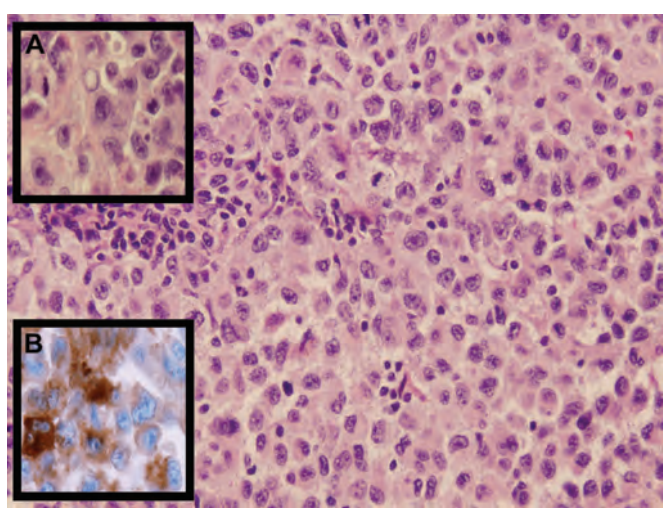

FIGURE 64-5 Melanoma of the breast. This lesion can be mistaken for a poorly differentiated carcinoma or a large cell lymphoma when melanin pigment is not readily seen. Insert A shows a characteristic intranuclear inclusion in a malignant cell. Insert B shows intense staining for HMB-45, confirming the diagnosis of melanoma.

TABLE 64-1

Recommended Excision Margins for Primary Cutaneous Melanoma

Tumor Thickness	*UK Trial (70)*[a]	*WHO Trial (71)*[a]	*Australian Trial (72)*[a]	*Dutch Trial (73)*[a]
In situ	2–5 mm	5 mm	5 mm	5 mm
<1 mm	1 cm	1 cm	1 cm	1 cm
1–2 mm	1–2 cm	1 cm[b]	1 cm	1 cm
2.1–4 mm	2–3 cm; 2 cm preferred	2 cm	1 cm	2 cm
>4 mm	2–3 cm	2 cm	2 cm	2 cm

[a]Reference numbers.
[b]For melanomas thicker than 1.5 mm, recommended excision margin is 2 cm.
Adapted from Lens MB, Nathan P, Bataille V, et al. Excision margins for primary cutaneous melanoma: updated pooled analysis of randomized controlled trials. *Arch Surg* 2007;142:885–891.
UK, United Kingdom; WHO, World Health Organization.

melanoma: ≥1 mm in thickness and clinically normal regional lymph nodes by physical examination (60). Histopathologic and immunohistochemical assessment of the SLN improve the detection of clinically occult nodal metastases, thereby distinguishing patients who might benefit from immediate lymphadenectomy from those for whom this procedure is unlikely to be helpful. This procedure also identifies patients who might be candidates for clinical trials of adjuvant systemic therapy. Clinical trials are ongoing to determine the clinical value of a variety of molecular prognostic markers in melanoma patients undergoing SLN assessment (62,63).

METASTASES TO THE BREAST

The incidence rate of metastases to the breast from extramammary sites ranges from 1.7% to 6.6% in autopsy series and 1.2% to 2% in clinical reports (64,65). The most common presentation is the development of metastasis from the contralateral breast by a cross-lymphatic route, especially in premenopausal women. Other malignancies that can metastasize to the breast include non-Hodgkin lymphomas, leukemias, melanomas, lung cancer, gastric cancer, and ovarian cancer. Rare cases of metastases from fallopian tube cancer, ovarian dysgerminoma, renal cancer, medullary thyroid cancer, carcinoid, medulloblastoma, malignant schwannoma, and pharyngeal carcinoma have been reported (66–68).

Radiographic imaging using mammography and ultrasonography are not sufficient to determine whether a tumor is primary or metastatic. Skin thickening and axillary lymph node involvement may be apparent. A fine-needle aspiration and/or a core needle biopsy are needed to make the diagnosis. Pathologic assessment for metastases to the breast includes conventional histology, immunohistochemistry, cytogenetics, flow cytometry, and electron microscopy analysis. Clinically, it is important to differentiate bilateral primary tumors from metastatic tumors that coexist with a primary breast cancer. All suspicious lesions should be biopsied to clarify the overall diagnosis and treatment approach. Factors suggesting contralateral metastatic breast cancer include short disease-free interval, multiple breast lesions, and known metastatic breast cancer at other distant sites (68). Factors suggesting non-breast metastatic disease include location in fat or subcutaneous tissue as opposed to breast parenchyma, lack of *in situ* disease histologically, bilateral or multiple lesions, and lack of microcalcifications on mammography (64,69).

Metastatic breast cancer to the contralateral breast is treated with systemic therapy directed to the primary tumor. Palliative surgery and/or radiation therapy is often used for local control. If it is not clear whether the tumor is a primary breast cancer versus a metastasis, it should be treated with curative intent as a primary breast cancer. If the tumor is clearly metastatic but its origin is uncertain, treatment planning should take into account the most probable histologic diagnosis and primary site of the tumor as well as the potential efficacy of systemic treatments available for the presumed primary tumor. As metastases to the breast are rare and have diverse origins, a multidisciplinary approach is necessary to determine optimal treatment.

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CHAPTER 65

Breast Cancer during Pregnancy and Subsequent Pregnancy in Breast Cancer Survivors

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CHAPTER CONTENTS

INTRODUCTION

Pregnancy and fertility issues have become a significant concern for younger breast cancer patients. Young breast cancer patients can be faced not only with the diagnosis and treatment of their breast cancer, but also with concerns regarding fertility, future pregnancies and, for some, breast cancer diagnosis and treatment during pregnancy. Gestational or pregnancy-associated breast cancer (PABC) is defined as breast cancer that is either diagnosed during pregnancy or within 1 year postpartum. Since women seem to be delaying childbirth to later ages than in previous generations, the incidence of breast cancer and pregnancy, as well as the importance of future pregnancies subsequent to successful treatment for breast cancer, must be considered as part of the informed decision process when discussing treatment of breast cancer with younger women. Given this special situation and the amount of reports in the literature, national societies such as the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) have both issued guidelines on how to approach the treatment of the pregnant cancer patient. We will review the diagnosis and treatment of breast cancer and concurrent pregnancy, the prognosis for those treated during pregnancy, effects of treatment for children exposed to systemic therapies in utero and, for women with successfully treated primary breast cancer, the breast cancer prognosis in relation to future pregnancies.

EPIDEMIOLOGY: BREAST CANCER AND CONCURRENT PREGNANCY

Breast cancer and cervical cancer are the most commonly diagnosed malignancies during pregnancy. In a large retrospective population-based study in California between 1991 and 1997, there were 1.3 cases of breast cancer per 10,000 live births (1). In women under the age of 50 who are diagnosed with breast cancer, approximately 0.2% to 3.8% are diagnosed during pregnancy (2,3). As women delay childbearing, the incidence of breast cancer coinciding with pregnancy may increase since the frequency of breast cancer diagnosis increases with age (4). In a population-based cohort study based on the Healthcare Cost and Utilization Project—Nationwide Inpatient Sample (HCUP–NIS), Abenhaim et al. reported 573 breast cancers identified in 8,826,137 births over a 10-year interval. The 10-year incidence was noted to be 6.5 cases per 100,000 births. The diagnosis of breast cancer was more common among women over 35 years of age (5).

In patients with breast cancer with a recent past pregnancy, some retrospective analyses have shown a worse prognosis. In a multi-institutional retrospective case-control study, Guinee et al. (6) examined the impact of recent prior pregnancy on breast cancer outcome in a group of 407 women, aged 20 to 29, with breast cancer. The women were matched for age and stage of disease and had never been pregnant. For each 1-year increment in the time between the latest previous pregnancy and breast cancer diagnosis, the risk of dying decreased by 15% (relative risk 0.85, $p = .011$) (6). In a study of 540 patients from Memorial Sloan-Kettering Cancer Center, patients with previous childbirth within 2 years of the diagnosis of breast cancer also were shown to have a worse prognosis with an adjusted relative risk (RR) of dying from the cancer of 3.1 (7). Kroman et al. from Denmark noted an increased RR of dying from breast cancer for those women who had childbirth within 2 years of diagnosis. After adjusting for age, cancer characteristics and stage, a breast cancer diagnosis within 2 years of

childbirth was significantly associated with death (RR = 1.58, 95% confidence interval 1.24–2.02) compared to patients who gave birth more than 5 years before their breast cancer diagnosis (8). These studies were not able to control for delay in diagnosis, treatment, or treatment modalities of the breast cancer. Future translational research may help identify whether or not there is a true biologic difference in breast cancers diagnosed soon after pregnancy to account for these differences. A recent case-control study concludes that current or recent pregnancy is associated with adverse pathologic features but breast cancer survival is not impaired (9).

BRCA1 and *BRCA2* Mutation Carriers and Pregnancy

Women who are more susceptible to breast cancers at younger ages, such as those with deleterious mutations in the *BRCA1* or *BRCA2* genes may be overrepresented in the population of pregnant breast cancer patients. Few studies, with small numbers of patients, have evaluated the potential increased risk in hereditary breast cancer patients (10,11). Women with genetic predispositions to cancer, such as those with *BRCA1* and *BRCA2* deleterious mutations, tend to develop breast cancer at earlier ages and therefore may be more likely to have cancer diagnosed during childbearing years.

Potentially, the relationship of number of pregnancies and age of parity may be significant in *BRCA1* and *BRCA2* mutation carriers. Antoniou et al. evaluated 457 mutation carriers who developed breast cancer and 332 mutation carriers without a history of cancer. Parous *BRCA1* and *BRCA2* mutation carriers had a lower risk of developing cancer, but only among carriers who were older than 40 years of age (hazard ratio 0.54, 95% CI 0.37–0.81). Patients with an increased age at first parity had an increased breast cancer risk if a *BRCA2* mutation carrier, but not if they were a *BRCA1* mutation carrier (12). Kotsopoulos et al. performed a matched case-control study on 1,816 pairs of *BRCA1* and *BRCA2* mutation carriers, and showed that age at first parity did not influence the development of breast cancer in mutation carriers. Also they did not show a difference between *BRCA1* and *BRCA2* mutation carriers in univariate or multivariable models (13). An Icelandic study examining 100 *BRCA2* mutation carriers did not show a decrease in risk of breast cancer in *BRCA2* mutation carriers with increased number of births as has been seen in nonmutation carriers (14). Not only was the protective effect of parity modulated in these patients, but also, in a large matched case-control study comparing 1,260 pairs of women with known *BRCA* mutations, increasing parity was associated with an increased risk of breast cancer in *BRCA2* mutation carriers compared to nulliparous women (OR 1.53, 95% CI 1.01–2.32, $p = .05$). *BRCA2* mutation carriers who were under the age of 50, when compared to nulliparous *BRCA2* mutation carriers, had a 17% increase in adjusted risk of breast cancer with each additional birth (OR 1.17, 85% CI 1.01–1.36, $p = .03$) (15).

Given the risk of a deleterious mutation in women who develop breast cancer at an early age, genetic counseling should be part of the clinical discussion and evaluation for all such patients. Having children at an early age does not appear to provide the same protective effects in patients with deleterious *BRCA1* or *BRCA2* gene mutations as for those without mutations. In fact, recent parity may increase the risk of being diagnosed with breast cancer potentially more notably in those with deleterious *BRCA2* mutations.

DIAGNOSIS OF BREAST CANCER DURING PREGNANCY

Pregnant women with breast cancer tend to present with similar physical examination findings as their nonpregnant counterparts including a palpable mass or breast thickening. Due to the physiologic changes in the breast that occur during pregnancy and lactation, including increased size and density of the breast tissue, there may be a delay in diagnosis of breast cancer as these physiologic changes can obscure detection (10). Pregnancy-associated physiologic changes in the breast may be even more pronounced in patients under the age of 30 (16). Therefore, women diagnosed with breast cancer during pregnancy often present with an advanced tumor stage and axillary lymph node involvement. Given the concern for delay of diagnosis, palpable masses or breast distortions persisting over 2 weeks should be investigated.

EVALUATION OF BREAST MASSES DURING PREGNANCY

Imaging of the Breast during Pregnancy

Mammography: Mammography should be ordered in pregnancy with abdominal shielding. With mammography the fetal radiation exposure is estimated to be 0.4 mrad (17). This level is substantially below the level of 5 rad, a level at which multiple studies have shown no known increase in congenital malformations or growth retardation (18).

Ultrasonography: Ultrasound (US) can distinguish between cystic and solid breast masses in approximately 97% of cases with no radiation exposure. One study diagnosed 100% of the breast masses as well as axillary metastases in 18 of 20 women (19). Ultrasound was also shown to be effective for evaluating response to preoperative chemotherapy in the pregnant breast (19).

Breast MRI: Magnetic resonance imaging (MRI) has not been studied for the diagnosis of a breast mass in pregnant or lactating women. Gadolinium-enhanced MRI may be more sensitive than conventional mammography; however, data regarding the safety of gadolinium during pregnancy are limited. Gadolinium has been shown to cross the placenta and be associated with fetal abnormalities in animal models (20,21). Animal studies have shown diverse fetal effects and gadolinium is considered a pregnancy category C drug (Table 65-1). There have been no controlled human studies to date, however; several studies have observed no significant toxicity when gadolinium has been given during human pregnancy. But there does remain some controversy as to the safety of gadolinium during pregnancy and therefore should be used with caution.

Staging and Diagnosis of Breast Cancer during Pregnancy

Biopsy

Any clinically suspicious breast mass requires biopsy, even if the ultrasound and mammogram are equivocal or nondiagnostic. Fine-needle aspirate (FNA) in the pregnant breast is well established. While FNA may provide cytologic confirmation of cancer, core biopsy is preferred because it can confirm invasive disease and provide tissue for biologic

TABLE 65-1

U.S. FDA Pregnancy Category Definitions

A	Controlled studies in women fail to demonstrate a risk to the fetus in the first trimester, and the possibility of fetal harm appears remote.
B	Animal studies do not indicate a risk to the fetus and there are no controlled human studies or animal studies to show an adverse effect on the fetus, but well-controlled studies in pregnant women have failed to demonstrate a risk to the fetus.
C	Studies have shown that the drug exerts animal teratogenic or embryocidal effects, but there are no controlled studies in women, or no studies are available in either animals or women.
D	Positive evidence of human fetal risk exists, but benefits in certain situations (e.g., life-threatening situations or serious diseases for which safer drugs cannot be used or are ineffective) may make use of the drug acceptable despite its risks.
X	Studies in animal or humans have demonstrated fetal abnormalities or there is evidence of fetal risk based on human experience, or both, and the risk clearly outweighs any positive benefit.

marker evaluation. Core or excisional biopsies can be performed safely with local anesthesia, with only one found report of the development of a milk fistula after a core needle biopsy (22).

Pathology of Breast Cancer Diagnosed during Pregnancy

The majority of breast cancer cases are infiltrating ductal adenocarcinomas with one prospective cohort showing 84% with poorly differentiated tumors (23). When compared to nonpregnant premenopausal women, pregnant patients are reported to have tumors with a lower frequency of ER and/or PR expression (23–26). Amplification of *HER2/neu* is seen in approximately 20% to 30% of breast cancers. In some series, *HER2/neu* amplification has been reported to be disproportionately amplified in pregnant patients (up to 58% vs. 16 % in nonpregnant counterparts) (27); however, another series show similar *HER2/neu* amplification (28%) in pregnant and nonpregnant patients (23).

Staging Evaluations during Pregnancy

The American Joint Committee on Cancer (AJCC) TNM staging system is used and, along with tumor biologic characteristics, forms the basis for treatment decisions. Staging procedures may need to be modified for the pregnant breast cancer patient with safety considerations for both the patient and the fetus. Staging is important, however, for better understanding of the full extent of disease, informing treatment recommendations, considering the potential influence of the treatment on cancer outcome and the potential impact of cancer treatment on the fetus and pregnancy. Radiation exposure for the fetus and outcomes regarding different imaging modalities are available (28).

Guidelines have been established regarding imaging and staging during pregnancy (29,30). A recent practice patterns analysis recommends an algorithm that pregnant patients with breast cancer be considered for chest CT scan if pulmonary metastases are suspected and that MRI of the abdomen and pelvis along with a bone scan may be considered if metastases at these sites are suspect (31). However, staging procedures need to be tailored to minimize fetal radiation exposure, provide adequate information to determine disease stage, and provide sufficient knowledge for informed decisions for clinicians and patients. Recommended initial staging should include the following: complete history and physical examination with special attention to breast and nodal basin examinations; comprehensive metabolic panel; and complete blood count with differential. It is important to note that pregnant patients may have anemia due to the increase in circulating plasma volume. They may have increases in serum alkaline phosphatase level that can be doubled or tripled due to the pregnancy itself. The physical examination of the breast and nodal basins needs to include tumor measurements when possible and an assessment of extent of clinical nodal involvement. Given that the sites of breast cancer metastases are most commonly bone, liver, and lung, these areas should be evaluated in the pregnant breast cancer patient who has a clinical stage II or higher breast cancer as is done in nonpregnant patients. These staging evaluations may include chest x-ray with abdominal shielding; echocardiogram prior to the use of an anthracycline-based chemotherapy regimen; ultrasound of the liver; and a screening noncontrast MRI of the thoracic and lumbar spine to exclude bone metastases. If there are concerns of liver metastases after ultrasound examination, an abdominal non-gadolinium-enhanced MRI may be considered, especially since the liver may tend to have fatty-replacement during pregnancy. Noncontrast MRI has been used routinely and safely in the pregnant patient for staging. CT scans and bone scans are not recommended for routine use due to concerns of excessive fetal radiation exposures (29). Radionuclide scanning, including bone scanning, has very limited safety data in the pregnant patient, and should be considered only if absolutely necessary with aggressive hydration and frequent voiding.

Locoregional Therapy

Surgery and Anesthesia

Breast surgery can be safely performed in all trimesters of pregnancy; however, patients and surgeons may choose to wait until after the 12th week of gestation when the risk of spontaneous abortion may be lower (29). Multiple studies evaluating the risks of anesthesia during pregnancy have not shown an increase in fetal abnormalities. Mazze and Kallen reported on a registry of 5,405 pregnant patients who had any kind of surgery during pregnancy. They observed no difference in the risk of fetal malformation when they compared the pregnant group to 720,000 women who did not have a surgical procedure during pregnancy. There was no difference in outcomes in women who had their surgeries in

the first trimester. There was, however, an increase in the frequency of low- and very-low-birth-weight infants. This was attributed to the underlying illness or trauma necessitating the surgery (32). In a Canadian report of 2,565 pregnant women who underwent surgery, Duncan et al. reported no increase in fetal abnormalities compared to a control population of pregnant women who did not have an operation (33). A recent review of surgery in the pregnant patient recommends that the preferred timing for surgical intervention is 16 to 20 weeks of gestation (34).

Although in the majority of published reports patients opt for mastectomies for breast cancer treatment due to concerns regarding radiation therapy, breast-conserving surgery is an option, especially in women in the third trimester of pregnancy who can receive radiation therapy after delivery. With the potential of preoperative chemotherapy during pregnancy, breast-conserving surgery can be done later in the pregnancy or after delivery (35).

Safety and efficacy of sentinel lymph node biopsies is currently an area of clinical interest. The sensitivity and specificity of sentinel lymph node biopsies in the pregnant woman with breast cancer has not been well established. Estimated radiation exposure to the fetus is low and calculated to a maximum of 4.3 mGy (36). However, isosulfan blue dye mapping is not recommended due to concerns of unknown effects for the fetus as well as risk of anaphylaxis for the patient. Sensitivity of sentinel lymph node mapping may be significantly decreased without using isosulfan blue. The concern with sentinel node procedure in the pregnant patient is not the technical aspects of the procedure but the accuracy of the diagnostic information obtained as a result of the procedure. Sentinel node excision has not been subjected to the same rigorous study in the pregnant population as in the nonpregnant population (37). Therefore prudent and careful clinical evaluation prior to the procedure is warranted.

Radiation Therapy

Completion of appropriate locoregional therapy should be obtained despite the diagnosis of cancer during pregnancy. If the patient meets criteria for postmastectomy radiation therapy or they have had breast-conserving surgery, radiation therapy should be administered and this is recommended only after delivery of the fetus. Radiation exposure during pregnancy may result in fetal death, malformations, growth and/or mental impairment, and induction of cancers or hereditary defects. Although actual radiation exposure at the time of treatment may be limited, a significant portion of fetal exposure can occur from internal radiation scatter from the mother, for which abdominal shielding may be ineffective. The quantity of radiation exposure to the fetus is dependent upon the energy source, field size, and distance of the fetus from the field center (38). The fetus is at the highest risk of damage to organogenesis in the first trimester and with each successive trimester would be exposed to a higher proportion of the standard 50 to 60 Gy used (18).

Information regarding clinical outcome for radiation exposure during pregnancy is limited to small series of patients treated for hematologic malignancies. Woo et al. from MD Anderson Cancer Center reported on 16 patients with Hodgkin disease treated with 3,500 to 4,000 cGy while in the second and third trimesters. This is approximately three-fourths of the total breast cancer treatment dose (39). All 16 of these women delivered normal full-term infants. Antolak and Strom reported a case of locally recurrent breast cancer treated with electron-beam radiation to the chest wall during pregnancy with a simulated fetal dose exposure with abdominal shielding to be less than 1.5 cGy (40).

Systemic Therapy

Chemotherapy

Systemic chemotherapeutic agents are designed as antiproliferative drugs. The U.S. Food and Drug Administration (FDA) delineates drugs by pregnancy risks into categories of risk describing safety for mother and fetus. Categories A and B agents generally felt to be safe for use in pregnant patients, with Category C reporting some teratogenic or embryocidal effects in animal studies but no information in humans. Category D describes positive evidence of human fetal risks (Table 65-1). Although most chemotherapeutic agents are Category D, there are data demonstrating that systemic chemotherapy can be given safely during pregnancy during the second and third trimester. Clinical consideration for the use of systemic therapies should be similar in pregnant and nonpregnant patients. Despite limited knowledge regarding pharmacokinetics of chemotherapeutic agents in breast cancer due to the physiologic changes of pregnancy (increased plasma volume, altered renal and hepatic function, and third spacing potential), several published patient cohorts have described successful administration of chemotherapies to pregnant breast cancer patients. Published reports demonstrate that first trimester chemotherapy exposure is associated with a 14% to 19% risk of fetal malformations while second and third trimester exposure is significantly safer with a fetal malformation risk of 1.3% (41). It is not recommended that chemotherapy be administered during the first trimester. Additionally, antifolates such as methotrexate have been shown to carry higher risks of teratogenesis and methotrexate is a known abortifactant (41). Therefore methotrexate and methotrexate-containing regimens such as CMF generally are not given during pregnancy.

Anthracycline-Based Chemotherapy

There are numerous case reports and series regarding different chemotherapeutic agents given during pregnancy, mostly with anthracycline-based regimens. MD Anderson Cancer Center has the largest prospective cohort of pregnant breast cancer patients treated on a standardized protocol with one published update of this ongoing prospective trial in 2006 (42). Fifty-seven women were treated with 5-fluorouracil 500 mg/m^2 intravenously on days 1 and 4, doxorubicin 50 mg/m^2 given by continuous infusion over 72 hours, and cyclophosphamide 500 mg/m^2 given intravenously on day 1 (FAC). A median of 4 cycles were administered during pregnancy. Patients were dosed upon actual weight at each visit and not dose adjusted from baseline (early pregnancy or nonpregnant) weight. Premedications included standard doses of dexamethasone, lorazepam, and ondansetron. Depending on the week of gestation at the time of delivery, most women receive four to six cycles of FAC chemotherapy during pregnancy. Chemotherapy should be held after the 35th week of pregnancy in order to avoid the potential for neutropenia at the time of delivery. All women who delivered had live births. One child has Down syndrome and two have congenital anomalies (club foot, congenital bilateral ureteral reflux). The children are healthy and those in school are doing well, although two children, including the child with Down syndrome have special educational needs. One mother died from a pulmonary embolus after a cesarean delivery (42).

Multiple retrospective case reports and series have been reported in the literature. Those with the greatest number of patients treated with chemotherapy during pregnancy are highlighted (Table 65-2).

The most recent report is from a multi-institutional, European registry that included 413 pregnant patients (43).

TABLE 65-2

Breast Cancer and Pregnancy: Tumor Stage, Number of Nodes, Histology, Differentiation, and Receptor Status

Reference	*T Stage (%)*	*Nodes (%)*	*Differentiation (%)*	*Histology (%)*	*Receptor Status (%) of tumors*	*Her-2/neu (%)*
Giacalone et al. (74) *n* = 20	I 5 II 40 III 30 IV 25	0 25 1–3 15 ≥4 15 Unknown 45	Grade 3 75 Grade 2 25 Grade 1	Ductal 100	ER+ 30 ER- 45 ER unknown 25	Not given
Healy et al. (75) *n* = 11	I — II 36 III 45 IV 18	N1 75	Not given	Ductal 90	Not given/ assessed	Not given
Ring et al. (76) *n* = 24 7 patients with NC 17 patients No NC	NC–mean tumor size 6 cm No NC–mean tumor size 3.6 cm	NC–(43% node+, 4 unknown) No NC (88% node+, 2 unknown)	Grade 3 (71) Grade 2 (25)	Ductal 79	ER+ 46 ER- 33 ER unknown 21	Positive 21 Negative 29 Unknown 50
Hahn et al. (42) *n* = 57	Clinical Stage[a] I II 53 III 38 IV	70% node positive	Grade 3 (82) Grade 2 (16)	Ductal 85 Other 15	ER- or PR- 69	29 of those evaluated
Loibl et al. (43) M0 patients with chemotherapy during pregnancy (*n* = 197)	1 17 2 51 3 21 4 a–c 10 4d 2	Neg 37 Pos 63	Grade 1 (2) Grade 2 (19) Grade 3 (79)	Ductal 98 Lobular 2	ER- or PR- 54 ER+ or PR+ 47	Negative 51 Positive 29

[a]Of the 32 patients who received surgery prior to chemotherapy. An additional 25 patients received neoadjuvant chemotherapy and were more likely (56% v. 38%) to have a stage III disease at diagnosis.
NC, neoadjuvant chemotherapy.

Chemotherapy consisted of a variety of regimens including taxanes, CMF and anthracyclines, all administered after the first trimester. The authors reported lower birthweight for infants exposed to chemotherapy in utero and they noted more complications than for those without fetal exposure. In this report preterm birth was associated with adverse events, prompting the authors to recommend that efforts to reach full-term delivery be emphasized.

Data describing the safety and use of dose-dense anthracycline-based regimens with or without taxanes during pregnancy have recently been reported by Cardonick et al. They reported on data of 10 women who received dose-dense Adriamycin/Cytoxan followed by taxane therapy during pregnancy. This group was compared with 99 patients who received "conventional" chemotherapy. Clinical chart review was used to confirm the accuracy of the data reporting for this voluntary registry study of chemotherapy exposure during pregnancy. The authors concluded that the risks of low birth weight, fetal anomalies, age at delivery, and maternal/fetal hematolgic complications did not differ between the two groups (44).

Taxane Therapy

There are case reports describing the use of taxanes (paclitaxel and docetaxel) during pregnancy. However, the use of taxanes is often delayed until after delivery due to the limited safety data during pregnancy. There are multiple case reports in the literature describing the use of taxanes during breast cancer with no apparent deleterious effects on the fetus. Zagouri et al. have conducted and reported a systematic review of taxane use for treatment of breast cancer during pregnancy. They gathered data from 50 patients and reported fetal and delivery outcomes. All patients received taxane after the first trimester. The authors noted that 77% of the neonates were "completely healthy at delivery" at mean 36 weeks. At 16 months of follow-up 90% of the infants were reported to be "completely healthy" (45). As the data continue to accrue regarding the use of taxanes during pregnancy, taxanes may become more frequently used as treatment during the second and third trimesters. The Zagouri et al. data along with the reports of taxane use during pregnancy in other malignant conditions provide some reassurance of fetal safety for use of taxanes during the second and third trimesters of pregnancy.

Biologic Agents

There have been multiple reports of trastuzumab administration during pregnancy. No fetal abnormalities have been reported; however, anhydramnios with its use has been described in 6 of the case reports and fetal death has been noted (46–52). One of the children born developed respiratory failure, capillary leak syndrome, infections, and

necrotizing enterocolitis and died from multiple organ failure 21 weeks after delivery (51). One report describes reversible heart failure in the mother but no anhydramnios in the fetus (49). Bader et al. described reversible renal failure in the fetus (52). Azim and colleagues reported on the data of trastuzumab exposure and pregnancy from the HERA trial. They grouped patients with regard to timing of tratuzumab exposure: pregnant during or within 3 months of exposure, pregnant more than three months after trastuzumab exposure, and those with pregnancy and no trastuzumab exposure. In the first group there were 16 pregnancies but only 5 continued to delivery (there were 4 spontaneous abortions and 7 induced abortions). Of those with live births there were no congenital anomalies and no reported episodes of oligohydramnios. All had term deliveries (53). Lapatinib exposure has also been described in a patient who conceived while on lapatinib. Despite approximately 11 weeks of in utero exposure, the pregnancy was uncomplicated with delivery of a healthy baby (54). Data on exposure to pertuzumab and TDM -1 have not been reported thus far. Given the very limited data of biologic agent use during pregnancy, it is recommended that they not be used as part of standard adjuvant treatment protocols.

Endocrine Therapy

Endocrine therapy, if indicated, should be initiated after delivery and completion of chemotherapy. Although there are case reports of fetal exposure to tamoxifen without with fetal damage, there are others that have reported Goldenhar syndrome (microtia, preauricular skin tags, and hemifacial microsomia) (55), ambiguous genitalia, and other birth defects as well as reports of vaginal bleeding and spontaneous abortion (29,56,57). Aromatase inhibitors are not indicated for use in premenopausal women.

Other Systemic Agents

Commonly used antiemetics are rated as pregnancy risk category C. Newer agents such as ondansetron and granisetron are rated as pregnancy risk category B and are used to manage nausea in pregnant women receiving chemotherapy. Dexamethasone also can be used for short-term for nausea prophylaxis but long-term exposure is not recommended. For neutropenia prophylaxis, there are no randomized trials evaluating the use of G-CSF (filgastrim)or GM-CSF in pregnant breast cancer patients, but G-CSF has been used in neonatal neutropenia and/or sepsis and safe use in pregnancy has been reported (58). There are no data regarding pegfilgastrim in pregnancy.

MONITORING THE PREGNANCY

Patients should be referred directly to a high-risk obstetrician. Evaluation of fetal viability prior to the initiation of therapy and confirmation of the age of the fetus must be determined prior to administering any systemic therapy. Frequent visits with well-coordinated communication among the patient, medical oncologist, surgical oncologist, and obstetrician are required. Obstetrical monitoring may include frequent ultrasonography, fetal nonstress testing, and biophysical profiles. When clinically appropriate, amniocentesis can be performed. Consideration of the timing of delivery is also important with the last administration of chemotherapy to be no less than 2 weeks from estimated date of delivery. This may minimize the risk of neutropenia for both the mother and the neonate. Pregnancy-related complications including preecclampsia and preterm labor should be treated according to standard care guidelines. Planned induction of labor or cesarean deliveries are often performed to avoid these complications (29). Of note, the MD Anderson case series had 51% vaginal deliveries (42).

BREAST-FEEDING

Many chemotherapeutic agents are excreted in breast milk and neutropenia in an infant breast-fed during maternal treatment with cyclophosphamide has been described (58,59). Therefore, breast-feeding during administration of chemotherapy, biologic therapy, endocrine therapy, and radiation therapy should be avoided.

PROGNOSIS

Many series describe advanced disease stage at diagnosis for pregnant versus nonpregnant patients. The advanced stage at diagnosis as well as delays in diagnosis and initiation of treatment may account for the apparently worse prognosis for breast cancer diagnosed during pregnancy. There are, however, some mixed results reported when comparing pregnant and nonpregnant patients.

Ribiero et al. reported on a series of 178 patients with pregnancy-associated breast cancer. One hundred twenty-one women had breast cancer during pregnancy and there was a significant decrease in survival. These women with pregnancy-associated breast cancer presented with more advanced disease including 72% with node-positive disease. Per the authors, the majority of patients received treatment postpartum and there was no description of any chemotherapy given during pregnancy (60).

Tretli et al. described 35 patients from 1954 to 1981 and matched the patients for age and disease stage at diagnosis. Twenty were diagnosed during pregnancy and 15 during lactation. The median diagnosis delay during pregnancy was estimated at 2.5 months and 6 months in the lactating group, with an RR of death for breast cancer patients diagnosed during pregnancy of 3.1 ($p < .05$). However, treatment and delay of treatment were not described in this case-control study (61). An additional retrospective multi-institutional study by Bonnier et al. evaluated 154 patients diagnosed with breast cancer between 1960 and 1993 either during pregnancy or within the first 6 months postpartum and found that breast cancer during pregnancy was an independent and significant prognostic factor for worse outcome (25). Chemotherapy was administered to some of these women; however, chemotherapies used and the time delays in starting chemotherapy were not addressed.

Other recent case-control studies cannot confirm a difference in prognosis. A case-control study from Saudi Arabia matched 28 pregnant women by age and stage of disease with 84 nonpregnant women. Adjuvant chemotherapy was given to 23 of the pregnant patients. No difference in overall or relapse-free survival was found (62). Several other studies also have shown pregnancy at the time of diagnosis is not an independent worse prognostic factor. In a Toronto-based study, there was no statistically significant difference in survival between these groups when matched for age, stage, and year of diagnosis (63). Several other studies, including one from Japan (10) and New Zealand (64), show similar results. A case-control study of pregnant women with breast cancer has been reported from MD Anderson Cancer Center. Litton et al. analyzed the outcomes of 75 pregnant women with breast cancer matched with two controls with matching on age, disease stage at diagnosis, histology, hormone receptor and *HER2/neu* status, and year of diagnosis. Disease-free and overall survival were calculated for the two groups, and were comparable . Hazard ratio estimates

actually favored improved survival for the pregnant population (65). Although some studies show a worse prognosis for pregnancy-associated breast cancer, those studies that diagnosed and treated breast cancer during pregnancy with local and systemic therapy did not show the same worse survival as older studies in which treatment often was not given until after delivery. Although many of the studies describe a worse prognosis for those women diagnosed with breast cancer in the first few months and years after a pregnancy, the grouping of women diagnosed during and after pregnancy may confound these overall results.

CONSIDERATION OF PREGNANCY TERMINATION

The decision to terminate or maintain a pregnancy is a highly personal decision that a fully informed woman should make in conjunction with her physician. Early data suggested that the combination of breast cancer and pregnancy was nearly lethal and that termination of pregnancy was warranted and even showed some possible improvement in patient survival (66). Gradually, the data regarding termination in this group of women that have emerged have shown that early termination of pregnancy does not been improve the outcome of pregnancy-associated breast cancer (67). There are two reports suggesting that early termination may have decreased patient survival (68,69). Although termination does not appear to improve survival or response to anthracycline-based therapy, some women may choose termination when diagnosed with an advanced cancer in the early weeks of pregnancy depending on their perceptions of the risks, harms, and burdens of treatment for themselves and the fetus, the viability of the fetus, and the presence or absence of detected fetal malformations.

SHORT- AND LONG-TERM COMPLICATIONS FOR THE CHILD

There is a paucity of data regarding the short-term and long-term effects of treatment for children exposed to chemotherapy for breast cancer in utero. The largest single prospective dataset reported for breast cancer during pregnancy is from the MD Anderson Cancer Center. Immediately after delivery, there may be early and reversible fetal toxicities from chemotherapy. These can include anemia, neutropenia, and alopecia. In the prospective series from MD Anderson Cancer Center, there were no miscarriages, stillbirths, or perinatal deaths. The majority of the children did not have significant neonatal complications and the frequency of complications appeared to be similar to the general population of neonates. The most common complication was difficulty breathing in 10%, and one child born at 38 weeks gestation had a subarachnoid hemorrhage 2 days postpartum. The age of children at the time of health survey ranged from 2 to 157 months. One child had Down syndrome and 2 children had congenital abnormalities (club foot, bilateral ureteral reflux). Overall, the children were healthy with 2 of the 40 children described having special educational needs (42).

Much of the children's health and outcomes data are derived from case reports of children exposed to chemotherapeutic agents for hematologic malignancies in the mother. A large study from Mexico described 84 children with follow-up of 18.7 years born to women who received chemotherapy in utero for hematologic malignancies. This review did not report any significant physical, neurologic, or psychological abnormalities (70,71). Reyonoso et al. described 7 cases of 8 children exposed in utero to chemotherapy for acute leukemia with follow-up ranging from 1 to 17 years. One of the children in a twin pregnancy was born with multiple congenital malformations and eventually developed a neuroblastoma and thyroid cancer. The other 7 children have had normal growth and development and malignant diagnoses (72). Cardonick et al. reported from a self-reporting national registry of 113 deliveries to women who received chemotherapy during pregnancy and reported a malformation rate of 3.8%, which is not higher than that reported in the general population (73).

Further evaluations of neurocognitive and cardiac function as well as prospective evaluation for future malignancies and reproductive history will need to be continued for children who have been exposed to chemotherapy in utero.

MANAGEMENT SUMMARY

The treatment of pregnancy and breast cancer should include a multidisciplinary approach with active communication among the patient, obstetrician, medical, surgical, and radiation oncologists. Appropriate diagnosis, biopsy, and imaging direct this multidisciplinary approach which can include surgery as well as preoperative or adjuvant systemic chemotherapy.

Radiation therapy and several biologic and endocrine therapies should be postponed until after delivery. Continued evaluation of the children exposed to chemotherapeutic agents in utero is warranted.

Management recommendations for the pregnant breast cancer patient are as follows:

Diagnosis

- Physical examination including nodal basins, mammography and breast and nodal basin ultrasound Biopsy core needle preferred.
- Breast imaging that includes physical examination, mammography, breast ultrasound.
- Staging that may include noncontrast MRI thoracic and lumbar spine and ultrasound based imaging.
- Pathology review that includes biomarkers.
- Genetics counseling.

Surgery

- Surgical management for breast cancer either with mastectomy or lumpectomy.
- Axillary lymph node dissection for clinically or cytologically involved nodes. Sentinel node excision based on a case-by-case clinical decision process.

Monitoring of pregnancy

- Maternal–fetal medicine evaluation of fetal growth and development.

Systemic therapy

- Chemotherapy with an anthracycline-based regimen may be considered after the first trimester and prior to the 35th week of pregnancy. Most of the data reported are with every 3-week doxorubicin given over a 72-hour infusion, such as in the FAC regimen. Taxanes have limited safety data but may be considered on a

case-by-case basis. Trastuzumab has been associated with oligo, and anhydramnios and should be avoided during pregnancy. Biologic agents should be avoided.

Radiation therapy

- To be completed after delivery as per standard guideline recommendations.

Communication

- A multidisciplinary approach to management emphasizing communication among the medical oncologist, surgical oncologist, radiation oncologist, and maternal–fetal specialist is necessary.

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CHAPTER 66

Occult Primary Cancer with Axillary Metastases

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CHAPTER CONTENTS

Breast cancer can sometimes present as an isolated axillary adenopathy without any detectable breast tumor by palpation or radiologic examination. These occult primary cancers are staged as T0, N1 (stage II in the Union Internationale Contre le Cancer/American Joint Committee classification). This staging requires that proper clinical *and* mammographic investigations be done to rule out the presence of a small breast tumor. If this is accomplished, axillary metastases of occult breast primary cancer represent a rare clinical entity first described by Halsted in 1907 (1).

FREQUENCY

The incidence of an occult primary tumor with axillary metastases is low. Incidence rates ranged from 0.10% to 1.0% of operable breast cancers in the largest reported series (2,3). Less than 1,500 cases have been reported in the literature since the 1950s. Because these series are limited and management policies have varied widely during this period, comparing characteristics of the patients, management, and results of treatment is difficult. Many of these patients had suspicious mammograms (4–6). Presumably, the constant improvement of the quality of mammography and ultrasonography as well as the use of magnetic resonance imaging (MRI) has decreased the rate of occult primary tumor with axillary metastases. Interpretation of these comparisons should only be done with caution.

The characteristics of the patients with T0, N1 breast cancer are similar to those of patients with typical stage II disease. The series from the Institut Curie included 59 patients treated between 1960 and 1997. The median patient age was 57 years (range, 36 to 79 years). Thirty-four patients (58%) were postmenopausal, including two patients under hormone replacement therapy. Fifteen patients (25%) had family histories of breast cancer. Twenty-eight (47.5%) had left axillary nodes, and 31 (52.5%) had right axillary nodes.

DIAGNOSIS

Axillary Adenopathy

Isolated axillary adenopathy is a benign condition in most patients. Lymphomas are the most frequently occurring malignant tumors. Adenocarcinoma in areas other than the breast may include thyroid, lung, gastric, pancreatic, and colorectal cancer (7). These tumors, however, rarely have isolated axillary metastases as the only presentation of disease. Although in the past an extensive search for primary adenocarcinoma other than breast cancer was not recommended (6,8,9), these patients, nowadays, usually have computed tomography (CT) scans of the chest and abdomen for evaluation of metastases. In addition, tumor markers may help in the diagnosis of metastatic colon or pancreatic cancers.

Axillary adenopathy usually consists of one or two involved nodes, sometimes with large diameters. The median axillary node size at presentation in the patients treated at the Institut Curie was 30 mm (range, 10 to 70 mm). The initial diagnosis of malignancy was achieved by node excision in 25 of 59 patients, by fine-needle aspiration in 26 patients, and by core-needle biopsy (drill biopsy) in 8 patients.

A primary breast cancer located in the axillary tail of the breast may be confounded with an axillary node. The presence of normal lymph node structure surrounding the foci of the carcinoma on the pathologic sample usually leads to the diagnosis of metastasis to a lymph node. The recognition of a metastatic lymph node can, however, be difficult because of massive involvement, with extension of the tumor into the axillary fat and disappearance of the lymphoid patterns.

Breast Cancer

Bilateral mammography should always be performed in the presence of metastatic adenocarcinoma in an axillary lymph node. Baron et al. (4) report an overall 44% accuracy in the diagnosis of occult breast cancer in a series of 34 patients, in which only nine mammographies were considered suspicious. Many of these tumors are missed owing to their relative small size and the fact that they are obscured on the mammogram by dense fibroglandular tissue (10). Nonetheless, any suspicious image should be removed for pathologic analysis.

Mammography and ultrasound have been the primary modalities for the diagnosis and the workup of breast cancer (10). Promising results were published of the use of MRI in characterizing nonpalpable, but radiologically detectable, breast lesions in patients (11,12). In patients with T0,

TABLE 66-1

Detection of Occult Breast Cancer with MRI

		Suspicious Lesions on MRI	
Author (Reference)	*No. of Patients*	*N*	*%*
Morris et al. (14)	12	9	75
Orel et al. (15)	22	19	86
Olson et al. (16)	40	28	70
Obdeijn et al. (17)	20	8	40
Buchanan et al. (18)	55	42	76
McMahon et al. (19)	18	14	78
Ko et al. (20)	12	10	83
Barton et al. (21)	20	7	35

N1 breast cancer, studies have shown that MRI could detect early contrast-enhanced images in the breast. A systematic review of 7 published studies estimated that breast MRI had a 90% sensitivity and a 31% specificity in detecting the primary cancer in the breast (13). The high sensitivity of breast MRI suggests that it could be used systematically in searching for a breast primary tumor. The results of several studies of MRI in patients with occult breast cancer are shown in Table 66-1. However, because of its low specificity and the difficulties in localizing small, early contrast-enhancing foci in some instances, difficult management problems may occur. The use of MRI-directed sonographic, mammographic, or scanographic guidance (17) can help to localize the breast tumor in most patients. MRI-guided localization and biopsy can be performed (22). At the Institut Curie, 15 patients with metastatic axillary nodes, negative breast clinical examination, and without any mammographic target had breast MRI between 1997 and 2000. Early contrast-enhanced images were detected in 14 of the 15 patients (93%). A surgical excision was performed in 11 patients: in 4 patients, a second MRI-guided ultrasound examination was able to disclose and localize the breast lesion; in 3 patients localization was achieved with an orthogonal mammogram, because of the superficial localization of the lesion and the small size of the breast; and finally in 4 patients the lesion was localized using CT-scan with bolus injection. Invasive breast cancer was found in 9 of the 11 patients (82%) who underwent surgery. There is limited published experience with the use of 18F-FDG PET/CT imaging in the specific setting of occult breast cancer with axillary adenopathy (23,24). However, though it has a high specificity when detecting breast lesions, its sensitivity is low, particularly in small tumors (25). Other new breast imaging procedures are under investigation in breast cancer diagnosis (reviewed in 26): they include ionizing techniques such as scintigraphy with specific radiotracers (MIBI), non ionizing radiation imaging techniques such as color Doppler sonography (27), and optical imaging and optical imaging with fluorescent dyes coupled to probes (28). No experience has been so far reported on the use of these new techniques in the diagnosis of occult breast carcinoma.

In patients who have nonpalpable breast masses and normal imaging workup, the mammary origin of a metastatic adenocarcinoma to an axillary lymph node cannot be established with certainty. Therefore, the diagnosis of occult breast cancer can only be highly presumed based on many elements, including sex, age, isolated adenopathy, and histologic diagnosis of adenocarcinoma.

High estrogen or progesterone receptors levels found in the metastatic axillary nodes can help to confirm a primary breast tumor (29); however, three series (4,30,31) reported that 50% to 86% of occult breast cancer cases were found to be negative for estrogen receptors. Because surgical excision of the palpable node was often the first diagnostic procedure, rarely was an attempt made to analyze the receptors by biochemical methods. In a series of 80 patients with occult breast cancer and axillary metastases, Montagna et al. (32) performed the immunohistochemical analysis of estrogen (ER) and progesterone (PR) receptors, and HER2 protein on the metastatic axillary nodes. They found that 46 (58%) were ER negative and PR negative (no expression), and 20 (25%) were HER2 positive. Using these as surrogate markers of biological subtypes, they found 14 (17.5%) luminal A (ER/PR positive, HER2 negative), 6 (7.5%) luminal B (ER/PR positive, HER2 positive, 28 (35%) HER2 enriched (ER and PR negative, HER2 positive), and 31 (39%) triple negative.

Natural History

After removal of an axillary adenopathy, a breast cancer eventually developed in the untreated breast in an average 42% of patients, as reported in one review (2), with time intervals below 5 years in all cases. Patient samples were limited in these series, however, and follow-up periods varied widely. In the Royal Marsden series (33), 10/13 patients (77%) who had negative breast imaging including mammography, ultrasound, and MRI, and no breast treatment, have recurred in the ipsilateral breast at 68 months median follow-up.

The number of pathologically involved lymph nodes seen after axillary dissection is high. Table 66-2 summarizes the results in five series, reporting a median number of involved nodes was close to three. Forty patients in the Institut Curie series had an axillary dissection as initial treatment. The median number of involved nodes was 3 (range, 1 to 20). During follow-up, 16 of the 59 patients in the series had distant metastases: 4 (25%) in the brain, 5 (31%) in the liver, 3 (19%) as cervical nodes, and 3 in multiple sites. One patient had isolated bone metastases. Ten patients had contralateral disease, which occurred in the contralateral breast alone in 6 patients. Of note, 4 patients had isolated contralateral axillary node metastases.

Treatment and Results

Mastectomy with axillary node dissection has been the most commonly used treatment in patients with occult primary tumors. The combined analysis of 10 published series has shown that breast cancer was found in the mastectomy specimen in 147 of 210 patients (70%) (Table 66-3). Invasive tumors were found in 36 of 210 patients (65%).

TABLE 66-2

Occult Breast Cancer Number of Involved Axillary Nodes

		% Involved Axillary Nodes	
	No. of Patients	*pN1–3*	*pN>3*
Merson et al. (31)	46	50	50
Montagna et al. (32)	80	53	47
Barton et al. (21)	34	47	53
Rosen et al. (33)	40	50	50
Wang et al. (34)	51	57	43

TABLE 66-3

Pathologic Report After Mastectomy

Investigators (Reference)	*Years*	*Patients with Mastectomy*	*In Situ Carcinoma*	*Invasive Carcinoma*	*Carcinoma (%)*
Ashikari et al. (5)	1946–1975	34	3	20	67
Bhatia et al. (29)	1977–1985	11	2	9	100
Baron et al. (4)	1975–1978	28	4	16	71
Ellerbroek et al. (30)	1944–1987	13	0	1	8
Fitts et al. (8)	1948–1963	11	0	7	70
Haagensen (35)	1916–1966	13	0	12	92
Kemeny et al. (9)	1973–1985	11	2	3	45
Merson et al. (31)	1945–1987	33[a]	0	27	82
Owen et al. (36)	1907–1950	27	0	25	92
Patel et al. (6)	1952–1979	29	0	16	60

[a]Includes six patients with superolateral quadrantectomy.

Table 66-4 shows the results of breast irradiation in several retrospective studies. The 5-year local recurrence rates in patients who received breast irradiation ranged from 7.5% to 17%, much lower than the rate in the groups who did not receive any breast treatment (36% to 66%). These data, along with the fact that nearly 50% of the patients who received no form of breast treatment will eventually have disease recurrence in the breast, support the recommendation that the breast be treated when no tumor can be detected clinically or mammographically. Whether mastectomy should be carried out in all patients, or breast conservation with whole-breast irradiation can be safely performed remains to be demonstrated. Vlastos et al. (38) retrospectively analyzed a series of 45 patients with occult breast cancer: 32 had a breast-conserving treatment with [25] or without [7] radiotherapy; 13 had a mastectomy with [7] or without [6] radiotherapy. At a median follow-up of 7 years, no differences in locoregional recurrences, distant metastases, disease-free survival, or overall survival were observed between those who had a breast-conserving treatment and those who had a mastectomy. Adjuvant systemic treatment was delivered to 84% and 46% of patients, respectively. Walker et al. (3) determined overall and cause-specific survivals of the 750 patients with occult breast cancer and axillary metastases identified in the SEER database, from 1983 to 2006. Median follow-up was 4 years. Patients with mastectomy or breast radiotherapy had significantly higher survival, but not cause-specific survival, than those with axillary lymph nodes dissection only, and those who had no locoregional treatments: 10-year rate of overall survival (OS) were 64.9%, 58.5% ($p = .02$), and 47.5%, respectively ($p = .04$); 10-year rates of cause-specific survival (CSS) were 74.6%, 71.2% ($p = .09$), and 71.9% ($p = .69$), respectively. No differences in OS or CSS were seen between the 268 patients who had mastectomy and the 202 patients who received breast irradiation.

After axillary node dissection, should irradiation be delivered to the remaining lymph nodes? Few data are available in the literature to support any treatment options. A substantial risk for nodal involvement of the upper axilla can be suspected, however, based on the fact that three involved nodes are expected to be found in one-half of the patients. In patients with axillary node involvement associated with an invasive breast cancer, irradiation of the upper axilla is typically delivered when four or more nodes are involved. Studies have shown that, in patients with axillary node involvement, postmastectomy irradiation of the chest wall and regional nodes (39), as well as breast and nodes irradiation after breast-conserving surgery (40) decreased the rate of long-term distant metastases and improved survival, even in patients who received adjuvant chemotherapy or hormone therapy. Therefore, by analogy with other stage II tumors, irradiation of the upper axilla can be recommended in these instances, providing that axillary dissection was performed. Of 59 patients treated at the Institut Curie, 58 received nodal irradiation. In most instances, only the upper axilla and supraclavicular nodes were treated after complete axillary nodal dissection, whereas the whole axilla was treated when a simple adenectomy had been performed. There were four axillary node recurrences: One was isolated, but three were associated with a breast recurrence. The indications for internal mammary node irradiation are currently much debated in patients with a breast mass and central or medial tumor or axillary involvement. Recommendations about treatment of the internal mammary nodes in patients

TABLE 66-4

Results of Breast-Conserving Treatments

		No. of patients		*% 5-year Local Recurrences*		
	Median F/U (months)	*Without RT*	*With RT*	*Without RT*	*With RT*	*p*
Ellerbroek et al. (30)	131	13	16	57	17	.06
Masinghe et al. (37)	108	12	41	35.8	16.4	.27
Barton et al. (21)	68	13	35	66	16	<.001
Institut Curie series	151	2	54	2/2	7.5	NA

with occult primaries and axillary adenopathy are difficult to formulate because the evaluation of internal mammary node irradiation in this rare form of breast cancer is impossible on the basis of limited retrospective series. Because the location of the primary tumor is unknown, the Institut Curie policy supports the irradiation of the internal mammary nodes in all patients.

The reported 5-year actuarial survival rates after treatment of occult breast cancer with axillary metastases range from 36% to 79% (Table 66-5). The 5- and 10-year survival estimates in the 59 patients treated at the Institut Curie were 84.5% and 74% with a median follow-up of 151 months (range, 22 to 458 months). These figures seem higher than those observed after treatment of patients with stage II disease and detectable breast tumor. This has been emphasized by several authors (8,9,31,35,36). These survival rate estimates are, however, derived from small series of patients with various durations of follow-up and heterogeneous treatment modalities. Rosen and Kimmel (33) attempted to evaluate the results more precisely by matching a series of 48 patients with occult breast primary and axillary node metastases with a series of patients with stage II breast cancer who presented with palpable breast tumor (T1, N1 and T2, N1). Although the difference was not statistically significant, higher overall survival and size- or node status–adjusted survival rates were observed in the group of patients with occult primary tumors.

Montagna et al. (32) have compared a series of 80 patients with occult breast cancer and axillary metastases to a matched control series of 80 patients with pT1c (≤20 mm) N0. Matching was done according to age, year of surgery, number of nodes involved, ER and PR status, and HER2 status. Patients with pT1c disease had more mastectomies (18% vs. 5%). Median follow-up was 6.1 years. No significant differences were observed between the group with occult breast cancer and the group with pT1c breast cancer in overall survival, disease-free survival, cumulative incidence of locoregional recurrences, or cumulative incidence of distant metastases.

Reliable prognostic analyses are difficult to perform because of the multiple selection biases in the retrospective series and the small sample size. Rosen and Kimmel (33) showed that survival was determined by the number of axillary nodes involved; patients with fewer than four nodes involved did better than those with more than four nodes involved. This was also demonstrated in the study by Vlastos et al. (38), and by our study at Institut Curie where survival was longer in patients with less than four involved axillary nodes: the 10-year survival rates were 88% and 60%, respectively (p = .04). Baron et al. (4) showed that estrogen receptor-positive patients fared better than estrogen receptor-negative patients. In their study of the SEER database, Walker et al. (3) performed a multivariate analysis in the 470 patients who had mastectomy or breast irradiation, and showed that unfavorable cause-specific survival was associated with ER-ve disease, more than 9 involved axillary nodes, and less than 10 nodes resected, but not with the type of treatment (mastectomy or breast irradiation). Montagna et al. (32) performed a multivariate analysis of prognostic factors in their series of 80 patients with occult breast cancer. Overall survival, disease-free survival, local recurrence risk, and risk of distant metastases were increased in patients with more than 3 involved nodes. Triple negative tumor phenotype (ER 0%, PR 0%, and HER2 overexpression or amplification) was associated with impaired overall and disease-free survivals, and with an increased risk of local recurrence.

Is there a role for adjuvant systemic treatment in patients with occult primary breast cancer? As mentioned previously, because of the rarity of this disease and the multiple selection biases, the efficacy of systemic therapy in patients with T0, N1 breast cancer is impossible to ascertain. By analogy with stage II node-positive breast cancer, the general tendency is to use the same criteria (i.e., axillary node involvement) to prescribe systemic chemotherapy or hormone therapy. Almost all patients included in the most recent studies (21,32,34,37) have received adjuvant systemic treatment with chemotherapy, hormone therapy, or both. Of the 59 patients treated at Institut Curie, 27 received adjuvant chemotherapy, with a regimen of cyclophosphamide, doxorubicin, and 5-fluorouracil. Patients who received chemotherapy were slightly younger and had more involved nodes than those who did not, but these differences were not statistically significant. Survival and metastases-free interval rates were not statistically different in the 27 patients who received chemotherapy and in the 32 patients who did not. This apparent lack of benefit from chemotherapy may be explained by the fact that in this particular group of patients, chemotherapy did not reverse the adverse prognostic influence of massive nodal involvement. Little is known about the effect of hormone therapy in these patients. Of 13 patients who received tamoxifen for at least 2 years in the Institut Curie series, only 1 developed distant metastases, 7 years after diagnosis. The numbers are too small to make significant statistical comparisons, but these results suggest that hormone treatment may be very effective and support its use, at least in patients who have high hormone receptor levels.

The common policy in most institutions is to give adjuvant systemic therapy to patients with involved axillary nodes. As suggested by the results of recent studies, the

TABLE 66-5

Five-Year Survival Rates for Patients with Occult Breast Carcinoma

Investigators	*Patients*	*Follow-up (mo)*	*Actuarial Survival Rate (%)*
Ashikari et al. (5)	42	NA	79
Baron et al. (4)	35	58 (mean)	75
Ellerbroek et al. (30)	42	131 (median)	72
Kemeny et al. (9)	18	NA	57
Merson et al. (31)	56	123 (median)	76.5
Institut Curie, present series	59	151 (median)	84.5[a]

[a]10-year rate: 74%.
NA, not available.

outcome of occult breast cancers with axillary metastases seems similar to that of stage II breast cancer, and the prognostic factors are probably identical. Therefore, the administration of adjuvant systemic treatments including chemotherapy, endocrine treatment, or trastuzumab should be recommended to patients with occult breast cancer and axillary metastases, with the same indications criteria as for patients with stage II breast cancer.

MANAGEMENT SUMMARY

- Occult primary breast cancer presenting as an axillary lymph node is rare and should not be confused with ectopic breast cancer localized in the axillary tail of the breast.
- The heterogeneity of treatment and the limited number of patients studied in the published literature make it difficult to standardize treatment options.
- After the diagnosis of adenocarcinoma has been established by a biopsy of an isolated axillary mass, extensive workup evaluation is not necessary. A thorough clinical examination, bilateral mammograms, breast metastatic work-up, and tumor markers are sufficient to establish a high presumption of axillary metastases of mammary origin.
- Breast MRI should be used in all cases. An early contrast-enhancing image of the breast should be localized by sonography or mammography for biopsy or surgical excision. CT scan localization, or MRI localization if available, must be used if sonographic or mammographic localization is impossible.
- An axillary dissection is generally performed to provide additional prognostic information and to provide local control in the axilla.
- The breast should be treated. Breast-conserving therapy in patients with an occult breast primary tumor by whole breast irradiation to a dose of 50 to 55 Gy limits the risk for disease recurrence and is an alternative to mastectomy.
- Irradiation of the upper axilla and supraclavicular area, to a minimum dose of 45 Gy, is recommended in patients with more than three involved axillary nodes. In cases of patients with one to three nodes, the value of this irradiation is debated. The whole axilla should be irradiated in patients who did not undergo axillary node dissection.
- Recommendations for adjuvant systemic therapy based on estrogen receptor, progesterone receptor, and HER2 in patients with an occult primary should be similar to that for other patients with node-positive breast cancer.

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SECTION X

Evaluation After Primary Therapy and Management of Recurrent Breast Cancer

CHAPTER 67

Surveillance of Patients following Primary Therapy

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CHAPTER CONTENTS

The success of therapy for breast cancer results in an increasing number of breast cancer survivors being monitored for the development of recurrent disease. It is estimated that there are approximately 3 million breast cancer survivors in the United States alone. The magnitude of the follow-up of this large population requires efficient, timely, and cost effective monitoring. The optimal monitoring for recurrence of disease requires knowledge of the risk for recurrence, common sites of recurrence, accuracy of methods of detection of recurrence, and potential benefits and risks of detection of early disease recurrence.

ASSESSMENT FOR RISK OF RECURRENCE OF DISEASE

Assessment for risk of recurrence of disease may be performed by the integration of the anticipated natural history of a breast cancer based upon anatomic and biologic prognostic factors and the anticancer treatment delivered. The hazard rates for recurrence of disease have been studied retrospectively among 3,585 patients enrolled in seven large clinical trials (1). The peak for annual hazard for recurrence occurred in year 1 to 2 and then decreased consistently to 5 years, and then declined slowly through year 12. The hazard for recurrence was especially high for those with 4 or more involved axillary lymph nodes during the first 5 to 6 years of follow-up, but thereafter was similar to those with fewer nodes involved. The hazard for recurrence was higher in those women with estrogen receptor negative versus receptor positive breast cancer during the first 3 years of follow-up, and then similar or lower thereafter.

Long-term follow-up studies have documented that the most common sites of recurrent disease are local soft tissue, bone, lung, liver, and brain. Multiple sites are often involved at the time of detection of first recurrence, and almost always during the course of the metastatic disease. Tumors that are estrogen receptor positive, progesterone receptor positive, low or intermediate grade, and with low mitotic rate are more likely to metastasize to bone than viscera when compared to tumors without those. In contrast, menopausal status, tumor size, and nodal status do not impact the frequency of bone versus visceral site of metastatic disease. Further, many factors associated with overall prognosis at diagnosis of early breast cancer retain prognostic significance for survival following first diagnosis of metastatic breast cancer. Long-term survival after recurrent breast cancer is relatively unusual, and apparent cures of disease are uncommon except for patients with ipsilateral in-breast tumor recurrences (2).

The goals of surveillance are to detect recurrence at a time that allows initiation of therapy to improve survival and to maintain a high quality of life. There is little high-level evidence that these goals are achieved by any surveillance program.

THE CONTRALATERAL BREAST

Frequency of Contralateral Disease

The occurrence of breast cancer in the contralateral breast of women with a known history of breast cancer may represent either a new primary tumor or a metastasis from the originally diagnosed breast cancer. While the determination of a new primary versus a metastasis may be difficult, a contralateral breast cancer represents a new primary if the cancer is of a different histology (e.g., ductal vs. lobular) or is associated with an *in situ* component. Metachronous second primary breast cancers are more likely to be *in situ* cancer, small size, and node negative (3). The risk of a metachronous, contralateral, second primary breast cancer is generally estimated at 0.5% to 1.0% per year (3,4). Recent data suggests that the frequency of metachronous, contralateral, estrogen receptor positive second primary breast cancer is declining, probably because of the risk reduction provided by adjuvant endocrine therapies (5). Factors that increase the risk include a known *BRCA1* or *BRCA2* mutation, young age at first primary, family history of breast cancer, lobular histology for first primary breast cancer, and prior radiation exposure. Factors that decrease the risk include prior chemotherapy or endocrine therapy (6). While there are no randomized studies of screening mammography of the contralateral breast, contralateral second primary breast cancers in women undergoing routine screening mammography are smaller, and more likely to be *in situ* and node negative than those in women not undergoing routine mammography (7). The occurrence of metachronous contralateral breast cancer has modest impact on overall survival (7).

Screening for Contralateral Disease

Conceptually, the monitoring for a new primary breast cancer in the contralateral breast may be viewed as monitoring in a high risk for breast cancer population with an increased risk of competing mortality secondary to the initial primary breast cancer. In the general population of women age 40 and older, the use of screening mammography has been demonstrated to decrease breast cancer mortality. It is thus likely that routine screening mammography would decrease breast mortality from a second primary tumor, although the mortality rate for second primary breast cancers is low.

Breast magnetic resonance imaging (MRI) screening has high sensitivity, moderate specificity, and high cost as an adjunct to the performance of mammography. No randomized clinical trials of breast MRI as screening or surveillance are available in any clinical setting. Non-randomized trials in women without known breast cancer but at high risk of breast cancer document a higher detection rate of breast cancer with the use of breast MRI scanning (8). To date, no similar prospective trial has been reported in the follow-up of women following diagnosis of breast cancer. The American Cancer Society currently recommends screening MRI as an adjunct to screening mammography, based upon non-randomized screening trials and observational studies, in women with known *BRCA* mutation, who have a first degree relative with a known *BRCA* mutation, who have a lifetime risk of greater than 20% to 25% based upon family history, who had radiation exposure to the chest between age 10 and 30 years, who have known Li-Fraumeni syndrome themselves or in first degree relatives, or who have Cowden and Bannayan-Riley-Ruvalcaba syndromes themselves or in first-degree relatives (9). The American Cancer Society makes no recommendation for or against screening MRI in women with a personal history of breast cancer. A study of breast MRI screening in women at risk of breast cancer and with negative mammograms included 245 subjects with a personal history of breast cancer (10). Breast cancers were documented in 4% of the subjects with a prior history of breast cancer, and the positive predictive value of MRI recommended biopsy was 32%. A retrospective study of women screened by MRI who had a personal, but no family, history of breast cancer documented 17 cancers in 144 subjects (11). Ten of the 17 cancers were detected by MRI only. The positive predictive value of MRI was 39%. The non-randomized nature of all of these studies prohibits assessment of the impact of breast MRI screening on breast cancer mortality.

The value of clinical breast examination has not been adequately studied, although the performance of clinical breast examination is a generally accepted part of routine healthcare of the adult female. Breast self-examination was found to be of no advantage in early detection or mortality reduction in a large, randomized clinical trial in a population of factory workers in China (12).

Based on the increased risk of a second primary breast cancer in the contralateral breast, it appears prudent to perform regular clinical breast examinations and mammography as a routine part of surveillance programs. The role of breast MRI screening is yet to be defined, but would appear reasonable in those with very high contralateral risk. Such high risk patients are those with a known, or a high risk for, genetic mutation conferring risk for breast cancer or a prior history of thoracic radiation. For other populations, insufficient information exists to allow for specific recommendations regarding the use of screening MRI. The value of breast self-examination has not been demonstrated.

LOCOREGIONAL RECURRENCES

Most patients with a locoregional recurrence of breast cancer following either breast conserving therapy or mastectomy present with symptoms. Approximately 40% of isolated locoregional recurrences are detected during routine examinations in asymptomatic patients and a similar number are diagnosed outside of routine follow-up examinations in symptomatic or asymptomatic patients (13).

Ipsilateral Breast Tumor Recurrence

Ipsilateral breast tumor recurrence following breast conserving surgery is experienced by 5 years in approximately 7% of patients with whole breast irradiation and 26% of patients without whole breast irradiation (14). The addition of a radiation boost to the tumor bed decreases in-breast recurrence rates by approximately 41% compared with whole breast irradiation alone (15). Most recurrences occur in the prior tumor bed, and positive pathologic margins, younger age, higher grade tumor, larger tumor size, negative estrogen receptor status, and involvement of axillary lymph nodes have all been reported to increase the risk of ipsilateral breast tumor recurrence (14–16). Approximately 70% of ipsilateral breast tumor recurrences occur within the first 5 years of primary diagnosis (14,16). Breast recurrence during the first 5 years of follow-up is associated with a substantially worse overall prognosis than are in-breast recurrences that manifest later.

Detection of ipsilateral breast tumor recurrence is often difficult because of post-surgical, post-radiotherapy changes in the breast. The sensitivity of mammography for ipsilateral breast tumor recurrences is approximately 50% to 70% and ultrasonography 80% to 85%. Overall, approximately two thirds of local recurrences are detected by the patient or on clinical examination (17,18).Detailed reviews of studies of screening mammography in women with a personal

history of breast cancer generally document that patients diagnosed with mammography detected only in-breast recurrences have superior survival to those with symptomatic recurrences (19,20). These studies all suffer from being relatively small in sample size and are non-randomized. Thus, it is impossible to correct for confounding by lead-time and length-time biases.

Breast MRI scanning has high sensitivity for detecting in-breast recurrences, but is expensive and is associated with highly variable specificity.

Local-Regional Recurrence Postmastectomy

Local-regional recurrence following mastectomy is experienced by 5 years in approximately 6% of patients with postmastectomy regional irradiation and 23% of patients without postmastectomy irradiation (21). In the overview analysis, axillary lymph node status strongly predicted for absolute risk for local-regional recurrence (21). In women with axillary lymph node-negative disease, the 5-year local recurrence risk following surgery alone was 6%, and this was reduced to 2% with the use of local-regional irradiation. In women with axillary lymph node-positive disease, the 5-year local recurrence risk following surgery alone was 23% and this was reduced to 6% with the addition of local-regional irradiation. Increasing tumor grade, tumor size, and number of involved axillary lymph nodes increases the risk of local-regional recurrence.

Detection of local-regional recurrences following mastectomy with or without radiation is typically the result of either patient identification or of a routine clinical examination. Local-regional recurrences are rarely detected by radiographs or other screening studies.

Distant Recurrences

Well established prognostic factors allow the estimation of risk for development of systemic disease following treatment for stage 0, I, II, and III breast cancer. Known prognostic factors include histologic subtype of breast cancer, tumor grade, tumor size, involvement of skin or chest wall, extent of involvement of regional lymph nodes, hormone receptor status, *HER2* level of expression or amplification, and multigene array expression profile.

Breast cancer metastases occur in a generally predictable pattern, with synchronous multiple sites of recurrence being common. Bone is the most common site of disseminated disease, and represents approximately 40% of first recurrences. The most commonly involved bones are the spine, ribs, pelvis, skull, femur, and humerus. Breast cancer metastasis to bone distal to the elbow or knee is rare. Other common sites for metastatic disease include lung, liver, lymph nodes, and soft tissue. The site of first metastasis from breast cancer is influenced by estrogen receptor status (Table 67-1). Estrogen receptor-positive breast cancer is more likely to spread to bone, while receptor-negative breast cancer is more likely to spread to viscera and soft tissues and is associated with a higher rate of early recurrence (Table 67-1) (22,23). Even in those patients undergoing routine surveillance during follow-up, most recurrent disease is symptomatic at time of diagnosis (24,25).

Infiltrating lobular breast cancer has a propensity for recurrences in intra-abdominal and retroperitoneal sites including stomach, intestine, peritoneum, and ureter (often bilateral) (26).

Currently available treatment of recurrent or metastatic breast cancer is rarely curative, even when the recurrence is limited (2). Further, the amount of tumor burden in asymptomatic or minimally symptomatic patients does not predict disease response to systemic treatment, ability to palliate symptoms, or overall survival. Thus, there is no advantage to diagnosing asymptomatic, early, subclinical disease.

Routine Blood Tests

The routine performance of blood tests for alkaline phosphatase, aspartate aminotransferase, γ-glutamyl transferase, bilirubin, calcium, and creatinine was studied by the International Breast Cancer Study Group in 4,105 women

TABLE 67-1

Location of First Recurrence in Randomized Trials of Intensive versus Routine Surveillance

Type of Recurrence	*GIVIO Trial (24)*		*National Research Council Project on Breast Cancer (46)*	
	Intensive Monitoring (n = 201 Recurrences or Deaths)	*Control (n = 196 Recurrences or Deaths)*	*Intensive Monitoring (n = 219 Recurrences)*	*Control (n = 174 Recurrences)*
Local regional recurrence alone	32 (15.9%	36 (18.4%)	55 (25.1%)	49 (28.2%)
Contralateral breast alone	12 (11.4%)	13 (6.6%)	Not stated	Not stated
Distant metastases	127 (63.1%)	127 (64.8)	164 (75.9%)	125 (71.8%)
Bone	52 (25.9%)	55 (28.1%)	84 (38.3%)	53 (30.5%)
Liver	13 (6.5%)	12 (6.1%)		
Lung/pleura	24 (11.9%)	21 (10.7%)	28 (12.8%)	18 (10.3%)
Other sites	19 (9.4%)	27 (13.8%)	22 (10.0%	21 (12.1%)
Multiple sites	19 (9.4%)	12 (6.1%)	30 (13.7%)	33 (19.0%)
Second Primary (not breast)	8 (4.0%)	11 (5.6%)		
Death without recurrence	11 (5.5%)	9 (4.6%)		

with invasive breast cancer (27). At the time of analysis, 2,140 patients had experienced a relapse, 93 had a second non-breast primary tumor, and 111 had died without relapse during 10-years median follow-up. In this analysis, only alkaline phosphatase was abnormal in at least 20% of patients with recurrent disease, and was abnormal in 32% of patients with bone metastasis and 71% of patients with liver metastasis. Aspartate aminotransferase and γ-glutamyl transferase were elevated in 62% and 75% of patients with liver metastasis. Bilirubin, calcium, and creatinine were of no value in detecting recurrent disease. Thus, while alkaline phosphatase was the most reliable of the blood tests, it was of low sensitivity for bone or liver disease. In another study of 1,371 patients with node positive breast cancer, serial alkaline phosphatase determinations were found to have low sensitivity and specificity for bone recurrence (28). Thus, monitoring of routine blood tests as a part of breast cancer surveillance is not recommended.

Circulating Tumor Markers

Tests of serum carcinoembryonic antigen (CEA) and MUC-1 antigen (CA 15-3; CA27.29) have been proposed as tumor markers for the surveillance of breast cancer recurrence. Elevations in these antigens are common in patients with newly diagnosed breast cancer, and their levels are prognostic in some studies. Prospective and retrospective studies using these markers in breast cancer surveillance following primary treatment demonstrate that recurrences of breast cancer may be detected with low to modest sensitivity approximately 5 to 6 months prior to the detection of metastatic or recurrent disease by other methods (29). However, false positive elevations in these markers are common with associated risk of incorrectly diagnosing recurrence of disease, and no advantage in overall survival or quality of life has been demonstrated with the use of these markers. Guidelines generated by expert panels consistently recommend specifically against, or do not recommend, surveillance using any serum tumor marker test (30–32). Thus, the monitoring of circulating tumor markers, including those measuring CEA or MUC-1 antigen appears to be of no value and is not recommended in the surveillance of women following treatment for early stage breast cancer.

Bone Specific Monitoring

Bone pain is a common symptom of bone metastasis from breast cancer. However, many patients with bone pain do not have recurrent cancer, and up to 32% of patients with bone metastasis do not have pain (33,34).

Radionuclide bone scanning is, in general, a sensitive and moderately specific imaging modality for breast cancer metastatic to bone. The NSABP has reported on the benefit of 7,984 routine follow-up bone scans in 2,697 patients with node positive breast cancer as a part of NSABP B-09 (35). Scans were obtained at baseline, every six months for 3 years, and then annually. At the time of the analysis, 779 patients had experienced a recurrence, and 163 of these were in bone only. In 146 of the patients with bone recurrence, information about the presence or absence of symptoms was available. Ninety-five patients had the bone recurrence detected by routine scheduled bone scans, and 35 of these patients were asymptomatic. All 51 patients who had the bone recurrence documented by a nonroutine bone scan were symptomatic. At most, only 0.6% of the total number of bone scans was positive in the absence of symptoms.

In a study of 241 patients with node positive breast cancer, the use of serial bone scans detected 25 patients with bone metastasis, only 13 of whom were asymptomatic (36). In a study of 1,601 women with node positive breast cancer, 1,441 had a baseline and repeat bone scan at one year of follow-up (28). This study documented the inability of the one year bone scan to predict for the eventual development of bone recurrence. With a median of 4 years of follow-up, those women with a normal one year bone scan had a 6.9% risk for development of first relapse in bone, while those with a doubtful one year bone scan had an 11.2% chance of first relapse in bone. Abnormal, radiologically confirmed, one year bone scans were present in only 1.2% of all patients.

Recent studies have suggested that the use of whole body MRI scanning may be more sensitive and specific for the early detection of bone recurrence. However, the routine use of whole body MRI scanning is currently cost-prohibitive.

There is, thus, no evidence supporting the use of routine surveillance for bone recurrences in women with a history of early stage breast cancer.

Liver Specific Monitoring

Prospective study of intensive surveillance including liver ultrasonography and liver function tests versus minimal testing have found no difference in the cumulative rate of detection of breast cancer hepatic metastasis during any time interval up to 5 years (24).

No prospective studies testing the value of computed tomography of the liver as surveillance have been reported. Existing data from other surveillance studies predict that computed tomography surveillance would be neither efficacious nor cost effective. Thus, there is no evidence supporting the performance of liver specific monitoring in the surveillance of women with a history of early stage breast cancer.

Lung Specific Monitoring

Most patients with pulmonary recurrences of breast cancer present with symptoms referable to the chest. Studies addressing the use of routine screening chest radiographs have demonstrated very low rates of metastases detection in the asymptomatic patient. In a study of 241 patients with node positive breast cancer who underwent serial chest radiography the first two years following diagnosis, 3.4% were found to have asymptomatic pulmonary metastasis (36). In a prospective randomized trial of intensive versus spontaneous surveillance, the utility of chest radiographs was specifically assessed (37). Neither disease free nor overall survival was improved with the routine performance of chest radiographs. Thus, the use of chest radiography in the surveillance of women with early stage breast cancer is discouraged.

SECOND NON-BREAST CANCERS

Individuals with breast cancer have a risk of developing second malignancies from a variety of potential causes including those associated with genetic mutations such as the *BRCA1* and *BRCA 2* mutations, secondary cancer related to treatment with chemotherapy, radiation, and endocrine agents, and the usual wide variety of other cancers unrelated to breast cancer and its treatment. A population-based study of 525,527 women with primary breast cancer reported an increased incidence following breast cancer diagnosis of stomach, colorectal, non-melanoma skin, endometrial, ovarian, kidney, and thyroid cancers, melanoma, soft tissue sarcoma, and leukemia (38). Whether these increased risks were attributable to underlying susceptibility, treatment, surveillance, or other factors could not be assessed within the cohort.

Radiation Therapy Treated Patients

In the Early Breast Cancer Trialists' Collaborative Group analysis of patients with early breast cancer treated with radiation therapy, the occurrence of second malignancies including lung cancer, esophageal cancer, leukemia, and soft tissue sarcomas were found to be increased, although the absolute risk was small (14). The impact of radiation postmastectomy or post breast conserving therapy on second cancers was the subject of a single institution study of 16,705 women with breast cancer. At 10-years of follow-up, an excess of sarcomas (relative risk 7.46; 95% confidence intervals 1.02–54.52, p = .02.) and lung cancers (relative risk 3.09; 95% confidence intervals 1.12–8.53, p = .022) was observed. The absolute risk of a second primary sarcoma or lung cancer was, however, extremely low with 35 of 13,472 patients treated with radiation therapy experiencing a sarcoma and 58 experiencing lung cancer. Of the patients experiencing lung cancer, 52 occurred in patients with a history of tobacco use.

Chemotherapy Treated Patients

An analysis of 2,465 patients studied in consecutive adjuvant programs utilizing cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy with or without doxorubicin found no excess second cancer risk at 15-years of follow-up (39). The Early Breast Cancer Trialists' Collaborative Group analysis of second cancers in patients with early breast cancer treated with poly-chemotherapy documented a decreased risk of contralateral breast cancer in women under the age of 50 years but no statistically significant difference in risk of any other second cancer (14). In an analysis of AC-based NSABP trials, the cumulative incidence of AML/MDS at 5 years was 0.21% (95% CI 0.11%–0.41%) with standard AC and increased to 1.01% (95% CI 0.63%–1.62%) with intensification of the cyclophosphamide (40).

Endocrine Treated Patients

The Early Breast Cancer Trialists' Collaborative Group analysis of second cancers in patients with early breast cancer treated with tamoxifen documented a decreased risk in contralateral breast cancer in women with a first breast cancer that was ER-positive or ER-unknown, and an increased risk of cancer of the uterus (14). The incidence of uterine cancer with tamoxifen was approximately 1.9 per 1,000 per year versus 0.6 per 1,000 per year without tamoxifen. There was no difference in second cancers at any other site. Similar rates of tamoxifen associated endometrial cancer have been documented by the NSABP (41). The increased risk of endometrial cancer associated with tamoxifen is limited to postmenopausal women, and no additional monitoring beyond routine gynecologic care is recommended (42). The vast majority of tamoxifen associated endometrial cancers are associated with symptoms of vaginal bleeding, bloody vaginal discharge, staining, or spotting. In the absence of these symptoms, routine gynecologic care is appropriate. In the presence of these symptoms, gynecologic evaluation to exclude the presence of benign or malignant endometrial pathology is appropriate.

Analysis of adjuvant endocrine therapy trials incorporating an aromatase inhibitor document a greater risk reduction for contralateral breast cancer than is achieved with tamoxifen alone. In the ATAC Trial, anastrozole compared to tamoxifen reduced the occurrence of contralateral breast cancer by 42% (95% CI 12%–62%; p = .01) and in the patients with receptor positive disease by 53% (95% CI 25%–71%; p = .001) (43). As the use of tamoxifen decreases the occurrence of contralateral breast cancer by approximately 50%, the use of an aromatase inhibitor would appear to decrease overall contralateral breast cancer by 70% to 80%, to contralateral rates of breast cancer not dissimilar to those of women without a history of breast cancer. Similar reductions in contralateral breast cancer have been observed in trials switching to an aromatase inhibitor after 2 to 3 years of tamoxifen or as extended adjuvant therapy (44,45).

There is thus no evidence that screening studies other than those recommended for general health maintenance (such as routine screening colonoscopy according to published guidelines) should be performed to detect second primary non-breast cancers in women under surveillance for recurrence breast cancer, other than routine gynecologic evaluation in women receiving endocrine therapy with tamoxifen.

PROSPECTIVE TRIALS OF SURVEILLANCE FOLLOWING BREAST CANCER TREATMENT

Several high quality multicenter randomized trials of follow-up strategies have been reported. The Gruppo Interdisciplinare perla Valutazione degli Interventi in Oncologia (GIVIO) investigators randomized 1,320 women with Stage I, II, and III primary breast cancer to an intensive surveillance program including physician visits; annual radionuclide bone scan, liver echography and mammography; bi-yearly chest radiographs; and alkaline phosphatase and γ-glutamyl transferase tests every 3 months versus the same frequency of physician visits and annual mammography alone (24). At a median follow-up of 71 months, there were no differences in deaths between the two groups (odds ratio = 1.12; 95% CI = 0.87–1.43) or in number of distant metastasis. The intense surveillance resulted in a less than 1 month difference in mean time to detection of a distant metastasis. Patterns of site of first recurrence were also similar between the two treatment groups (see Table 67-1). Even in the intense follow-up group, only 31% of recurrences were found in asymptomatic patients. Assessment of quality of life did not differ across multiple dimensions between the two treatment groups.

In another randomized trial performed by the National Research Council Project on Breast Cancer, 1,243 patients with non-metastatic invasive breast cancer were randomized to intensive surveillance with physical examination; radionuclide bone scan and chest radiography every 6 months; and mammography every year versus the control group who underwent physical examinations and mammography at the same intervals (46). Relapse free survival was inferior in the intensive follow-up group, presumably because of earlier diagnosis of recurrent disease, but there was no difference in overall survival (5-year mortality 18.6% in the intensive follow-up group versus 19.5% in the clinical follow-up group). Sites of recurrent disease were similar between the two groups (see Table 67-1). A more recent follow-up of this trial reported 10-year mortality of 34.8% with intensive follow-up compared with 31.5% in the control group (47). Survival analysis revealed a hazard ratio of 1.05 (95% CI 0.87–1.26).

In another study, 472 patients with localized breast cancer following primary treatment were randomized to receive follow-up visits either every three or six months and also randomized to receive routine blood counts, calcium, sedimentation rate, liver enzymes, and CA 15-3 at every visit, chest x-ray every six months, and liver ultrasound and bone scan every second year, or to no routine testing (37,48). At a median follow-up of 4.2 years, there were no significant

differences in number of recurrences detected, disease free survival, overall survival, number of patient initiated phone calls concerning breast cancer, or extra medical visits. Costs of care were specifically assessed, and the intensive surveillance increased follow-up costs by more than twofold.

In a trial of 196 women with breast cancer, the subjects were randomized to regular follow-up surveillance visits or to yearly visits at the time of mammography (49). The number of recurrences was too low at the time of the report for assessment. However, the vast majority of participants found their clinic visits reassuring and the majority wished to continue their follow-up with the specialist clinic. However, 25% of the regular follow-up group and 35% of the annual follow-up group preferred less frequent follow-up evaluations in the future.

A study randomized 296 women with breast cancer to specialist follow-up or to follow-up in generalist practices (50). No difference was observed for time to diagnosis of recurrence by practice setting, and most recurrences (69%) presented as interval events between scheduled visits. A separate study randomized 968 patients who were 9 to 15 months following diagnosis and at least 3 months following completion of adjuvant chemotherapy and radiotherapy to follow-up through a tertiary-care cancer center or to follow-up with their own primary care physician (51). The primary care physicians were provided with a one-page guideline that outlined recommended follow-up and diagnostic tests to investigate signs or symptoms suggestive of recurrent or new primary cancer. Patients were to be referred back to the cancer center if recurrence or new primary tumor developed. The primary endpoint of the study was recurrence related serious clinical events such as spinal cord compression, pathologic fracture, and hypercalcemia. Health related quality of life was a secondary endpoint. The results document equivalent rates of serious clinical events between cancer center versus primary care physician follow-up groups. Health related quality of life did not differ between the two treatment groups throughout the study period.

Studies using the Surveillance, Epidemiology, and End Results-Medicare data bases have evaluated the use of routine testing, including mammography, bone scans, tumor antigen tests, chest radiographs, and other chest/abdominal imaging (52,53). These analyses demonstrate that women seeing medical oncologists, radiation oncologists, or surgeons are more likely to undergo routine mammography than women seeing other specialists. Women with breast cancer being followed by medical oncologists are also more likely than those followed by other specialists to undergo testing including tumor antigen testing, chest radiographs, and chest/abdominal imaging, although the rates of utilization are falling most rapidly among medical oncologists. To what extent the differing utilization of testing among specialists reflects differing risk populations versus inappropriate routine testing could not be determined from the SEER-Medicare data base. A prospective study comparing follow-up surveillance by specialists versus primary care physicians found relatively modest rates of compliance with ASCO-recommended testing in both groups, but with higher compliance among the specialist group (54).

Patients are usually highly accepting of breast cancer surveillance performed by advanced practice nurses, especially if there are occasional visits with a physician. Limited data suggests that telephone follow-up performed by nursing may be medically adequate follow-up, although most patients strongly prefer face-to-face contact (55).

Thus, the optimal surveillance of women following treatment for breast cancer requires relatively little testing, and can be performed by an interested, informed primary care provider, specialist provider, or nurse. As the long-term treatment of women with breast cancer occurs, such as with the extended adjuvant therapies of hormone receptor positive disease, one of the major challenges of primary care follow-up is the need to keep the primary care provider up to date regarding changes in optimal practice.

OTHER CONSIDERATIONS

Patient Expectations of Surveillance

Despite the extensive data demonstrating limited value of routine testing, many patients expect routine follow-up from their physicians (56). To a substantial degree this is because patients have unrealistic expectations of tests and their healthcare provider to detect recurrent breast cancer and to implement treatment for recurrence of disease so that it impacts overall survival substantially. During the follow-up period, patients require education about the importance of self-reporting symptoms, and the limited value of routine blood tests and radiographic studies other than annual mammography.

Opportunity to Assist with Survivorship Issues

Medical visits focusing on surveillance for recurrence also allow the provider and patient the opportunity to explore other issues of concern. Issues or concerns relating to fatigue, anxiety, sexual dysfunction, bone health, cognitive dysfunction, exercise, maintenance of ideal body weight, nutrition, and others are common among breast cancer survivors. During routine surveillance visits, patients with identified issues or concerns may be provided access to appropriate resources. Alternatively, patients may be referred to a survivorship program for follow-up including breast cancer surveillance if the survivorship program has the appropriate expertise and resources.

RECOMMENDED SURVIELLANCE

The large number of patients alive without recurrence of disease following treatment of early stage breast cancer and the availability of multiple studies addressing surveillance for recurrence of disease presents an opportunity for the widespread application of evidence-based surveillance. Given the large number of women alive with a history of breast cancer, the use of evidence-based surveillance monitoring has a large economic impact. A number of professional organizations have evaluated the evidence relating to surveillance and issued recommendations for evidence-based follow-up. Recommendations from representative major organizations are outlined in Table 67-2. As can be seen, there is remarkable consistency among the recommendations.

The optimal surveillance for breast cancer recurrence involves routine follow-up history taking and physical examination, yearly mammography of any retained breast, and monitoring for treatment related endometrial carcinoma in patients treated with tamoxifen and bone health in women experiencing a treatment related menopause or receiving an aromatase inhibitor. The guidelines are very consistent in not recommending surveillance radiographs, blood counts, blood chemistries, tumor markers, radionuclide scans, etc. for the asymptomatic patient. Patients with symptoms, physical findings, or concerning abnormalities on follow-up mammography warrant a full, expeditious, symptom- or finding-directed evaluation.

TABLE 67-2

Comparison of Guideline Recommendations for Surveillance of Women Following Primary Therapy of Breast Cancer

	National Comprehensive Cancer Network (30)	*American Society of Clinical Oncology (32)*	*European Society of Medical Oncology (57)*	*Canadian Breast Cancer Initiative (31)*
History and physical examination	Every 4–6 mo for 5 y, then annually	Every 3–6 mo for 3 y, then every 6–12 mo for 2 y, then annually	Frequency not specified	According to individual patient's needs
Mammography	Every 12 mo	Every 12 mo	Every 12 mo	Every 12 mo
Breast self-exam		Monthly		If a woman wishes
Gynecologic assessment	Every 12 mo for women on tamoxifen if uterus present	Regular gynecologic follow-up		For women taking tamoxifen, important to ask about vaginal bleeding
Bone health assessment	Ongoing monitoring of bone health			Postmenopausal, premenopausal with risk factors for osteoporosis, or taking an aromatase inhibitor should have screening bone mineral density test Patients should be counseled on exercise and adequate intake of calcium and vitamin D. Osteoporosis treatment should include a bisphosphonate.
Encourage adherence to endocrine therapy	Ongoing			
Encourage active lifestyle and ideal BMI	Ongoing			

MANAGEMENT SUMMARY

- Breast cancer recurrences are most common in soft tissues, bone, lung, liver, and brain.
- Second primary breast cancers are common in women with a history of early breast cancer, and yearly mammography of the contralateral breast and the ipsilateral breast, if conserved, is appropriate.
- Ipsilateral in-breast recurrences following breast conserving therapy are usually found by the patient, on clinical examination, or by mammography.
- Periodic follow-up visits should include history taking and focused physical examination.
- Distant recurrences are uncommonly detected by routine surveillance studies in asymptomatic patients without physical findings.
- No high-level evidence supports the surveillance for breast cancer recurrence with routine chest x-rays, computed tomography, ultrasounds, MRI scans, bone scans, liver function tests, alkaline phosphatase, tumor markers, or blood counts. The use of any or all of these tests is, therefore, to be discouraged in surveillance for breast cancer recurrence. Patients who have symptoms or physical findings concerning recurrent disease should have a focused, expeditious evaluation appropriate for the organ system of concern.
- Women treated with tamoxifen should have a yearly gynecologic assessment, and postmenopausal women with vaginal spotting should be promptly evaluated for the presence of endometrial carcinoma.
- Women experiencing treatment related ovarian failure or who are treated with an aromatase inhibitor should have monitoring of bone health.

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CHAPTER 68

Surgery for the Primary in Patients with Distant Metastases

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CHAPTER CONTENTS

The traditional dogma that surgery is reserved for the palliation of symptoms in stage IV breast cancer is being challenged by advances in breast cancer diagnosis and treatment. Widespread mammographic screening and increased awareness have resulted in fewer patients presenting with inoperable disease; improved imaging technologies have resulted in the detection of low-volume metastatic disease in patients who would have previously been classified as having early-stage disease; and improved efficacy of modern chemotherapy regimens, including the use of targeted hormonal and biologic therapies, has resulted in prolonged survival for women with metastatic disease. Thus, in modern breast cancer treatment, the goals of therapy for patients with metastatic disease often extend beyond palliation; however, the role of local treatment in this setting remains uncertain.

Although the mean survival for patients with metastatic breast cancer remains 18 to 24 months, the range of survival extends from a few months to many years, and reports of improved survival in the more-recent decades of treatment raises the possibility of cure for a select group of patients in the future. Andre et al. (1) reported survival rates over two time periods for 724 consecutive breast cancer patients presenting with metastatic disease at diagnosis; overall 3-year survival for patients treated from 1987 to 1993 was 27%, which increased to 44% for those treated from 1994 to 2000. Clinical characteristics were similar in the two time periods, suggesting that the survival trend was related to treatment advances that occurred after 1993. Giordano et al. (2) also demonstrated a trend toward improved survival with more-recent year of recurrence and treatment in a multivariate analysis of 834 women who developed recurrent breast cancer between 1974 and 2000. Each more-recent year of recurrence was associated with a 1% per year reduction in the risk of death. Neither of these two datasets included the benefits obtained from newer therapies, such as trastuzumab and other targeted therapies, yet both demonstrate that improvements in systemic therapy have resulted in demonstrable improvements in survival for patients with metastatic disease.

Targeted therapy with the monoclonal antibody trastuzumab has further improved both survival and quality of life in patients with *ERBB2* (formerly HER2/neu) positive metastatic breast cancer (3). Patient selection based on amplification of the *ERBB2* gene was critical to the success of this therapy and highlights the need to address breast cancer in biologically meaningful subtypes (see Chapter 29, *ERBB2* Testing: Assessment of Status for Targeted Therapies, and Chapter 50, Adjuvant Treatment of *ERBB2*-Positive Breast Cancer, for a detailed discussion). Whether or not this rationale can be applied to the role of local surgery in the setting of metastatic disease is now a matter of great interest and debate.

HISTORICAL PERSPECTIVE

Conventional wisdom suggests that surgical excision of the primary tumor is unlikely to offer the patient any survival advantage and therefore should be reserved for the palliation of symptoms. However, this approach stems from a time before modern advances in systemic treatments and supportive care. Patients with metastatic cancer were often debilitated, not considered fit for general anesthesia, and often had bulky tumors in the breast and axilla that required extensive surgical procedures for complete extirpation. Survival after the diagnosis of metastatic disease was often brief, leading to the desire to avoid unnecessary morbidity from surgery. In the modern era, this concern is largely outdated, as many patients will experience prolonged survival (4,5) and the morbidity of common surgical procedures for breast cancer is exceedingly low (6).

Other historical arguments against surgery have included the desire to follow easily measurable disease for response to therapy, and the fear that removal of the primary tumor would result in increased angiogenesis and growth of otherwise dormant metastatic disease (7,8). Animal models suggest that resection of the primary tumor may be accompanied by release of growth-enhancing factors and induction of temporary immunosuppression (9,10). Further, circulating antiangiogenic factors, such as angiostatin and endostatin, are felt to result directly or indirectly from the presence of the primary tumor, and function to at least partially control angiogenesis of existing dormant micrometastatic tumors (11). According to the angiogenesis concept, upon removal of the primary tumor, angiogenesis is switched on and dormant cells begin to grow. Although

this has been documented in the Lewis lung animal model (8), there are few data to support this theory in humans.

BREAST CANCER GROWTH AND METASTASIS

The growth mechanisms of breast cancer have important implications both biologically and clinically. The fundamental question that has been debated over the past century is whether breast cancer is a *local* disease that spreads in an orderly fashion and becomes systemic, or whether breast cancer is a *systemic* disease at its inception. These two opposing theories, classically referred to as the Halstead and Fisher paradigms, formed the basis for breast cancer treatment in the 20th Century. The increasing acceptance of the Fisher paradigm over Halstead's theory resulted in a shift away from more radical surgery to increasing use of systemic therapies in recent decades; however, the increasing body of evidence demonstrating that local control does impact survival suggests that the truth is likely in the middle. Breast cancer may be, but is not universally, systemic at its inception, and local-regional treatments are important.

At present, metastatic disease is largely incurable and remains so due to a limited understanding of the molecular mechanisms of metastasis. A variety of models suggesting that genetic alterations resulting in metastases are acquired over time are unstable and may overgrow the primary tumor have been proposed. Experimental evidence supporting these theories exist, but their relevance to metastatic breast cancer in humans is uncertain. In the genomic era, new concepts of metastatic dissemination have been proposed. The ability of gene expression profiles of human primary breast cancers to predict metastatic potential (12) suggests that the ability to metastasize is an early and perhaps inherent, genetically predetermined property of the primary tumor cell. Support for this concept includes the finding of similar gene expression profiles from pairs of human primary breast tumors and their distant metastases (13), as well as similar gene expression patterns between premalignant, preinvasive, and invasive breast cancers (14). Kang et al. (15) have proposed that within the population of tumor cells with metastatic capacity, subpopulations of cells also have a superimposed tissue-specific gene expression profile that predicts the site of metastasis. Mathematical models suggest that not only does this "escapee" cell have the capacity to seed distant sites, but it may also metastasize back to the primary tumor (self-seed), thereby contributing both to the ongoing growth and destruction at the site of primary disease, as well as to an ever-growing source of disseminating tumor cells (16). Within the context of metastatic breast cancer, this theory of self-seeding would strongly support complete excision of the primary tumor.

The analysis of human-disseminated cancer cells has led to another model, termed the *parallel evolution model*, which proposes that the dissemination of metastatic cancer cells occurs early and is independent of later changes that may be acquired in tumor cells at the primary site (17). This theory is based on the finding that disseminated tumor cells in the bone marrow of patients without metastatic disease do not share the same genomic abnormalities as cells from the primary tumor; however, in patients with known metastatic disease, these cells are similar to the primary tumor. This theory challenges the concept of clonal genomic evolution, yet the true biologic potential, and therefore clinical significance, of disseminated cells found in the bone marrow of patients with early-stage disease is unknown, and multimodal therapy, including surgery, remains standard care for these patients (18).

Finally, there is an growing body of evidence supporting the *cancer stem cell theory*. This theory proposes that rare cells with indefinite proliferative potential are responsible for the formation and growth of tumors (19), and have the exclusive potential to proliferate and form metastasis (20). Other areas of investigation that may contribute to the understanding of the role of local treatment in metastatic disease include the study of the tumor microenvironment and the immune system (16,21).

In contrast to the conventional model, the newer concepts of metastases all support removal of the primary tumor to reduce either self-seeding, tumor cell dissemination, or the population of native cancer stem cells, followed by effective systemic therapy. There is a biologic rationale that supports a proper evaluation of the role of surgery for the primary tumor in stage IV disease, and this question is increasingly important as outcomes in stage IV disease continue to improve with newer targeted systemic agents. The question also has wider implications than for the population of women who present with stage IV disease and an intact primary, such as for those women who present with a synchronous in-breast recurrence and distant metastases.

LOCAL CONTROL AND SURVIVAL

It is now well established that local control does impact survival in stage I to III breast cancer, and this is particularly evident in patients with positive nodes and those at higher risk of local relapse (22). If preventing local recurrence decreases the incidence of distant relapse in earlier-stage disease, a natural extension of this argument is to consider whether optimizing local control, by removal of the intact primary tumor, may benefit select patients with metastatic disease. In 2002 Khan et al. (23) first challenged the traditional thinking with a report of 16,023 patients presenting between 1990 and 1993 with stage IV disease as captured by the National Cancer Database (NCDB) of the American College of Surgeons. Surprisingly, 9,162 (57.2%) patients underwent either partial [3,513] or total mastectomy [5,649] in the setting of stage IV disease, and surgical removal of the primary tumor was associated with a 39% reduction in the risk of death. Adding further support to the argument for local control, women treated surgically with clear margins had a 3-year survival of 35%, as compared to 26% for those with positive margins, and 17% for those not having surgery ($p < .0001$). Additional studies, both population-based and single-institution series, examining survival outcomes relative to surgical resection or radiotherapy (24) of the intact primary tumor, have now reported remarkably similar results, with an observed reduction in the hazard of death ranging from 40% to 50% (23–41).

Since the first such publication by Khan et al., at least 19 retrospective studies have evaluated the role of local therapy for the primary tumor in patients presenting with *de novo* stage IV breast cancer. The six multi-institutional registry and population-based studies provide information on over 27,000 patients, 14,443 (52%) of whom underwent surgery for the primary tumor, with all but one study, which excluded patients who received systemic therapy before surgery (29) demonstrating an association between surgery and improved survival (Table 68-1). Similarly, the single-institution studies provide information on over 4,000 patients, 1,670 (41%) of whom underwent surgery for the primary tumor, with over half of the studies demonstrating a similar association between surgery and improved survival (Table 68-2).

TABLE 68-1

Population-Based and Tumor Registry Series Examining the Impact of Surgery for the Primary Tumor in Patients Presenting with Stage IV Breast Cancer

Study (reference)	*Years*	*Source*	*n*	*No. of Patients Who Had Surgery*	*Radiation*	*Survival*		*Primary End Point*	*Adjusted HR in Surgical Group (95% CI)*	*Characteristics Associated with OS in MVA*
						Surgery	*No Surgery*			
Khan et al. (23)	1990–1993	NCDB	16,024	9,162 (57.2%)	5,806 (36%) unknown site primary vs. metastatic	27.7%–31.8% (3 yrs)	17.3% (3 yrs)	OS	R0 = 0.61 (0.58–0.65) R1= 0.75 (0.71–0.79)	Clear margins, systemic therapy, number of metastatic sites
Rapiti et al. (38)	1976–1996	Geneva Cancer Registry	300	127 (42.3%)	Higher in surgery group 21% vs. 5%; $p < .01$	27%	12% (5–yr BCSS)	5-yr DSS[a]	0.6 (0.3–0.7)	Age <60, ER+, surgery with negative margins, bone-only mets, nodal burden, hormonal tx
Gnerlich et al. (31)	1988–2003	SEER	9,734	4,578 (47.0%)	Surgery group: RT 1,875 (41%) No surgery: RT 1,752 (38%)	36 mos (median)	21 mos (median)	OS	0.63 (0.60–0.66)	NR
Ruiterkamp et al. (40)	1993–2004	Netherlands	728	288 (39.6%)	Higher in surgery group 34% vs. 10%, $p < .001$	40% (3 yrs)	25% (3 yrs)	OS	0.62 (0.51–0.76)	Surgery, age, number of metastatic sites, systemic tx
Cady et al. (28)	1970–2002	MGH and BWH tumor registries[b]	622	234 (37.6%)	NR	42% (3 yrs)	25% (3 yrs)	OS	NR	Young age, bone-only metastasis
Dominici (29)	1997–2007	NCCN Breast Cancer Outcomes Database	290	54 (18.6%)	Surgery group: any RT 13% No surgery: any RT 9%	3.5 yrs (median)	3.4 yrs (median)	OS	0.94 (0.84–1.05)	NR

[a]Breast cancer specific.
[b]Matched-pair analysis.
HR, hazard ratio; CI, confidence interval; OS, overall survival; MVA, multivariate analysis; NCBD, National Cancer Database Study; BCSS, breast cancer–specific survival; DSS, disease-specific survival; ER, estrogen receptor; SEER, National Cancer Institute Surveillance, Epidemiology, and End Results; RT, radiation therapy; NR, not reported; NA, not applicable; MGH, Massachusetts General Hospital; BWH, Dana-Farber Cancer Institute, Brigham and Women's Hospital; NCCN, National Comprehensive Cancer Network.

TABLE 68-2

Single-Institution Series Examining the Impact of Surgery for the Primary Tumor in Patients Presenting with Stage IV Breast Cancer

Study (reference)	*Years*	*Source*	*n*	*No. of Patients Who Had Surgery*	*Radiation*	*Survival*		*Primary End Point*	*Adjusted HR in Surgical Group (95% CI)*	*Characteristics Associated with OS in MVA*
						Surgery	*No Surgery*			
Babiera et al. (25)	1997–2002	MDACC	244	82 (33.6%)	NR	95% (3 yrs)	79% (3 yrs)	OS PFS	0.5 (0.21–1.19) 0.54 (0.38–0.77)	Single metastatic site, HER2+, Caucasian ethnicity
Blanchard et al. (27)	1973–1991	Baylor College of Medicine	395	242 (61.3%)	RT:1 (0.3%) No RT: 361 (91%)	27.1 mos (median)	16.8 mos (median)	OS	0.71 (0.56–0.91)	Surgery, ER+, PR+, number of metastatic sites
Fields et al. (30)	1996–2005	Washington University	409	187 (45.7%)	NR	26.8 mos (median)	12.6 mos (median)	OS	0.53 (0.42–0.67)	Surgery, site of metastasis
Bafford et al. (26)	1998–2005	Boston[a]	147	61 (41.5%)	Higher in surgery group 38% vs. 16%, $p < .01$	3.52 yrs (median)	2.36 yrs (median)	OS	0.47 ($p = .003$)	Surgery, ER+, HER2+, no CNS disease
Le Scodan et al. (24)	1980–2004	Centre Rene Huguenin (France)	581	71 (12.2%)[b]	RT + surgery: 320 (55%) No local therapy: 261 (45%)	43% (3 yrs)	27% (3 yrs)	OS	0.70[c] (0.58–0.85)	Single metastatic site, young age, LRT, site of mets, nodal status
Hazard et al. (32)	1995–2005	Northwestern Memorial Hospital	111	47 (42.3%)	RT 60 (54%) No RT 48 (43%) RT higher in surgery group 67% vs. 29%, $p < .001$	43% (3 yrs)	37% (3 yrs)	OS TTFP	OS 0.80 (0.40–1.52) 0.49	NR
Shien et al. (41)	1962–2007	Japan[d]	344	160 (46.5%)	NR	27 mos (median)	22 mos (median)	OS	NR	NR
Ngyuen et al. (54)	1996–2005	British Cancer Agency (British Columbia, Canada)	733	378 (51.6%)	RT+ surgery: 41 (11%) RT alone: 82 (22%)	21% (5 yrs)	14% (5 yrs)	OS	0.78 (0.64–0.94)	Surgery and/or RT, age, tumor stage, ER+, negative margins, systemic tx

(Continued)

TABLE 68-2 *(Continued)*

Single-Institution Series Examining the Impact of Surgery for the Primary Tumor in Patients Presenting with Stage IV Breast Cancer

Study (reference)	*Years*	*Source*	*n*	*No. of Patients Who Had Surgery*	*Radiation*	*Survival*		*Primary End Point*	*Adjusted HR in Surgical Group (95% CI)*	*Characteristics Associated with OS in MVA*
						Surgery	*No Surgery*			
Leung et al. (33)	1990–2000	Virginia Commonwealth	157	52 (33.1%)	RT: 58 (37%) No RT: 99 (63%)	25 mos (median)	13 mos (median)	OS	NS	Chemotherapy
Neuman et al. (34)	2000–2004	MSKCC	186	69 (37.1%)	RT + surgery: 9 (13%)	40 mos (median)	33 mos (median)	OS	0.71 (0.46–1.09)	ER+, PR+, HER2+
Rashaan (39)	1989–2009	Two Dutch hospitals	171	59 (34.5%)	NR	NR	NR	OS	0.9 (0.59–1.37)	Age <50, Charlson ≤5
Pathy (36)	1993–2008	University of Malaya Medical Centre	375	139 (37.1%)	RT higher in surgery gp 67% vs. 14% $p < .001$	46.3% (2 yrs) 21.3 mos (median)	21.2% (2 yrs) 10.1 mos (median)	OS	0.72 (0.56–0.94)	Clear margins, age <65
Perez-Fidalgo (37)	1982–2005	Hospital Clinico of Valencia	208	123 (59.1%)	RT + surgery: 57 (46%)	40.4 mos (median)	24.3 mos (median)	OS	0.52 (0.35–0.77)	ER+

[a]Dana-Farber Cancer Institute, Brigham and Women's Hospital; and Massachusetts General Hospital.
[b]Number of patients having surgery as only form of local therapy.
[c]HR is for local therapy: surgery + RT versus no local therapy.
[d]National Cancer Center Hospital, Okayama, Japan.
HR, hazard ratio; CI, confidence interval; OS, overall survival; MVA, multivariate analysis; MDACC, University of Texas MD Anderson Cancer Center; NR, not reported; PFS, progression-free survival; RT, radiation therapy; ER, estrogen receptor; PR, progesterone receptor; CNS, central nervous system; LRT, local-regional therapy; TTFP, time to first progression; NS, not significant; MSKCC, Memorial Sloan-Kettering Cancer Center.

However, nearly all of these studies also revealed that surgery for the primary tumor was more likely to be pursued in women who were younger, had fewer metastatic sites, and had bone-only or estrogen-receptor (ER) positive disease, leading some to question whether these results truly reflected a consistent benefit from local therapy or consistent bias in patient selection.

Efforts to address some of these potential biases have included a case-matched pair analysis using the tumor registries from two large hospitals (28) and a second matched analysis using the National Comprehensive Cancer Network (NCCN) Breast Cancer Outcomes Database (29). In the first study, Cady et al. (28) performed a matched pair analysis of 622 Massachusetts residents who presented with an intact primary tumor and metastatic disease from 1970 to 2002. Cases and controls were matched by age (±5 years), date of diagnosis (±5 years), location of metastases, ER status, and use of systemic therapy. Among the group as a whole, overall survival (OS) was better for the 234 (38%) of patients who had surgery ($p < .0001$), and when case matching was performed, association between surgery and improved survival persisted for all groups except those with visceral metastases ($p = .09$), which reflected a population of 100 women. In the second matched analysis, Dominici et al. sought to eliminate "response to systemic therapy" as a potential selection bias for surgery by including only those patients who received surgery first, followed by systemic therapy or systemic therapy alone. Among 1,048 patients in the NCCN Breast Cancer Outcomes Database diagnosed with stage IV breast cancer from 1997 to 2007, 609 were eligible for the study and 551 patients had data available for matching by age, ER status, HER2 status, and number of metastatic sites. Ultimately, 236 patients who received systemic therapy alone were matched to 54 patients who received surgery, and there was no difference in survival between the two groups (median 3.4 years no surgery vs. 3.5 years surgery), suggesting that extirpation of the tumor itself may not be responsible for the survival benefit demonstrated in other series. This study, however, is limited by the small number of patients having surgery, the lack of information regarding the indications for surgery or timing of surgery available in the database, as well as and greater use of surgery in earlier time periods, all of which may have biased the study toward improved survival in the patients treated in the later years.

Although the survival benefit is less consistent among the single-institution studies listed in Table 68-2, an advantage of single-institution series is their ability to provide greater detail regarding specifics of treatment, course of the disease, and other patient factors. The Washington University series included an adult comorbidity evaluation (ACE-27) score that categorized comorbid conditions as none, mild, moderate, and severe; they found that this score was not significantly predictive of survival in patients with metastatic breast cancer (30). They also included patients who underwent surgery at any point in their disease course, and in about half of the cases (53%), surgery was undertaken to palliate symptoms associated with the primary lesion. In contrast, 43% of patients were believed to undergo surgery in the setting of unknown metastatic disease, which was then discovered on subsequent staging examination performed within one month of surgery. In related reports from Northwestern Memorial Hospital (32) and Memorial Sloan-Kettering Cancer Center (MSKCC) (34), 26 of 47 (55%) and 34 of 69 (49%) women with stage IV breast cancer underwent surgery for the primary tumor prior to staging, respectively, suggesting a potential bias toward a lower burden of metastatic disease.

To assess the impact of potential *stage migration bias*, Bafford et al. (26) examined the survival for women diagnosed with stage IV breast cancer prior to surgery as compared to those diagnosed after surgery in their series of 61 patients and found that the benefit of surgery was only realized among patients operated on before the diagnosis of metastatic disease. This is in contrast, however, to series from Spain (37) and the Netherlands (45) which found no differences in overall survival based on the timing of surgery relative to the diagnosis of metastatic disease. Unfortunately, the frequency with which unsuspected metastatic disease is diagnosed after surgery is not ascertainable from population-based registries, yet this may partially account for the finding that younger patients with smaller tumors were more likely to undergo surgical resection in all reported series. Alternatively, surgery may be a surrogate for more aggressive therapy overall in select patients with metastatic disease.

Data from single-institution series can also be used to generate hypotheses about which subsets of patients may benefit from more aggressive local therapy. Fields et al. (30) found that women with bone-only metastatic disease lived longer than those with metastases at other sites, regardless of whether surgical resection was performed (adjusted HR 0.76; 95% CI 0.58–0.98). This is consistent with the known indolent course of osseous metastases and supports the findings from the stratified analysis of the Geneva Cancer Registry (38). Modern series that include patients treated in the era of molecularly targeted therapy also demonstrate that patients with ER, progesterone-receptor (PR), and/or HER2 positive disease have an improved OS (25,26,34). In the series from MSKCC, which was limited to patients treated in the time period following the introduction of trastuzumab for HER2 amplified disease (2000–2004), the association between surgical therapy of the primary tumor and improved OS was evident in patients with ER, PR, and/or HER2 amplified disease, but not for those with triple-negative disease, suggesting that the impact of local-regional control may vary by molecular subtype in the setting of stage IV disease just as it does in earlier-stage disease (35,42). Viewed in aggregate, all series reported over the last decade consistently demonstrate that about half of women presenting with *de novo* metastatic breast cancer undergo resection of the primary tumor, and the majority of the studies suggest that women undergoing surgery survive longer than those treated without resection. Although all available studies are retrospective and therefore inherently biased by the inability to control for patient selection and other treatment factors, a recent meta-analysis of 15 of the aforementioned studies, which included meta-regression to balance for number and type of metastatic sites, ER/HER2 status, age, use of radiotherapy, and systemic therapies, confirms the results of the individual series. Surgery of the primary tumor was an independent factor for improved survival in multivariate analysis, with an HR of 0.69 (0.63–0.77, $p < .00001$) (43). Further, the meta-regression analysis demonstrated that the survival benefit for surgery was independent of age, extent or site of metastatic disease, and HER2 status, but was most evident in the setting of multimodality care; the more treatment modalities that were offered to patients (systemic therapies and/or radiotherapy), the more the benefit of surgery emerged. Interestingly, populations with fewer ER positive breast cancer patients derived more benefit from surgery in this meta-analysis. While this may reflect the known indolent course of ER positive osseous metastases, these findings provide further evidence that the dogma to reserve surgery only for the palliation of symptoms in stage IV disease may be outdated in the era

of multidisciplinary care and molecularly targeted therapy, and support the rationale to address the role of local therapy for the primary tumor in stage IV disease according to biologically meaningful subtypes.

SURGERY FOR LOCAL CONTROL

In addition to the potential impact on survival, there are many other questions regarding the role of surgery for the primary tumor that remain unanswered. The rationale for surgery in the 50% of patients with stage IV breast cancer in all reported series is uncertain, but may have been related to "fear of advanced local-regional disease" or patient preference. The low morbidity of breast surgery compares favorably with toxicity profiles of many systemic therapy agents used in the metastatic setting, perhaps adding to the appeal of surgical local control. In a retrospective review of surgical practice patterns over a 15-year period at MSKCC (44), the frequency of mastectomy in the setting of any stage IV disease remained stable at 1.7% of all mastectomies performed, yet the indication for mastectomy as cited by the treating surgeon changed over time. The rate of traditional "toilet" mastectomy or mastectomy performed for "symptoms" of local disease decreased from 41% to 25% between the two time periods analyzed (1990–1995 and 2000–2005), while rates of "local control" mastectomy increased from 34% to 66%. Among 84 patients presenting with *de novo* stage IV disease from the same study, a more detailed review of treatment data demonstrated that the most frequent indication for surgery of the primary tumor was to "optimize local control" in the setting of a complete, good, or stable response of distant disease to systemic therapy. Surgery was performed for symptom control in 30 of 84 (36%) patients in this series presenting with *de novo* stage IV disease.

One cannot assume that the primary tumor will respond to systemic therapy in parallel with metastatic sites of disease, and progressive local disease may lead to impaired quality of life and the need for palliation. The true frequency with which unresected local disease becomes a "local control" problem or "symptom control" problem requiring surgery in the modern era is difficult to ascertain without prospective collection of patient information. Single-institution data range from a low of 9% (7 of 82 patients) undergoing palliation in the University of Texas MD Anderson Cancer Center (MDACC) series (25), to 36% in both the MSKCC dataset (44) and the Northwestern series (32), to 53% reported in the Washington University series (30). All of these figures are likely biased by the culture of the individual institution and the inherent inaccuracy of abstracting "subjective" information by retrospective chart review. Data regarding the frequency of recurrent local disease at time of death are also limited. In the MSKCC series, patients undergoing surgery for local control (n = 128) had an 11% incidence of death with recurrent local disease (median follow-up, 35 months), and patients undergoing surgery for palliation of symptoms (n = 49) had a 10% incidence of death with recurrent local disease (median follow-up, 29 months).

Perhaps the strongest evidence to date in favor of surgery for local control is that from Hazard et al. (32), who reported that surgery is strongly protective against uncontrolled chest-wall disease, and further, that a controlled chest wall mediates the survival benefit of surgical resection. In their report from Northwestern University, surgery was strongly protective against symptomatic chest wall disease in 47 patients with stage IV breast cancer undergoing surgery either at diagnosis or following response to systemic therapy, as compared to 64 patients managed either nonoperatively or with delayed (palliative) surgery (odds ratio [OR] 0.14, 95% CI 0.04–0.50, p = .002) (32). Ultimately, 23 of 64 patients (36%) required delayed local palliation. A Translational Breast Cancer Research Consortium prospective, multi-institutional registry study TBCRC 013 examining the role of surgery for the primary tumor in *de novo* stage IV disease has recently completed accrual and data presented at the 2013 San Antonio Breast Cancer Symposium demonstrated that the need for true surgical palliation of symptoms is infrequent in the modern era (45).

Additional support for the rationale of optimizing local control includes the identification of a larger population of patients with oligometastatic or low-volume metastatic disease, many of whom would have been treated aggressively for cure in the era before widespread magnetic resonance imaging (MRI) and positron emission tomography (PET). The natural history of this category of stage IV breast cancer is largely unknown, yet conceptually, they may not be very different from patients with earlier-stage disease who are found to harbor occult bone marrow micrometastases. Studies suggest that bone marrow micrometastases are present in up to 30% of stages I to III patients at the time of diagnosis and are associated with a poor OS and breast cancer disease-free survival (46), yet surgical treatment and adjuvant therapy are routinely performed in these patients, resulting in a significant number of long-term survivors. Hortobagyi (47) has also suggested that an aggressive multimodal approach that includes surgery produces long-term, disease-free survival or cure in a subset of patients with limited metastatic breast cancer. These long-term survivors with stage IV disease are typically young, with limited metastatic disease and excellent performance status (47,48).

An analogous situation is the breast cancer patient with a solitary recurrence or metastatic lesion that is resected surgically or treated with radiotherapy at curative doses, rendering them stage IV NED (no evidence of disease). Although this again represents a minority of patients with metastatic disease, a review by Singletary et al. (49) demonstrates that surgery combined with adjuvant therapy, compared with radiation or systemic therapy alone, can result in significantly better survival in select patients with metastatic disease to the lung, liver, brain, or sternum. Across the four disease sites (lung, liver, brain, bone), better patient outcomes after surgery were associated with good performance status, long disease-free interval after treatment of the primary tumor, complete resection of the tumor, and restriction of metastasis to single tumors or to a single site.

Additional theoretical advantages for removing the primary tumor include cessation of tumor-cell seeding into the circulation and decreasing the overall tumor burden. The level of circulating tumor cells (CTC) before treatment is an independent predictor of progression-free survival and OS in patients with metastatic breast cancer, and patients who experience a decrease in the level of CTC after the initiation of therapy have a better prognosis than those who do not (50). Whether or not these theories are valid in the setting of metastatic breast cancer with an intact primary is uncertain and awaits the results of ongoing randomized trials.

ADDITIONAL QUESTIONS AND THE VALUE OF RANDOMIZED TRIALS

The benefit for surgery of the primary tumor demonstrated by the meta-analyses (43) is consistent with a now well-established body of evidence that local therapy has an impact on survival in the setting of multimodality therapy for breast cancer patients with stage I to III disease (see Chapter TKTK for full discussion). However, the meta-analysis cannot determine

which type of surgery—mastectomy or lumpectomy—is better, and it cannot fully assess the role of radiotherapy or axillary surgery. Historically, surgery in stage IV disease was limited to palliation, hence the term *toilet mastectomy*; however, in the series from Rapiti et al. (38) and Khan et al. (23), 31% and 46% of all patients, respectively, had T1 and T2 tumors. Only 12% and 16% of all patients, respectively, had T3 tumors, suggesting that many primary tumors in patients with metastatic disease are amenable to treatment with lumpectomy, a procedure with very low morbidity, yet the role of radiotherapy in this setting is uncertain. Prospective randomized trials of breast conservation in early-stage disease provide consistent evidence that lumpectomy with negative margins *plus* radiation therapy are important in local control; however, in the metastatic setting, data regarding the use of regional radiotherapy are limited, and there are no guidelines for treatment.

The use of local radiation cannot be distinguished from radiation to metastatic sites in the National Cancer Database Study, and although most other series report that the use of radiation was higher in the surgery groups (Tables 68-1 and 68-2), only the Geneva Cancer Registry reported the lack of radiotherapy in women treated with lumpectomy to be independently associated with an increased hazard of death. Some authors have also suggested that radiotherapy to the primary site may be an acceptable alternative to surgery with potentially decreased morbidity (24,51). In the series by Le Scodan et al. (24), surgery was used in only 71 of 320 patients who received local-regional radiotherapy, and when compared to patients who received no local-regional therapy, radiotherapy was significantly associated with improved survival on multivariable analysis (HR 0.70, CI 0.58–0.85, $p < .001$). Confirmation of the role of radiotherapy following surgery in the setting of metastatic disease will be achieved only through randomized trials.

If removal of the primary tumor improves survival by reducing tumor burden, one might also assume that reduction of the tumor burden in the axillary nodes would be beneficial, yet it remains controversial as to whether there is a survival benefit for any patient with breast cancer who undergoes axillary dissection. This procedure continues to be performed, however, in stage II and III breast cancer, primarily for local control, and to obtain prognostic information and guide treatment. In the metastatic setting, neither Khan (23) nor Rapiti (38) were able to demonstrate a benefit for axillary dissection, although it has been suggested that this was likely due to the small number of axillary dissections performed and their correlation with excision to negative margins (52). In a report from MDACC (53), among the 82 patients who underwent surgical intervention at the primary site in combination with appropriate systemic therapy, including trastuzumab, patients who underwent axillary lymph node dissection demonstrated a trend toward improved OS on univariate analysis compared to patients who underwent sentinel lymph node biopsy alone or no axillary surgery (log rank test, $p = .051$). Axillary clearance is encouraged for patients with positive nodes in all but one of the ongoing randomized trials.

The timing of surgery, or how and when to integrate surgery into the multidisciplinary management of patients with stage IV breast cancer, is also relevant to the hypothesis that local therapy of the primary tumor is beneficial. If the tumor functions as a source of new metastatic deposits, treating it early in the course would intuitively seem to have greater benefit. Yet, the available data are limited and conflicting. In addition to the two series described above that assessed the timing of surgery relative to the diagnosis of metastatic disease (26,37), in the report from MDACC (53), patients having surgery 3.0 to 8.9 months after diagnosis or greater than 9.0 months after diagnosis had a longer metastatic progression-free survival that those having surgery within 3.0 months of diagnosis. There were several other significant differences between these surgical groups, such as use of chemotherapy or hormonal therapy alone, margin status, type of surgery, and indication for surgery, making it difficult to draw any meaningful conclusions. Yet, this study clearly suggests that delaying surgery until after primary systemic therapy, as is done in cases of locally advanced breast cancer, may be beneficial.

Prospective randomized trials designed to examine the role of local-regional treatment in patients with stage IV disease are now underway in five countries (Table 68-3). The first trial from Tata Memorial Hospital opened in 2005 with an accrual goal of 350 patients randomized to complete resection, including axillary surgery or no surgery following six cycles of chemotherapy. Preliminary results reported at the 2013 San Antonio Breast Cancer Symposium suggested no difference in overall survival between those who received surgery and those who did not; however, the authors stated concern over what appeared to be a shorter time to distant disease progression after surgery. A multicenter study initiated in Turkey in 2007, the Turkish Federation study (MF07-01) addresses the question of whether surgery before systemic therapy versus systemic therapy alone is associated with improved survival. In this trial, local-regional treatment could be mastectomy or lumpectomy followed by radiation therapy, with or without axillary dissection in patients with positive nodes. Early results from this trial were also presented at the 2013 San Antonio Breast Cancer Symposium, again showing no improvement in survival with surgery. However, as both of these studies were only presented in abstract form, additional information about the details of the patient populations and systemic therapies they received are needed to draw firm conclusions.

Similar to the Turkish Federation study, the Danish Breast Cancer Trialists Group recently opened the SUBMIT (Systemic therapy with or without up-front surgery of the primary tumor in breast cancer patients with distant metastases at initial presentation) study, with an accrual goal of 258 patients in each arm and an anticipated accrual time of 60 months.

Finally, the Eastern Cooperative Oncology Group trial in the United States (E2108) and the Japan Clinical Oncology Group Study (JCOG1017) trial, are both designed to address the role of surgery for the primary tumor in patients who are not refractory to upfront optimal systemic therapy. The choice of primary systemic therapy in both studies is made with consideration of biologic subtype (ER, HER2 status) and disease burden, and randomization to surgery or no surgery is performed after a predefined period of treatment. Complete resection with clear margins is required in both studies; however, the trials differ with respect to the role of axillary clearance and radiation therapy.

CLOSING REMARKS

New insights into cancer biology have led to an increased focus on biologic subtypes and targeted therapies, resulting in improvements in OS for patients with both early- and late-stage disease. A growing body of evidence suggesting that local treatment may have a greater influence on breast cancer survival than previously thought has now also led to the opening of several well-designed prospective trials to answer the question of whether local-regional treatment can further improve outcomes for patients with metastatic breast cancer. These trials raise intriguing questions, and in parallel with new biological concepts of breast cancer metastasis, challenge the traditional surgical approach to stage IV disease.

TABLE 68-3

Ongoing Randomized Trials Evaluating the Role of Surgery in Stage IV Breast Cancer

	Opened	*Accrual Goal*	*Eligibility*	*Stratification*	*Treatment Prerandomization*	*Local-Regional Therapy*	*Primary End Point*	*Secondary End Point*
Tata Memorial Hospital, India (55–57)	2005	350	M1 disease, resectable primary tumor	HR status, visceral vs. bony mets, no. of met sites	6 cycles chemotherapy	Complete resection including ALND + RT as indicated	OS	6-mo PFS
Turkish Federation (MF07-01) (58)	2007	271	M1 disease, resectable primary tumor	None	None	Complete resection, ALND if positive nodes, RT for all cases with BCS, PMRT per individual protocol	OS	PFS, QOL
Danish Breast Cancer Trialists Group (SUBMIT) (59)	2012	516	M1 disease, resectable primary tumor	Age, site of metastasis, HR status, HER2/neu status	None	Resection with clear margins, RT if margins not clear, ALND encouraged for positive nodes	2-yr survival	OS, QOL
Eastern Cooperative Oncology Group (ECOG E2108) (60)	2011	880 (assumes 616 randomized)	M1 disease, intact primary, stable disease or objective response to optimal systemic therapy	HR status, HER2/neu status, endocrine therapy, chemotherapy, number of metastatic organs	Optimal[a] therapy 4–6 mos	BCS or mastectomy, clear margins, ALND if positive nodes, RT for all cases with BCS, PMRT per individual protocol	OS	Local control QOL
Japan Clinical Oncology Group (JCOG 1017) (41)	2011	500 (assumes 410 randomized)	M1 disease, resectable primary tumor, no brain mets, stable disease or objective response to 3 cycles optimal therapy	ER status, HER2 status, metastatic site(s), institution	Optimal therapy[a] × 3 cycles	Complete resection of primary tumor, no axillary clearance, no RT	OS	Distant PFS, local PFS, need for palliation, adverse events[b]

[a]Optimal therapy defined according to ER and HER2 status, and sites/burden of metastatic disease; use of standard clinical guidelines encouraged.
[b]Includes adverse events of chemotherapy, operative morbidity, and serious adverse events.
HR, hazard ratio; ALND, axillary lymph node dissection; RT, radiation therapy; OS, overall survival; PFS, progression-free survival; BCS, breast-conserving surgery; PMRT, postmastectomy radiation therapy; QOL, quality of life; ER, estrogen receptor; BCT, breast-conserving treatment.

MANAGEMENT SUMMARY

- Survival in patients with metastatic breast cancer is improving due to more sensitive imaging modalities, resulting in an increased rate of diagnosis in asymptomatic patients with a low disease burden, and to improvements in systemic therapy.
- The role of surgery of the intact primary tumor on survival in patients with metastatic disease is uncertain. Multiple retrospective studies suggest a survival benefit, but selection bias in these studies prohibits firm conclusions. The available data suggest that local-regional treatment may be considered as part of a multimodality treatment in patients with favorable clinicopathologic characteristics, including young age, limited metastatic disease burden, and ER-positive tumors.
- Surgery is an effective means of maintaining local control on the chest wall during the patient's lifetime. Either mastectomy or lumpectomy are appropriate approaches when surgery is chosen. The data on axillary surgery are extremely limited, but if surgery is undertaken, removal of all gross disease seems prudent.
- The benefit of radiation therapy following surgery is uncertain, and decisions regarding its use should be made on a case-by-case basis.
- Formal randomized trials to examine the role of surgery in patients with *de novo* stage IV breast cancer are currently underway in five countries.

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CHAPTER 69

Management of Local Regional Recurrences after Primary Breast Cancer Treatment

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CHAPTER CONTENTS

INTRODUCTION

Contemporary treatments for early-stage breast cancer have minimized the risk of local-regional recurrence (LRR) to a cumulative frequency that is typically <1% per year (1,2). While multimodality advances in surgical approaches, radiation, and systemic therapy (chemotherapy, targeted drug therapy) all contribute to these low recurrence rates, the management of LRR remains challenging with limited data to guide subsequent treatment. The confirmation of a recurrent diagnosis may have widespread psychological and social implications for the patient, in addition to leading to loss of the conserved breast after breast conservation therapy (BCT), or causing uncomfortable and potentially difficult to control chest-wall disease after mastectomy. The care of each patient with LRR must be tailored to that individual's needs, using a multidisciplinary team approach. The treatment strategy delivered to each patient with LRR should include a combination of active therapy and symptom palliation, with the ultimate aim of ensuring that the patient's quality of life is maintained at an optimum level for as long as possible.

Initial clinical-pathologic features that lead to increased risk of LRR include number of involved lymph nodes, primary tumor size, and ultimate stage of disease. Other prognostic factors that may affect a patient's risk for LRR include margin status after definitive surgery, tumor grade, patient age, hormone receptor status, receipt of adjuvant radiation, receipt of systemic therapy, and possibly primary tumor oncogene expression. LRR is most often detected clinically after mastectomy, and radiographically after BCT. Signs and symptoms of LRR include palpable nodules or induration, skin ulceration or other suspicious skin changes, thickening of the breast/chest wall, and abnormally enlarged or hard lymph nodes (Fig. 69-1).

When a patient experiences a LRR, the disease can recur locally and/or regionally, with or without distant metastasis. A local recurrence is defined as recurrent cancer in the previously treated ipsilateral intact breast (BCT) or along the chest wall (postmastectomy). Regional recurrences, which generally occur in under 4% of patients (3), arise most often within the lymph nodes of the axilla or supraclavicular fossa and less frequently in the infraclavicular chain or internal mammary nodes. While distant metastasis from breast cancer can occur anywhere in the body, the most common sites include bone, liver, and lungs.

The overall prognosis after a LRR is related to the disease-free interval before recurrence, with early recurrences (≤2 years) carrying a worse overall prognosis than LRRs that occur later (4). Other factors affecting overall prognosis after LRR include the extent of local-regional disease, presence of metastatic disease, hormone receptor status and HER-2 status at the time of recurrence, and patient age. A significant portion of patients with LRR will present with simultaneous distant metastasis, but for those with isolated local recurrence, aggressive treatment can offer patients long-term survival. While the hazard ratios for LRR are highest in the first few years after diagnosis of breast cancer, there is a persistent rate of relapse beyond 15 years (5).

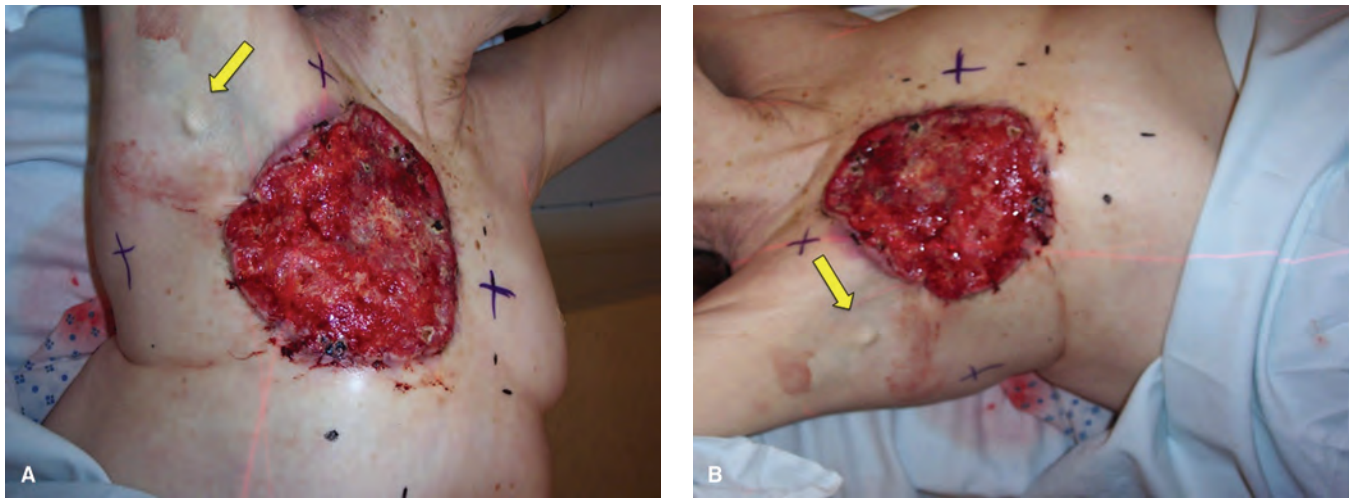

FIGURE 69-1 **(A)** and **(B)** An advanced CWR in a patient who was not a candidate for surgical resection due to her elderly age and poor performance status. The CWR was ulcerated at presentation and continued to grow despite chemotherapy. Only superficial debridement was performed. Note the arrow highlighting the large, fixed palpable lymph node in the axilla.

Thus, long-term follow-up for breast cancer patients at risk of LRR is warranted.

Because new primaries should theoretically have a prognosis independent of the primary breast cancer, attempts have been made to distinguish LRR as 'true recurrence' versus 'new primary' based on location/quadrant of the recurrence (i.e., whether the recurrence is in or near the quadrant of primary disease, or is distant from the primary tumor) and histopathologic features (Fig. 69-2). Additionally, radiation oncologists have further classified ipsilateral breast tumor recurrence (IBTR) as a 'marginal miss' if the recurrence is adjacent to, but not within, a previously radiated area. Retrospective series suggest that true recurrences have an earlier median time to presentation, are located near the lumpectomy cavity or scar, have histology similar to the primary tumor, and are characterized by a more aggressive natural history and a higher association with concurrent metastasis, earlier metastasis, and shorter survival (6,7). While earlier studies may have misclassified true recurrences versus new primaries, recent improvements in the classification of breast cancers and molecular analysis of clonal differences may help to distinguish patients with true recurrences who carry an overall worse prognosis (8). Nevertheless, given evidence suggesting the association of LRR with the development of distant failure and subsequent diminished overall survival (5), aggressive management of isolated LRR in a patient without documented distant metastasis is of paramount importance. Even for a patient with documented distant metastasis at the time of LRR, optimal local-regional therapy can significantly reduce the morbidity of uncontrolled LRR; however, the potential toxicity of local-regional treatment modalities needs to be weighed against possible benefits in quality of life.

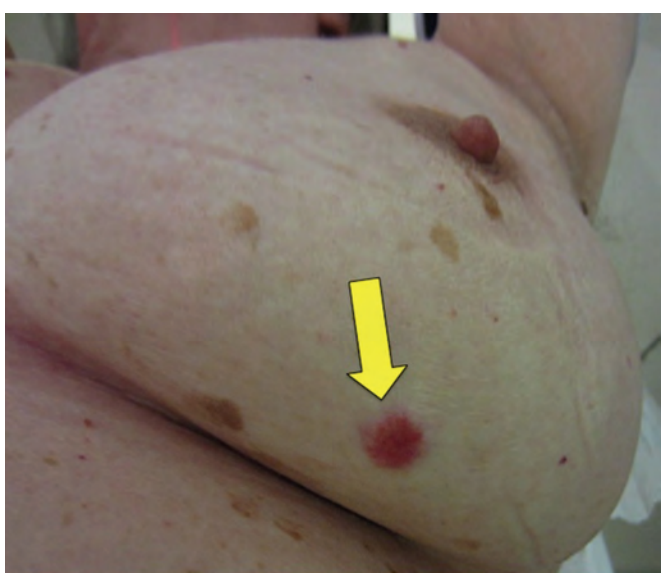

FIGURE 69-2 Ipsilateral breast tumor recurrence in a patient previously treated with breast conservation. Despite the patient's other skin lesions, the index of suspicion remained high, and a biopsy confirmed a local recurrence in the previously treated breast. The tumor recurrence was located in a separate quadrant remote from the primary tumor.

SCREENING AND EVALUATION FOR LRR

Routine surveillance for LRR after treatment for breast cancer should be conducted with regularly scheduled follow-up visits including a complete history/physical examination, yearly mammography (after BCT), and routine self-examination. Any additional work-up should generally be symptom-directed. To date, there are no data supporting the routine use of any diagnostic imaging (outside of breast imaging), laboratory testing, or tumor markers to detect recurrence in an asymptomatic breast cancer survivor.

Approximately one third of all IBTRs are found on surveillance mammography alone; the remainder are detected by physical examination with or without follow-up imaging (9). Most IBTR located close to the lumpectomy site tend to occur earlier than those remote from the primary tumor site (10), and tend to have the same mammographic appearance

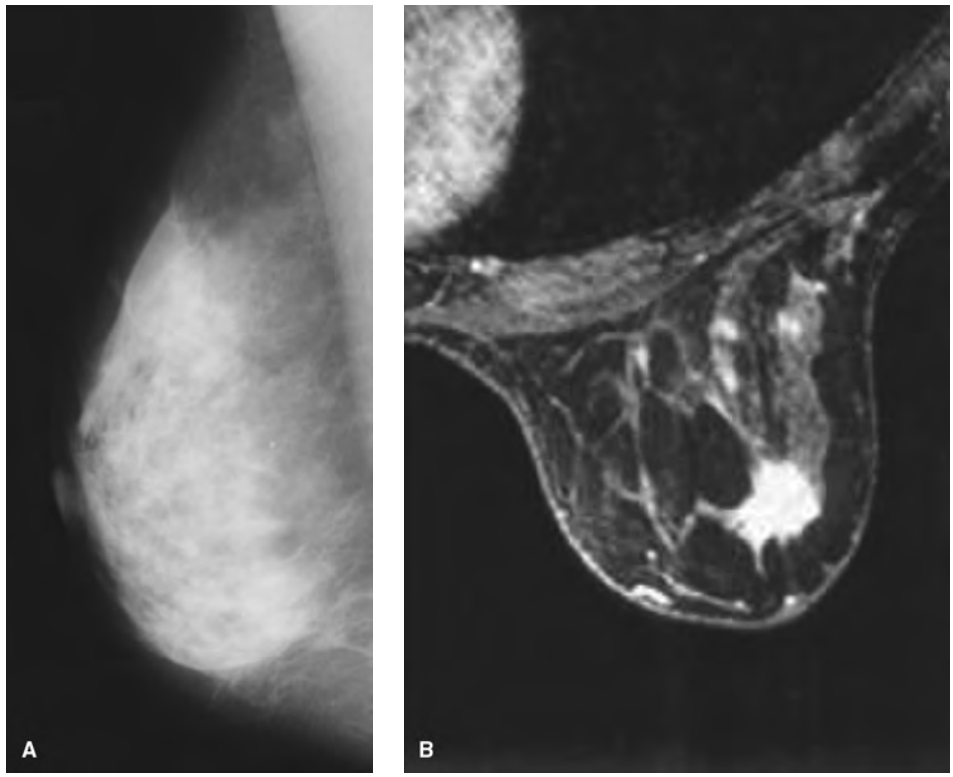

FIGURE 69-3 Imaging of an ipsilateral breast tumor recurrence in a patient previously treated with breast conserving surgery and radiation. Given the density of the breast and scar tissue, mammogram was unable to detect recurrence. MRI was more sensitive in discerning density and scar tissue from tumor.

as the primary tumor (11). Detection of IBTR by mammography alone can be challenging due to post-operative and post-radiation scar tissue development, but detection of IBTR is higher when recurrent tumors are associated with calcifications.

Breast MRI can also be utilized to screen for LRR (Fig. 69-3), though the evidence to support the benefit of its use, particularly to detect LRR, needs to be established. Sensitivity of MRI for detection of recurrence ranged from 75% to 100%, while specificity ranged from 66.6% to 100% (12). Both sensitivity and specificity increase when MRI is performed after a longer time interval from the original surgery, although long-term follow-up data supporting this observation is limited to approximately 3 years (12). Other conditions (such as fat necrosis, foreign body cysts, bony nodules, or unrelated second primary tumors) may resemble a LRR; thus, the area of concern should always be pathologically confirmed with a biopsy.

At the time of biopsy, molecular subtype and variations in hormonal receptor and HER-2 status of the LRR should be reevaluated, as discordance between the primary tumor and recurrent tumor will be important for systemic treatment-related decisions. There should be a relatively high level of suspicion for simultaneous distant metastasis when LRR are detected, and thus, a full metastatic workup is warranted, which may include CTs, MRIs, PET/CT, and/or bone scan. This workup should be performed to determine the extent of recurrent disease prior to rendering decisions regarding aggressive local-regional management. For breast-conserved patients, in addition to routine diagnostic mammography and ultrasound, a breast MRI may help to elucidate multifocal or more extensive disease, and may be able to differentiate recurrence from scar tissue, as invasive recurrence often enhances on MRI whereas scar tissue does not (12). While a chest x-ray is typically not beneficial, a CT scan may be particularly useful in the postmastectomy recurrence setting to determine the extent of disease in superficial tissue versus more extensive pectoralis muscle or transmural involvement, in differentiating between radiation-induced versus tumor-induced brachial plexopathy, and in determining presence of visceral metastasis or enlarged lymph nodes. For any patient with suspicion of metastatic disease, efforts should be made to confirm the metastasis histopathologically when technically feasible.

MANAGEMENT RESULTS

IBTR after BCT

A standard treatment for optimizing local control in the definitive setting for early stage breast cancer is breast conservation therapy, which typically includes breast conserving surgery followed by adjuvant radiation therapy (5). Definitive adjuvant radiation therapy generally entails a course of whole breast radiation therapy, typically 44 to 50 Gy in 1.8 to 2.0 Gy per fraction (standard fractionation), often followed by a 10–16 Gy boost dose to the lumpectomy cavity, which is delivered over 5 to 6.5 weeks. Alternatively, patients may receive hypofractionated radiation, which delivers biologically equivalent doses of radiation in 3 to 4 weeks and has been demonstrated to be as safe and efficacious as standard fractionation (13). Over the last several years, increasing numbers of women have been treated with partial breast radiation (typically

delivered twice daily over 1 week) as a faster alternative to conventionally fractionated whole breast radiation. While the existing data on definitive partial breast irradiation cohesively suggest excellent local-regional control comparable to that of whole breast radiation, prospective data with long-term outcomes and safety are lacking (14). Irrespectively, given the limited tolerance of normal tissue after these definitive doses of radiation to the breast, IBTRs occurring in previously radiated BCT patients are often treated with mastectomy, which is generally felt to be the standard management approach. For patients who have not been treated with radiation therapy as a component of their initial treatment, a repeat breast conservation procedure with excision of the recurrence followed by a course of radiation therapy can be considered. It remains uncertain whether mastectomy after IBTR improves outcomes compared with lesser surgery. A number of studies comparing mastectomy and breast conservation as treatment for IBTR are detailed in Table 69-1. Together, these studies suggest that the rates of recurrence are greater after a second local excision compared with mastectomy, but whether this ultimately translates to improved survival outcomes remains unclear (15).

Second attempts of breast conservation in previously radiated patients with small, histologically favorable local relapses have been reported. The initial experiences of salvaging an IBTR with a breast conserving approach utilized a wide local excision alone. In carefully selected patients with mobile tumors measuring less than 2 cm in size and favorable pathologic features, 5-year local control approaches nearly 80%, and is significantly better for patients in whom a negative margin was attained on the second local excision surgery (20). The published data cohesively suggests that with a second local excision without additional radiation therapy, local relapse rates range from approximately 20% to 50% as shown in Table 69-1.

Based on the observation that the risks of local relapse reported after a second breast conserving surgery approximates the risk of local relapse experienced after primary breast conserving surgery (~35%), there have been efforts in evaluating re-irradiation after second local excision for IBTR, with the hopes of decreasing the local relapse rates with a similar magnitude of benefit as seen in definitive settings (approximately two-thirds risk reduction). In previously radiated BCT patients, a repeat breast conserving approach should only be attempted if the patient is refusing salvage mastectomy, and re-irradiation should only be utilized on protocol where toxicity and efficacy can be monitored, documented, and reported.

With existing knowledge and expertise using partial-breast irradiation in the primary setting, various techniques to deliver a second repeated course of radiation for LRR have been investigated. Low-dose rate interstitial brachytherapy, which has the longest clinical experience for partial breast irradiation in the definitive setting (14), has been utilized in the hands of experienced clinicians to deliver a re-irradiation dose to the tissue surrounding the lumpectomy cavity. The rationale for re-irradiation with a partial breast technique is based on the hypothesis that focal treatment can eradicate microscopic disease while maintaining normal tissue tolerance, and thus have acceptable side effects. Various methods of re-irradiation of IBTR have been described; these include interstitial brachytherapy, where multiple interstitial catheters are inserted into the high-risk area (typically 1–2 cm surrounding the lumpectomy cavity). The catheters are after-loaded with low-dose-rate sources to deliver 30 to 55 Gy to the previously radiated breast (22). Furthermore, intra-operative radiation has been described to deliver a targeted x-ray to the IBTR resection cavity at the time of the resection surgery (23). Lastly, utilization of high dose-rate intraluminal brachytherapy (i.e., Mammosite®) (24) and external-beam partial breast techniques (25) for re-irradiation of the high-risk area after repeat BCT have also been reported. The results of published studies are shown in Table 69-2. For patients who received partial breast irradiation as part of their primary, definitive treatment who subsequently experience IBTR, the data to salvage these patients with a repeat breast conserving approach are very limited.

Factors to consider when evaluating a patient for re-irradiation after BCT include interval between initial radiation treatment and recurrence, anatomic considerations (such as close proximity to skin) that may preclude safe and cosmetically favorable delivery, and whether there is ample residual breast volume amenable to re-irradiation. It is important to note that because safe thresholds for normal breast tissue, skin, muscle, bone and subcutaneous tissue are not established in this setting and existing data are limited, all BCT patients being considered for a second breast conserving approach with re-irradiation should be treated on Institutional Review Board (IRB)-approved protocols with the informed consent of the patient.

Currently, a phase II national trial, RTOG 1014, is underway and will evaluate the adverse events associated with the use of a repeat breast conserving approach after IBTR. In this trial, patients who experience an IBTR less than 3 cm in size with a time interval of greater than one year from completion of their initial course of radiation will undergo a second

TABLE 69-1

Surgical Treatment of IBTR

		Mastectomy			*Breast conservation*		
Study	*Med FU (months)*	*N*	*2nd LR (%)*	*5 yr OS (%)*	*N*	*2nd LR (%)*	*5 yr OS (%)*
Abner (15)	39	106	7	79	16	31	81
Alpert (16)	146	116	7	66	30	7	58
Dalberg (17)	156	65	19	59	14	50	NR
Gentilini (18)	44	127	NR	NR	161	24	82.2
Ishitobi (19)	40	46	NR	NR	78	22	72.4
Kurtz (20)	53	43	12	53	55	32	NR
Salvadori (21)	73	134	4	70	57	19	85

Med FU, median follow-up; 2nd LR, second ipsilateral local tumor recurrence; OS, overall survival; NR, not reported.

TABLE 69-2

Results of Re-irradiation Using a Partial Breast Technique after Repeat Breast Conservation for Local Relapse

Study	*Technique of rPBI*	*N*	*Median FU (months)*	*2nd LR N (%)*	*5 year OS*
Deutsch (25)	EBRT, electron	39	51.5	8 (21%)	78%
Hannoun-Levi (22)	LDR	69	50	11 (16%)	92%
Chadha (26)	LDR	15	36	1 (7%)	100%*
Trombetta (24)	Interstitial or intra-cavitary	26	38	1 (4%)	NR
Resch (27)	Pulsed dose rate (+EBRT)	17	59	5 (29%)	76%
Maulard (28)	LDR	38	40	8 (21%)	NR
Mullen (29)	EBRT	16	NR	4 (25%)	NR
Kraus-Tiefenbacher (23)	Intraoperative radiation	15	26	0 (0%)	100%
Guix (30)	High dose rate	36	89	1 (89%)	NR
Kauer-Dorner (75)	High dose rate	39	57	2(93%)	

*Reported at 3 years (not 5-years).
rPBI, re-irradiation with partial breast irradiation; LR, local relapse; OS, overall survival; N, number of patients

local excision followed by partial breast irradiation utilizing 3D-conformal external beam radiation techniques to deliver 45 Gy in 1.5 Gy fractions bid. The primary endpoint being evaluated is adverse effects after re-irradiation, with secondary endpoints including in-breast recurrence rates, mastectomy-free survival, overall survival, monitoring/correlating circulating tumor cells with relapse, and cosmesis (Fig. 69-4).

LRR after Mastectomy

Mastectomy in the definitive setting is associated with excellent local control in the majority of breast cancer patients. While breast conserving surgery is associated with greater odds of LRR than mastectomy (pooled OR: 1.561; 95% CI, 1.289–1.890), LRRs still occur in approximately 8.5% of mastectomy patients (31). Chest wall recurrences (CWRs) have been reported in up to 40% of patients depending on primary tumor characteristics and initial treatment (32).

The diagnosis of CWR, defined as a breast cancer recurrence in the skin, subcutaneous tissue, muscle, or underlying bone after mastectomy, requires a high index of suspicion. Many CWRs occur within two to three years after mastectomy, but can be detected more than 10 years after initial treatment occasionally. Careful surveillance of the chest wall after mastectomy is therefore required. LRRs after mastectomy are generally detected by physical

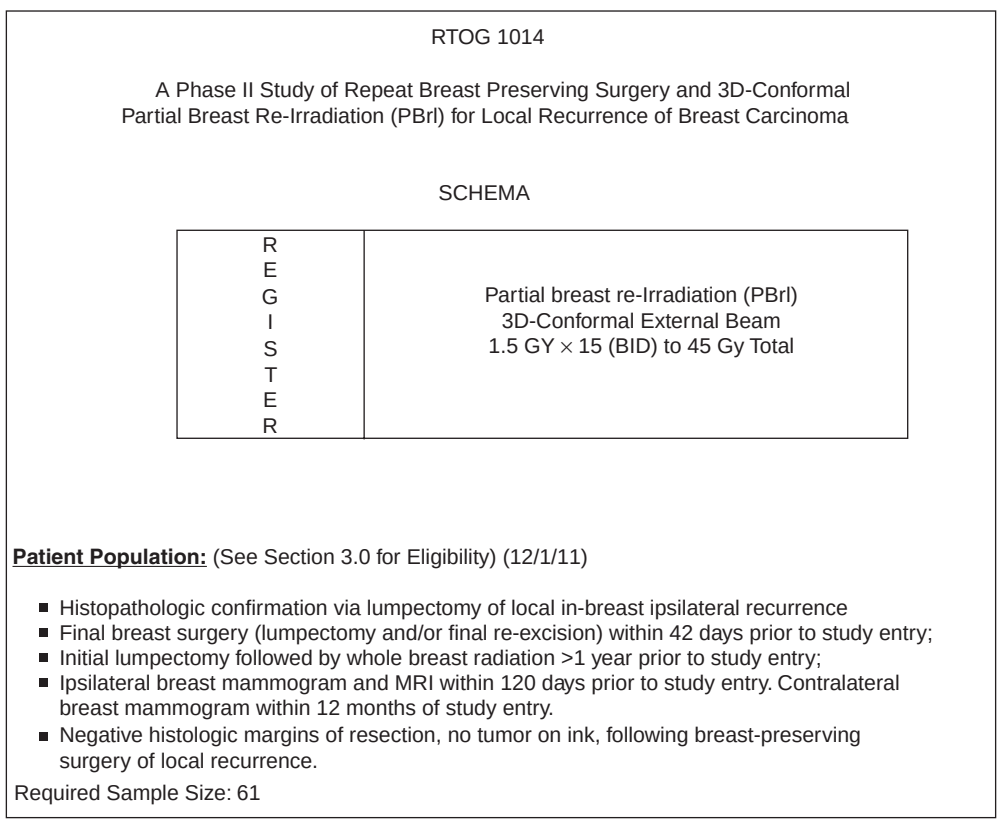

FIGURE 69-4 RTOG 1014: Study schema, patient eligibility, and target accrual.

examination, as imaging surveillance has not been shown to be particularly useful. The majority of CWRs present as asymptomatic nodule(s) in the skin or a slight erythematous rash. Often, this involves the previous mastectomy scar, and may be mistaken for foreign body granuloma, fat necrosis, or radiation-induced injury. Histologic confirmation is, therefore, required, and can be obtained with a punch biopsy.

While CWRs are often considered to be a harbinger of metastasis with an ominous prognosis, not all of these patients will fare poorly. Initial attention should be paid to evaluating for the presence of concomitant distant metastatic disease, which is present in up to a third of patients (4). Patients with a reasonable prognosis include those who: are without distant metastases, were node-negative at their initial cancer diagnosis, were disease-free for more than 24 months prior to their CWR, and are candidates for chest wall radiation therapy. In this more favorable subgroup, median overall survival is 141 months (10-year actuarial survival 75.4%), and more aggressive local-regional treatment may be warranted.

Additionally, outcomes are most favorable for those patients who are able to undergo complete surgical excision of the LRR followed by radiation therapy. Despite high response rates with the use of radiation therapy alone for CWR, 60% to 70% experience a second failure, thus surgical resection should be strongly considered for any patient with localized, recurrent disease. For patients in whom surgical resection is not feasible, radiation alone can provide meaningful palliation of localized symptoms, but is unlikely to provide a durable response or cure. Systemic therapy should be considered, either initially to decrease the burden of tumor prior to local-regional therapy, or after local-regional treatment.

CWR Following Mastectomy

If technically feasible, the standard of care for a CWR is surgical resection, which provides excellent local control, and is particularly useful in patients who have previously had radiation therapy or those in whom radiation therapy is contraindicated. For patients with isolated recurrences involving only the skin or the surgical scar, resection of the CWR is often straightforward. Resection with primary closure is generally feasible and can provide excellent local control. With more extensive disease, closure of the chest wall with either a skin graft or autologous flap may be needed, and preoperative consultation with a plastic surgeon is advised. Every attempt should be made to attain wide negative resection margins. For patients with deep CWR extending to underlying bony elements, the utility of resection of ribs and sternum remains controversial. Such extensive resections are often associated with significant morbidity, although some authors have reported reasonable long-term results of full-thickness resections in selected patients (Table 69-3).

In patients who have not received previous radiation therapy, definitive doses of adjuvant postmastectomy radiation therapy should be delivered to maximize local-regional control. The technique should be similar to that utilized in the postmastectomy setting, with tangential chest wall fields which are matched to the supraclavicular field anteriorly, and the use of a posterior axillary boost if indicated, based on the presentation of the recurrence, the individual patient's body contour, and the dose distribution obtained (41). Importantly, field size should always cover the entire chest wall (as opposed to a limited field encompassing just the local recurrence site) and regional lymph nodes, as limited treatment of the chest wall increases the risk of failure elsewhere on the chest wall and in the supraclavicular and axillary nodal basins. Typically, 50 Gy is delivered to the entire chest wall followed by a 10 Gy boost to the recurrence site, if feasible, and 46 to 50 Gy to the regional lymph nodes. A 0.5 cm to 1.0 cm bolus is placed over the entire chest wall to maximize skin dose, and can be utilized every other day during the course of chest wall irradiation or alternatively, for the first 20 Gy (10 fractions). Standard radiation fields are shown in Figure 69-5.

TABLE 69-3

Survival following Full-Thickness Chest Wall Resection

Study	*N*	*5 yr OS*
Downey (33)	38	15%
Santillan (34)	28	18%
Snyder (35)	24	29%
Shah (36)	52	41%
Friedel (37)	63	46%
Faneyte (38)	44	47%
Miyauchi (39)	23	48%
Palmeijer (40)	22	71%

CWR Following Mastectomy with Reconstruction

It has been well demonstrated that reconstruction does not increase the incidence of CWR after mastectomy, nor does the incidence of CWR vary with the type of reconstruction (42). The majority of CWRs following skin-sparing mastectomy with reconstruction occur under the skin, and are easily palpable on clinical examination (42). While the length of time between mastectomy and finding a CWR may be slightly longer in patients who have had reconstruction, the prognosis between these patients and those who develop a CWR after a conventional mastectomy is not significantly different (43). Surveillance remains physical examination, and patients who present with a subcutaneous nodule should be treated with a high index of suspicion; punch biopsy may provide a histologic diagnosis.

Patients who present with a CWR following autologous reconstruction do not necessarily require complete removal of the reconstruction (43,44). In patients who have had transverse rectus abdominis myocutaneous (TRAM) or latissimus flap reconstruction, the CWR can often be resected with local flap rearrangement to preserve the breast mound. In patients who have had implant-based reconstruction, on the other hand, removal of the implant may be warranted in order to facilitate subsequent radiation therapy. Patients who have not previously received postmastectomy radiation should receive full doses of radiation therapy to the chest wall and regional lymph nodes after surgical resection of LRR to further diminish local regional relapse rates (as state earlier).

CHEST WALL RECURRENCE IN PREVIOUSLY IRRADIATED PATIENTS

In a patient who has been previously radiated, surgical resection of a CWR may be technically more challenging due to the added sequelae of radiation, but surgical resection should, nevertheless, be considered. Because the local control failure rates after postmastectomy CWR treated with a chest wall resection alone remain unacceptably high (approximately 33% at 5 years (45)), re-irradiation of the chest wall with curative intent has been utilized and seems

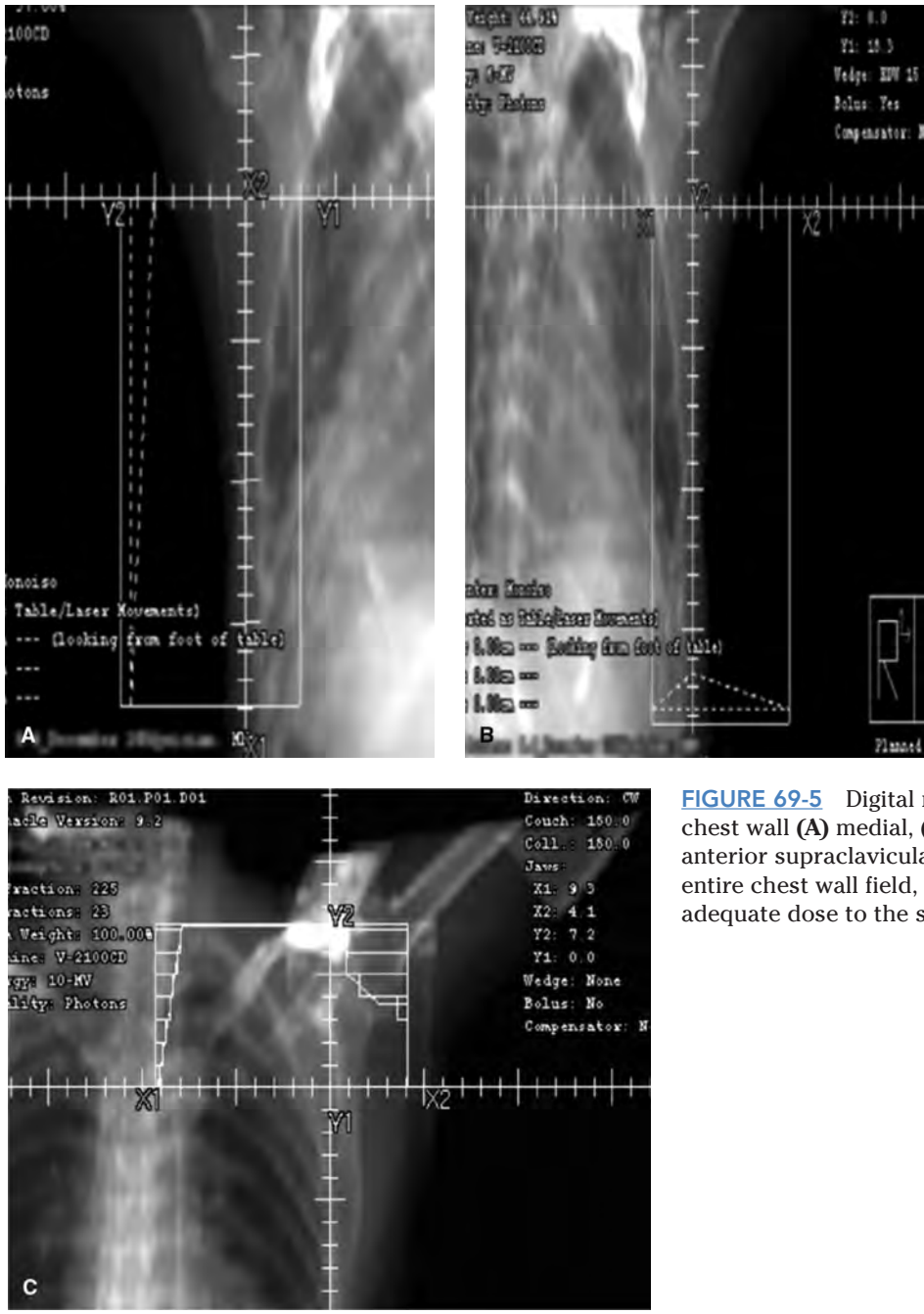

FIGURE 69-5 Digital reconstructed images of standard chest wall **(A)** medial, **(B)** lateral tangential fields, and **(C)** an anterior supraclavicular/axillary field. Bolus is placed on the entire chest wall field, irrespective of the disease, to ensure adequate dose to the skin.

to improve the prognosis of previously radiated women with CWR. In one recently published series of re-irradiation of the chest wall, no patients had treatment related death, brachial plexopathy, pericarditis, or higher than Grade II pneumonitis. While skin toxicity was elevated with the re-irradiation, (Grade III 7% at 1°RT course vs. 19% at re-irradiation), no patients developed Grade IV toxicity, suggesting that re-irradiation to the chest wall to definitive doses is relatively well tolerated with acceptable acute and late toxicity (46). Typically, doses of 40 to 50 Gy to the chest wall followed by a boost to the recurrence site utilizing electron beams are utilized (Fig. 69-6). In these cases, re-irradiation of the regional nodes is contraindicated. Radiation fields need to be tailored to encompass the gross disease with a 2–3-cm margin at a minimum, with particular attention to ensure that the brachial plexus dose does not exceed tolerance.

HYPERTHERMIA

Hyperthermia, or heating of the tumor beyond physiologic temperatures, has been evaluated for decades as a method for cytoreduction of superficial malignancies. Laboratory and *in vitro* data suggest a biologic rationale for hyperthermia, including a direct cytotoxic effect on the cycle in the S phase (a phase in the cell cycle with increased resistance to radiation), inhibition of sub-lethal damage repair, and improved intratumoral oxygen content (facilitating free radical-mediated cytotoxic damage from radiation). Fundamental differences in mechanisms of activity and resistance for hyperthermia and radiation support a rationale for concomitant delivery, theoretically providing a synergistically anti-tumor effect. Hyperthermia may also function as a radiosensitizer, allowing for lower total doses of radiation to

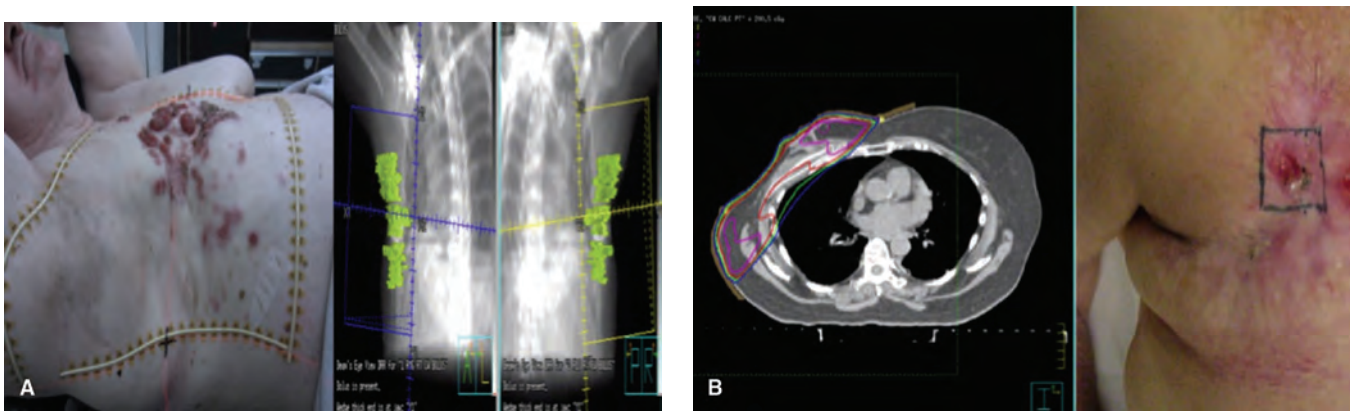

FIGURE 69-6 **(A)** Patient with CWR after mastectomy and postmastectomy radiation (previously received 50 Gy to the chest wall and regional nodes). **(B)** Digital reconstructions of the re-irradiation field volume that was targeting the CWR. This volume received 40 Gy. **(C)** Dosimetry plan showing an axial slice of the treatment plan, depicting the 95% (prescription) line in green covering the clinical target volume, which was achieved with mixed photon and electron beams with bolus. **(D)** Image of chest wall at the completion of 40 Gy. The two areas with residual disease were boosted with an additional 10 Gy each. The patient had a complete clinical response to treatment.

be therapeutic. Typically, hyperthermia involves heating the tumor bed to a temperature range of 40° to 45°, concomitant with delivery of radiation. Radiotherapeutic management of LRR presents specific challenges, including potential resistance to radiation, dose limitations in previously radiated patients, and poor vasculature (and thus poor oxygenation) after radiotherapy; hyperthermia may thus offer an additional modality with local cytotoxic benefit.

To date, it remains unclear whether the addition of hyperthermia to radiation for recurrent breast cancer is beneficial in improving long-term outcomes. While multiple randomized trails have been undertaken, many of these protocols included multiple tumor sites, and several of these studies have never been published in manuscript form. Furthermore, of the published data, heterogeneous patient populations, differences in eligibility and treatment protocols, and weaknesses in study design, adherence to protocol requirements, and selection of complete response as the primary endpoint assessed instead of local control, disease-free, or overall survival, have limited the ability to draw conclusions regarding the benefits of hyperthermia. In one series of 134 patients previously treated with radiation with recurrent breast cancers, re-irradiation with doses of 32 Gy delivered in 8 fractions with concurrent hyperthermia (and no chemotherapy) resulted in complete response (CR) rates of 71%; unfortunately, local disease free survival was not reported (47). The International Collaborative Hyperthermia Group (ICHG) conducted a meta-analysis of 5 randomized trials of re-irradiation of CWR with or without hyperthermia. The mean re-irradiation dose was 30 Gy in their cohort of 210 patients. Patients randomized to concurrent HT had a CR rate of 59%, whereas those randomized to re-irradiation alone had a CR rate of 41% ($p < .001$) (48). Despite this apparent benefit in the field treated with hyperthermia, three-fourths of these patients progressed outside of the radiation field following treatment, and there was no impact on survival with a median of 18 months with or without hyperthermia. Thus, while the use of hyperthermia may be an option in patients who have had previous radiation with limited additional options, additional controlled studies are needed to discern any long-term benefit.

REGIONAL NODAL RECURRENCE (AFTER BCT OR MASTECTOMY)

In addition to improving rates of IBTR and CWR, the use of multi-modality therapy in the definitive setting improves regional relapse rates, and thus the overall incidence of isolated regional nodal recurrences in the definitive setting is generally low (under 4%) (3). The manifestations of a regional lymph node relapse in most patients are usually minimal, most often presenting as an asymptomatic mass. Only a minority of patients will present with symptoms such as pain, arm edema, decreased range of motion or other physical impairments, or neurologic symptoms (49). In patients with symptoms suggestive of brachial plexopathy or arm edema without obvious lymphadenopathy, it may be difficult to distinguish clinically between tumor recurrence in the axilla or deep supraclavicular fossa and the effects of previous postoperative radiation treatment. The use of MRI may be helpful in this regard, as local enhancement with gadolinium suggests the presence of tumor, rather than radiation related fibrosis.

Regional lymph node recurrences generally confer a poor prognosis, and the risk of distant metastasis, whether simultaneously at the time of relapse or subsequently after salvage treatment, is high (>50%). Prognosis is related to the site of the disease, with supraclavicular, internal mammary, or multiple sites of nodal disease conferring a worse overall prognosis than axillary recurrences alone (50). Nevertheless, combined utilization of both surgical resection and radiation therapy confer higher disease-free and overall survival than using either modality alone, and thus, ideally, both modalities need to be considered.

AXILLARY AND SUPRACLAVICULAR RECURRENCES

The management of axillary recurrences is typically limited by the extent of disease and previous therapy that the patient has received. The surgical management of axillary recurrences has evolved, primarily due to the increased use

of sentinel lymph node (SLN) biopsy. In a patient who has an axillary regional recurrence after only SLN biopsy, a full level I/II axillary dissection is warranted. In a patient who has undergone a full axillary dissection (+/- axillary radiation), re-dissection is typically not a technically viable option, but axillary exploration and resection of gross disease may be considered for small, mobile, isolated recurrences. In contrast, the technical feasibility of performing a sentinel lymph node biopsy for IBTR, regardless of previous axillary sentinel node biopsy or dissection, has been demonstrated (51). In the re-operative setting, the sentinel node can be identified approximately 87% of the time when 10 or less lymph nodes were removed at original surgery (51). Repeat surgical assessment of the axilla may be particularly useful given the significant risk of concomitant IBTR and regional recurrence, and may prove to provide prognostic information useful in guiding management decisions for recurrences. Because of altered drainage patterns in these patients, particularly in those that have had 10 or more lymph nodes removed, clinicians should utilize a preoperative lymphoscintigram when considering repeat surgical axillary assessment (9).

For a patient who has an isolated nodal recurrence in a previously radiated field, regional re-irradiation with therapeutic doses is generally not considered safe, but limited field re-irradiation may be considered as a salvage option in patients unresponsive to systemic treatment or those with unresectable disease. Particularly for supraclavicular and axillary recurrences, utilization of standard external beam techniques would result in doses to the normal structures that are well beyond threshold. For example, with re-irradiation to the supraclavicular fossa or axilla, threshold doses to the brachial plexus would be exceeded, which could result in significantly debilitating and painful brachial plexopathy. While technological advancements in the delivery of radiation using intra-operative electron beam therapy have allowed for promising preliminary investigation of re-irradiation of the axilla (52), this technique warrants further investigation prior to its routine use. Furthermore, the requirements for an intra-operative linear accelerator and a dedicated, shielded operating room prohibit the widespread utilization of this technique in many radiation therapy centers.

There is ongoing debate as to whether supraclavicular lymph node involvement should be considered as local-regional disease or distant metastases, as overall, most are associated with a grave prognosis. Clearly, outcomes of regional relapses in the supraclavicular fossa are worse than those in the axilla (53). The largest and most recent series of supraclavicular recurrences comes from the Danish Breast Cancer Cooperative Group Database, reporting on 305 patients with an isolated supraclavicular recurrence with or without other local-regional metastases but no distant metastasis. Additional sites of synchronous local-regional disease were present in 38% of the patients. Nineteen percent had gross removal of the tumor, 33% had curative radiation, 26% had combined local-regional treatment and systemic therapy, and only 10% underwent surgery plus radiation. Combined local-regional and systemic therapy resulted in the highest rate of initial remission (67%) compared to either local-regional therapy alone (64%) or systemic therapy alone (40%), but the 5-year progression-free and overall survival were only 15% and 24% percent, respectively, with the only significant predictor of favorable outcomes on multivariate analysis being receipt of combined local-regional and systemic therapy (54). These data are consistent with other retrospective series suggesting that patients with isolated supraclavicular recurrences have long-term disease free survival ranging from 15% to 30% with the utilization of multi-modality therapies (55). Therefore, patients with isolated supraclavicular recurrences without distant metastasis should be considered for curative multimodality therapy whenever possible.

INTERNAL MAMMARY NODAL CHAIN RECURRENCES

Nodal recurrence in the internal mammary nodal (IMN) chain is rare, despite the fact that these nodes are the second lymph node drainage basin of breast cancer and are typically not intentionally treated after definitive surgery in most breast cancer patients (Fig. 69-7). With IMN recurrence rates ≤2% after definitive treatment (56), there are limited data on the effects of surgical resection, systemic therapy, and/or radiation therapy in this setting, with the existing published literature consisting of only a few small series and case reports. One of the largest series of IMN recurrences in breast cancer describes 133 patients with IMN failure after definitive treatment. The 5-year survival rate of patients with IMN recurrences was approximately 30% overall, while that for those with isolated IMN recurrence was generally higher, approximately 45% (57). The factors that were found to significantly correlate with improved disease-free survival rates after IMN recurrence on multivariate analysis included: no concurrent distant metastases (HR: 0.7, 95% CI, 0.4–0.9; p = .031), presence of endocrine therapy for ER/PR+ patients (HR: 0.2, 95% CI, 0.1–0.5; p = .001), and presence of radiotherapy delivered to the IMN area after recurrence (HR: 0.3, 95% CI, 0.1–0.9; p = .026). While surgical resection of an isolated IMN recurrence has been described utilizing various techniques and appears to be associated with a low mortality rate, the surgery itself is typically very extensive requiring en bloc resection of the recurrence, surrounding chest wall, ribs, sternum, and previously radiated areas and often requires reconstruction of the chest wall defect (58). One series reported

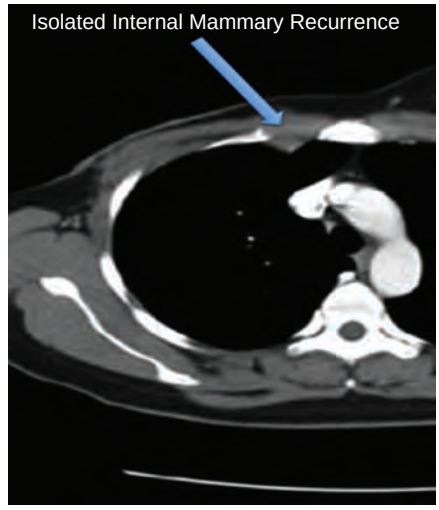

FIGURE 69-7 An isolated internal mammary recurrence 3 years after definitive treatment in a patient who underwent neoadjuvant chemotherapy, mastectomy, and axillary lymph node dissection for a triple negative clinical Stage IIIA (cT3c, N1c, M0) and pathologic Stage IIA (ypT2, ypN1) breast cancer. She received adjuvant postmastectomy radiation therapy: 50 Gy to the chest wall, a 10 Gy boost to the mastectomy scar, and 46 Gy to the supraclavicular fossa. The internal mammary radiation nodes were not intentionally included in her definitive treatment.

25 IMN recurrences treated with surgery, for which the en-bloc resection entailed a portion of the sternum, a mean of 3 (range 2–5) adjacent ribs, with the vast majority undergoing an omentoplasty for reconstruction of the chest wall. No post-operative deaths were reported, but 38% (11 patients) had adverse post-operative events which included 2 that required re-operation for necrosis of the omentum (n = 1) and overlying skin (n = 1) (59). More recently, a less invasive technique for treating IMN recurrence using a thoroscopic approach has been described (60). Because it remains unclear whether such extensive surgery provides a durable survival benefit compared with radiation therapy (+ systemic therapy) for IMN recurrences, for patients who have not previously received radiation, the mainstay of treatment for IMN recurrences is radiation therapy, typically to doses of 40 to 60 Gy.

SYSTEMIC THERAPY FOR LRR

Given the increased risk of distant failure after LRR, there is interest in whether systemic therapy can reduce the development of metastatic disease. Selection of systemic therapy for management of LRR presents challenges, as the benefit of additional, or a change in, systemic therapy after LRR is not well described by clinical trial data. Often decisions regarding systemic therapy for LRR become individualized based on tumor subtype, type of prior therapy if any, and interval since prior treatments.

Endocrine Therapy

For LRR confirmed to be hormone receptor (HR) positive, introduction of, or change in, endocrine therapy is generally considered. One prospective randomized trial has assessed the role of endocrine therapy use in the recurrent setting. The Swiss Group for Clinical Cancer Research (SAKK) trial 23/82 randomized 167 patients with LRR after mastectomy and "good risk" features (HR positive disease or disease-free interval >12 months with 3 or fewer nodules measuring 3 cm or smaller) to tamoxifen until relapse or observation (61). All patients underwent complete resection of disease and radiotherapy. The addition of tamoxifen improved median disease-free survival (DFS) from 2.7 to 6.5 years (p = .053), with notable improvement observed in postmenopausal patients. A benefit in overall survival was not observed. As prior adjuvant endocrine therapy was not utilized in this patient population, contemporary interpretation of this data is limited. However, given the good-risk profile of most endocrine agents, the risk-benefit balance favors use of highly effective, low-toxicity endocrine therapies in the setting of LRR.

Selection of the endocrine agent depends on prior and current exposures as well as menopausal status. In the setting of LRR during exposure to an endocrine agent, it is prudent to consider changing to an alternative endocrine agent. If the patient is already postmenopausal and was on an aromatase inhibitor, then change to tamoxifen could be considered. Alternatively, if premenopausal on tamoxifen, initiation of ovarian suppression and change to aromatase inhibitor can be discussed. The role of continuation of endocrine therapy in the setting of HR negative LRR after HR positive primary disease is not well understood.

Chemotherapy

The use of chemotherapy for LRR is frequently considered, yet not well established. Attempts to ascertain the value of offering chemotherapy for LRR through randomized trials have been complicated by limited accrual and trial design. Historic experiences include small trials evaluating the addition of actinomycin-D (n = 32) (62) and alpha-interferon (n = 32) (63). In addition to the endocrine question, the SAKK trial also offered chemotherapy to "poor risk" patients with LRR, and randomized 50 to observation versus chemotherapy (adriamycin, cyclophosphamide, vincristine) after excision and radiation. Unfortunately, this section of the trial was closed due to poor accrual and results were never formally published (64). Two ongoing European studies, the German GBSG GABG 6 and the French FNCLCC-FACS 03, aim to randomize patients with LRR after resection to observation versus polychemotherapy, but are not yet completed.

The most contemporary completed clinical trial to assess the role of adjuvant systemic therapy for LRR is the BIG 1-02/IBCSG 27-02/NSABP B-37 "CALOR" (Chemotherapy as Adjuvant for Locally Recurrent Breast Cancer) study (65). This trial enrolled patients with an isolated local and/or regional invasive recurrence after complete surgical resection, and randomized to subsequent chemotherapy of physician choice, or no chemotherapy (Fig. 69-8).

The CALOR protocol recommended at least 2 agents of chemotherapy for the duration of 3 to 6 months. Radiotherapy was recommended (and mandatory for those with involved margins) in both arms, endocrine therapy was mandatory for estrogen receptor positive disease, and trastuzumab was optional for HER2 positive disease. The primary endpoint of the study was disease free survival; initial goal accrual was close to a thousand patients; however, the trial was closed after 8 years due to low accrual after enrolling 162 patients. Results were presented at a median follow-up of 4 years.

The accrued study population included about 60% with prior breast conserving surgery, and 60% to 70% with prior adjuvant chemotherapy exposure. Over 50% had in-breast recurrence, with the rest recurring on scar/chest wall or in regional lymph nodes; over 60% of the recurrent tumors were estrogen receptor positive. In the treatment arm, most patients (69%) received polychemotherapy. Over 90% of estrogen receptor positive tumors received endocrine therapy, and less than 10% received trastuzumab. The primary analysis showed that the addition of chemotherapy led to a significant improvement in 5-year disease-free survival from 57% to 69% (HR 0.59, 95%, p = .0455), as well as an improvement in the secondary endpoint of 5-year overall survival, from 76% to 88% (HR 0.41, p = .02). Results remained significant for both disease-free and overall survival in multivariable Cox proportional hazards modeling controlling for location of recurrence, disease-free interval, estrogen receptor status, and prior chemotherapy. Significant benefit was seen in the pre-specified analysis of estrogen receptor negative disease (35% vs. 67%, HR 0.32, p = .007) but not for estrogen receptor positive disease (69% vs. 70%, HR 0.94, p = .87).

Given the results of the CALOR study, it is reasonable to offer chemotherapy following definitive surgical resection after LRR, particularly for estrogen receptor negative tumors.

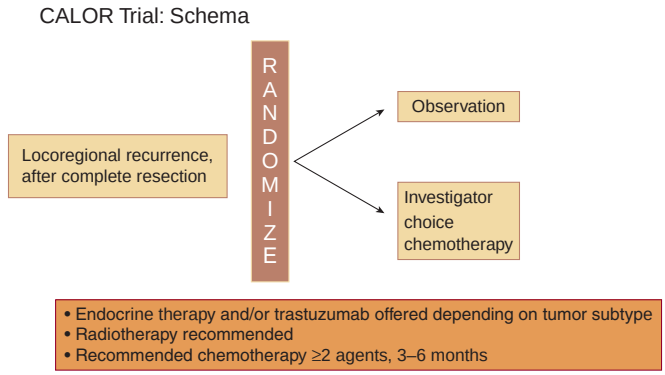

FIGURE 69-8 Schema of the BIG 1-02/IBCSG 27-02/NSABP B-37 CALOR study.

TABLE 69-4

Factors to Consider in Risk Assessment and Systemic Treatment Decision-Making for LRR of Breast Cancer

Disease-Related Factors	*Patient-Related factors*
Disease-free interval	Patient preferences
Previous therapeutic exposures and response	Pre-existing toxicities, performance status
Biological factors (hormone receptors, HER2)	Menopausal status
	Patient co-morbidities and biologic age

Adapted from Cardoso F, Fallowfield L, Costa A, et al. Locally recurrent or metastatic breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol* 2011;22 (Suppl 6): vi25–30.

However, broad extrapolation may be restricted by limitations in trial design, as well as evolution in optimal adjuvant management at the time of primary diagnosis. In current situations of LRR, decisions regarding the role of additional chemotherapy remain quite personalized and reflect both disease- and patient-related factors (Table 69-4). Generally, in patients with a longer disease-free interval, who have not received both taxane and anthracycline previously, and who have tumor biology suggestive of chemosensitivity (e.g., HR negative, higher grade, etc.), consideration of a course of non-cross resistant chemotherapy should be considered (66). In situations presenting with a shorter disease-free interval since comprehensive adjuvant chemotherapy, or where disease is not thought to be chemosensitive (e.g., HR positive lower grade), the role of further chemotherapy is less certain.

Targeted Therapy

For individuals with HER2+ breast cancer with LRR who are trastuzumab naive, consideration of a course of trastuzumab and chemotherapy followed by extension of trastuzumab monotherapy is appropriate. Benefit from continuation of HER2-directed therapy has been observed after metastatic disease progression on trastuzumab (67); therefore, consideration of retreatment with trastuzumab-based therapy can be considered if previously received or if recurrence occurs while receiving trastuzumab. Partner chemotherapies typically include taxane or vinorelbine. Alternatively, consideration of treatment with an alternative HER2-directed agent, such as lapatinib, could be considered. At the time of writing, the use of other biologics approved in the metastatic setting, including everolimus, pertuzumab, and TDM1, is not appropriate in the setting of LRR; however, consideration of clinical trial enrollment is strongly encouraged.

Other Therapies for LRR

Photodynamic treatment (PDT) uses laser light in combination with a photosensitizing drug (a hematoporphyrin derivative) for the treatment of cancer. In small series that have utilized PDT for chest wall recurrences, the complete response rates have been highly variable (69). Most patients included in these series were heavily pretreated and often had extensive disease, although better results were noted for smaller nodular tumors or limited sites. PDT can cause pain and prolonged superficial skin necrosis, although surgical repair is rarely needed (70).

Additional local therapies investigated in small studies include intra-arterial regional chemotherapy, topical chemotherapy (Miltefosine), biologic response modifiers, and interferon (71–74).

TIMING OF TREATMENT

Systemic therapy in the absence of best efforts at surgical resection and radiotherapy is of limited value, and tends to be discouraged. Increasingly, if systemic therapy is planned for local-regional recurrence, providing therapy prior to planned surgical resection in a "neoadjuvant" fashion may be considered. Advantages of this strategy include not only downsizing a tumor and facilitating excision, especially if not operable at presentation, but also allowing *in vivo* observation of tumor sensitivity to the agent of choice. Careful multidisciplinary planning is crucial in the care of a patient with LRR.

GENOMIC TESTING

Genomic testing, using methods such as OncotypeDX, has become commonplace in treatment decision-making for stage 1 and 2 HR positive tumors (see Chapters 29 and 44). The role of commercial genomic testing in the setting of local-regional recurrence is unclear. As the OncotypeDX test was originally constructed and validated using tumor tissues naive to endocrine chemotherapies, the utility of the test in the setting of recurrent tumor is unknown. An analysis of OncotypeDX testing before and after receipt of neoadjuvant chemotherapy showed scores remained correlated, suggesting receipt of chemotherapy did not alter the expression levels measured in the testing algorithm (68). However, until further confirmatory data is available, or unless a local recurrence is thought to be a primary tumor, use of commercial genomic testing to guide systemic therapy in the setting of local-regional recurrence is not recommended.

SURVEILLANCE

Continued surveillance after local-regional recurrence should follow traditional paradigms for primary breast cancer (Chapter 67). Additional serologic or radiologic investigations are not recommended in the absence of worrisome symptoms.

MANAGEMENT SUMMARY

Local Recurrence after Breast-Conservation Treatment

- Local recurrence after breast-conservation treatment is most often detected by breast imaging. A biopsy should be performed to confirm the recurrence, with pathologic confirmation and determination of hormone receptor and HER2 status. Patients should undergo a metastatic workup to rule out distant metastasis.
- Mastectomy is the standard treatment.
- There are limited data utilizing a repeat breast conservation approach. The existing published data suggest that this approach is feasible in a patient refusing mastectomy, but with a substantially higher risk of subsequent local recurrence than with mastectomy. Patients treated with re-irradiation should ideally be treated on an Institutional Review Board (IRB)-approved protocol.

Local Recurrence after Mastectomy

- Local recurrence after mastectomy is most commonly detected by physical examination.
- The index of suspicion for recurrence should be high, and a biopsy is indicated for confirmation and marker studies.
- All patients who develop a chest wall recurrence (CWR) after mastectomy should undergo a full metastatic workup, as concomitant metastasis occur frequently.
- CWR should be considered for surgical excision followed by radiation therapy to optimize local control. The volume of radiation treatment should include the entire chest wall and appropriate nodal regions (depending on prior axillary surgery and current extent of disease). The area of CWR should receive a total dose of at least 60 Gy (including a boost to the recurrence site).
- Patients who present with a CWR following autologous reconstruction may not require reconstruction removal; the CWR can often be resected with local flap rearrangement to preserve the breast mound.
- If the local recurrence is not operable, systemic treatment should be considered to render the recurrence operable.
- For patients with a local recurrence after mastectomy and postmastectomy radiation therapy, there is no standard treatment. Re-irradiation to gross disease may be reasonable in a patient in whom surgery and system therapy are not options. Hyperthermia or photodynamic treatment may provide additional therapeutic options for these patients.

Regional Lymph Node Recurrence

- The diagnosis of a regional nodal recurrence needs to be confirmed by biopsy.
- Concomitant local relapse should be ruled out, and a full metastatic workup is indicated.
- If the regional recurrence is operable, surgical resection of the recurrence should be pursued.
- After surgical excision, the role of systemic treatment is not defined.
- In view of the wide variation in presentations of regional lymph node recurrence, the overall treatment program must be individualized based on site(s) of recurrence and prior treatment.

Systemic Therapy In LRR

- For recurrences that are found to be hormone receptor (HR) positive, introduction of, or change in, endocrine therapy should be considered.
- Based on the CALOR study, it is reasonable to offer chemotherapy following definitive local treatment after LRR, particularly for HR-negative tumors. The decisions regarding the role of additional chemotherapy need to be personalized to the individual patient.
- For patients who have HER2+ recurrences and are trastuzumab naive, a course of concomitant chemotherapy with trastuzumab followed by trastuzumab as monotherapy is appropriate. Alternatively, another HER2-directed agent, such as lapatinib, may be utilized in patients who have received trastuzumab.
- Systemic therapy may also be considered in the setting of an isolated recurrence in a "neoadjuvant" fashion to downsize the recurrence prior to resection.

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CHAPTER 70

Treatment of Metastatic Breast Cancer: Endocrine

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CHAPTER CONTENTS

INTRODUCTION

The optimal management of patients with metastatic breast cancer (MBC) remains a challenge. Systemic drug treatments such as chemotherapy, endocrine therapy, biological targeted therapy, and supportive therapies, including bisphosphonates for bone disease, are the mainstay of care. The clinical decision as to which is the most appropriate treatment option is based on a number of patient- and disease-related factors (Table 70-1). Approximately two-thirds of human breast carcinomas express estrogen receptors (ER) and thus may be dependent on estrogen for their growth, and for patients in whom their breast cancer (either primary tumor or biopsy of accessible metastatic disease) is positive for ER and/or progesterone receptor (PgR), endocrine therapy is an important treatment option to consider that has minimal toxicity.

For patients with ER/PgR positive (+ve) breast cancer and an estimated low risk of rapid progression of their advanced disease (i.e., soft tissue and/or bone metastases as their dominant site, absence of life-threatening visceral involvement, disease-free interval greater than 2 years, limited sites of metastatic involvement), endocrine therapies can be very effective in the treatment of their advanced/metastatic disease. For example, locally advanced ER +ve disease within the breasts of elderly women is often slow growing and extremely hormone sensitive. Excellent clinical responses can be achieved with simple well-tolerated endocrine therapy such as the antiestrogen tamoxifen, albeit maximal response and tumor shrinkage may take between 6 and 9 months to occur (Fig. 70-1A,B). However, sites of visceral metastases such as the liver may also respond well to endocrine therapy provided appropriate selection of patients is undertaken. For example, postmenopausal patients with strongly ER/PgR+ve disease with a long treatment-free-interval of many years after completion of adjuvant tamoxifen may then develop metastatic disease within the liver but with a limited number of tumors and preserved organ function (i.e., normal liver function tests). They may lack any symptoms from their advanced disease and show good overall performance status. Such patients can have an excellent clinical response to endocrine therapy alone with, for example, aromatase inhibitors (AIs), which may last for 18 to 24 months before their disease progresses and patients require chemotherapy (Fig. 70-1C,D).

Although evidence from randomized trials directly comparing endocrine therapy to chemotherapy as initial first-line treatment for MBC is limited, a Cochrane review found no survival differences but more toxicity associated with initial chemotherapy (1). Therefore, appropriate selection of patients who are suitable for initial endocrine therapy is therefore crucially important in order to maximize the benefits from such treatments, in particular as long-term disease control for up to 18 months with minimal side effects is not uncommon. In this chapter the evidence for each of the current endocrine therapy options that are available for advanced disease in both post- and premenopausal women are reviewed in more detail, together with the emerging strategies that might be used in the future to further enhance their effectiveness. In particular, recent results from several key clinical trials of endocrine therapy (including those in combination with various targeted signaling inhibitors) will be discussed, along with the implications for the optimal sequence of endocrine therapies in advanced breast cancer.

However, one of the key factors that determine whether endocrine therapy will be an effective option for metastatic disease relates to prior exposure to adjuvant endocrine therapy and to the level of hormone receptor expression. These two factors are among the most important in determining a tumor's underlying endocrine sensitivity, and whether "intrinsic de-novo" or "acquired resistance" will influence the outcome and response to endocrine therapy in the metastatic setting. These issues will be addressed first, before reviewing the clinical data that are available with each of the various current endocrine treatments in first- and second-line settings and the future strategies that might be used to circumvent/prevent endocrine resistance.

TABLE 70-1

Clinical Parameters Utilized in Decision Making for Systemic Therapy Options in Advanced Breast Cancer

Patient Factors
Age
Menopausal status
Performance status
Severity and nature of symptoms
Presence/absence of visceral disease
Organ function (i.e., liver/renal/bone marrow function)
Disease and Treatment-Related Factors
Tumor biology (ER/PgR status; HER2 status)
Dominant site of disease (i.e., bone/soft tissue vs. visceral metastases)
Number of sites of metastases (tumor burden)
Prior adjuvant systemic therapies
Duration of treatment-free period (i.e., sensitive vs. resistant disease)

IMPLICATIONS OF PRIOR ADJUVANT THERAPY AND ER EXPRESSION

Impact of Adjuvant Endocrine Therapy

The use of adjuvant endocrine therapy has significantly improved survival of women diagnosed with ER+ve early stage breast cancer (2). Until recently tamoxifen had been the gold standard of adjuvant endocrine therapy for ER+ve breast cancer. Tamoxifen is a nonsteroidal ER antagonist that inhibits breast cancer growth by competitive antagonism of estrogen at the receptor site. However, its actions are complex due to partial estrogenic agonist effects that in some tissues (i.e., bone) can be beneficial (3) but in others may be harmful, increasing the risk of thrombo-embolism and uterine cancer (4).

The results of the most recent Early Breast Cancer Trialists Collaborative Group overview involving over 21,000 women has shown that tamoxifen for about 5 years reduces the risk of death by around one-third in the first 15 years (RR 0.71) (2). The proportional risk reduction was not significantly affected by age, the use of chemotherapy, nodal status, or expression of PgR, with the absolute benefit relating to absolute risk of recurrence. Despite the significant clinical benefit from tamoxifen in early breast cancer and its impact on improving overall survival (OS), a significant annual hazard rate for recurrence persists in ER+ve breast cancer, with over half the recurrences occurring after 5 years of therapy has completed (2). This raises the issue of whether tamoxifen can be used again in MBC if it has already been given in the adjuvant setting.

In the recent past, AIs have demonstrated superior risk reduction over tamoxifen in postmenopausal early breast cancer. In the ATAC (Arimidex, tamoxifen, Alone or in Combination) trial, anastrozole was compared with tamoxifen and with the combination of the two drugs and was shown to be superior to both in terms of disease-free survival (DFS) (hazard ratio [HR] 0.86, 95% CI, 0.78–0.95; p = .003) in hormone-receptor-positive patients at a median follow up of 120 months (5). Similarly, the BIG 1-98 trial letrozole was significantly better than tamoxifen in terms of both DFS (HR 0.82, 95% CI, 0.74–0.92) and OS (HR 0.79, 95% CI, 0.69–0.90). (6) There have also been several trials that have reported a benefit in risk reduction with the use of adjuvant AIs given after an initial 2 to 3 years of tamoxifen versus tamoxifen for 5 years. While the use of adjuvant AIs in postmenopausal breast cancer has further improved outcomes, for those who still subsequently relapse, this has created new challenges to determine the most appropriate endocrine therapy strategies to utilize in women with metastatic disease.

Initial sensitivity to adjuvant therapy in early breast cancer can be an important predictor for the likelihood of response to further endocrine therapy in the metastatic setting. Some patients relapse very early while taking their adjuvant endocrine therapy. These tumors might be expected to have intrinsic "de-novo" endocrine resistance. Alternatively, some patients may relapse at the end, or shortly after completing adjuvant endocrine therapy, and as such could have developed "acquired" resistance, which may still allow response to alternative endocrine therapies. Alternatively, patients may relapse at a much later time point many years following completion of their adjuvant endocrine therapy (late relapse), and cancer cells in this situation may have retained full endocrine sensitivity. Thus the time point for relapse from diagnosis (disease-free interval) and also from prior adjuvant therapy (treatment-free interval) both might determine the response to further endocrine therapy in the metastatic setting (Fig. 70-2).

Change in Receptor Expression in MBC

It is well recognized that the level of ER expression in breast cancer cells determines the extent of endocrine sensitivity, and therefore the magnitude of benefit that can be obtained from adjuvant endocrine therapy. In the EBCTCG tamoxifen overview, highly ER+ve disease (≥200 fmol/mg as measured by ligand-binding assay) was associated with the greatest benefit with a hazard rate ratio for breast cancer mortality with tamoxifen of 0.53, while those women with the lowest but still measurable ER levels (<9 fmol/mg) did not derive any benefit from adjuvant tamoxifen (2). Utilizing more modern immuno-histochemistry (IHC) assays to measure ER, it was initially thought that tumors where only 1% of cells stained positive for ER by could benefit from adjuvant tamoxifen (7,8). However, more recent molecular studies have categorized different subtypes of ER+ve breast cancer that may better relate to likely hormone sensitivity and suggest that very few of the ER weak tumors (i.e., those with only 1% to 9% cells ER+ve) show a similar molecular feature to those strongly ER+ve tumors (9). Likewise, tumors that are ER negative (-ve) but express PgR may have a low expectation of clinical benefit from endocrine therapy. As such the primary breast tumor's level of ER expression (and possibly its molecular subtype) could predict the benefit from endocrine therapy for tumors that recur at loco-regional or distant sites many years later.

Increasingly, it has become important to establish whether the receptor status in the tumor changes during progression from early breast cancer to regional or metastatic recurrence, because this itself may be the most important factor in determining the likelihood of response to further endocrine therapy. Several studies comparing receptor expression between paired biopsies have showed that receptor expression may change, with either a reduction or loss of ER expression in up to 35% of tumors and gain of the human epidermal growth factor receptor 2 (HER2) expression in up to 10% of ER+ve breast cancers (Table 70-2) (10–13). Either or both of these phenotypes is known to account for acquired endocrine resistance, but may still allow response to alternative endocrine therapy strategies as illustrated

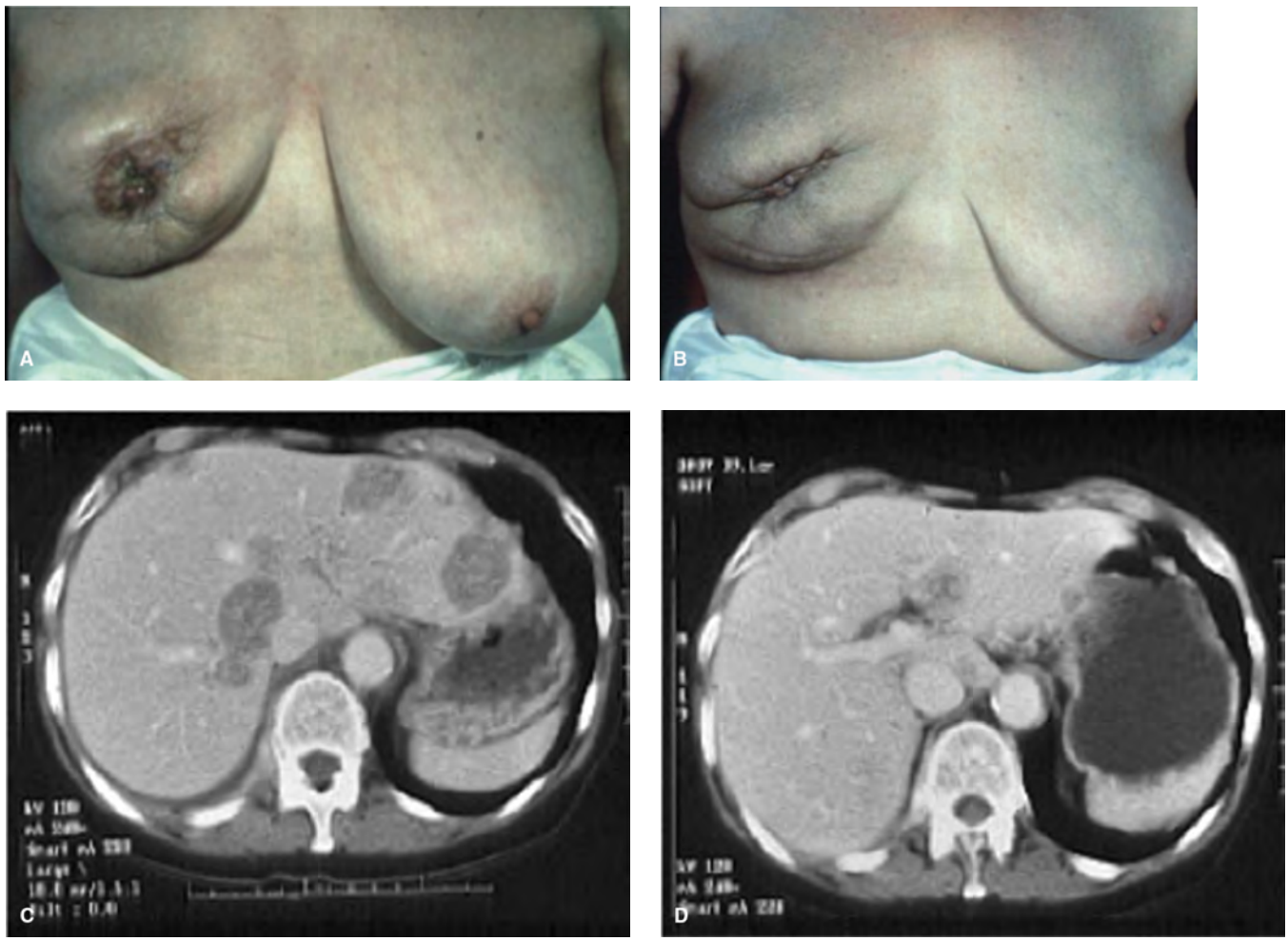

FIGURE 70-1 **(A)** An elderly woman with a locally advanced ER positive (+ve) slow growing right breast cancer at the time of diagnosis prior starting systemic treatment. **(B)** Excellent response with significant tumor shrinkage after 6 months of endocrine therapy (tamoxifen). **(C and D)** Transaxial scan CT images of a patient with limited number of lesions and preserved organ function at baseline (C) and after aromatase inhibitor-based therapy (D) showing partial response.

below due to partial non-cross resistance between different endocrine treatments.

As such, re-biopsies taken from sites of metastatic disease whenever clinically appropriate and feasible are increasingly recommended in order to plan appropriate systemic further therapy, in particular whether an endocrine approach will be effective option. This has been emphasized in the recent 2012 International Consensus Guidelines for the treatment of advanced disease, recognizing the importance of first- and second-line endocrine therapy as preferential options for patients with potentially endocrine-responsive MBC (14). The options available to these patients are discussed in the next two sections.

FIRST-LINE ENDOCRINE THERAPY OPTIONS FOR POSTMENOPAUSAL MBC

Tamoxifen

Historically, the selective estrogen receptor modifier (SERM) tamoxifen was the standard first-line treatment option for hormone receptor-positive MBC in postmenopausal patients, especially in those presenting with advanced disease or in whom adjuvant endocrine therapy had not been given. In 86 clinical studies involving 5,353 patients, the objective response rate (ORR including complete response [CR] + partial response [PR]) of 34% was observed, with an additional 19% of patients achieving stable disease (SD) for at least 6 months (15). A median duration of response up to 24 months was observed. Response rates (RR) tended to increase with age, with a 27% response in patients younger than 50 years compared with 43% in those over 70. Tamoxifen was generally well tolerated with a low incidence of serious side effects, including a low but significantly increased incidence of endometrial cancer and thromboembolic events due to its partial estrogenic agonist effects (16).

Tamoxifen was compared with many other endocrine therapies (high-dose estrogens, megestrol acetate (MA), oophorectomy, and other SERMs) in randomized trials, and although these trials are small and lacking statistical power by modern standards, tamoxifen was consistently shown to be at least as effective or better, and often with a better toxicity profile (17–30). However, the majority of women with

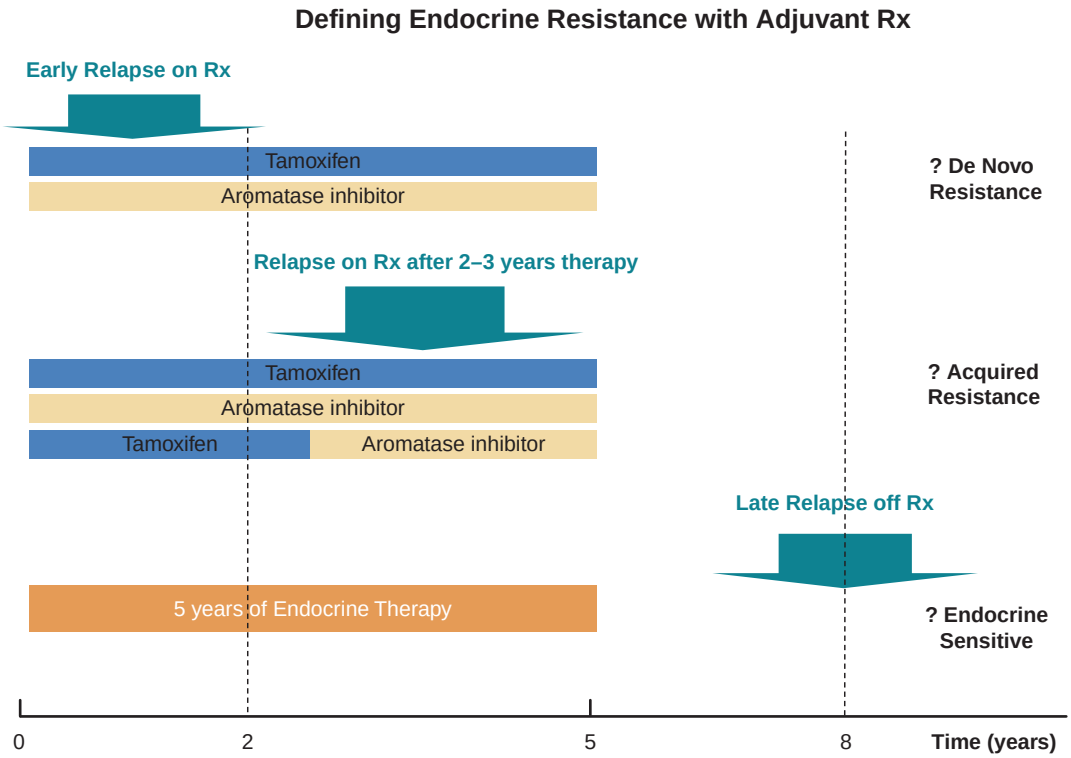

FIGURE 70-2 Conventional definitions of endocrine sensitivity/resistance to adjuvant endocrine therapy. The time-point for relapse from diagnosis (disease-free interval) and also from prior adjuvant therapy (treatment-free interval) both might determine the response to further endocrine therapy in the metastatic setting.

ER +ve breast cancer have already been treated with tamoxifen in the adjuvant setting, and while in the past tamoxifen therapy was often used again if there was a treatment-free period of several years, nowadays alternative endocrine approaches that deprive tumors of circulating estrogens are utilized in preference as first-line therapy.

Aromatase Inhibitors

From the mid 1990s, the potent third-generation oral AIs become the standard first-line treatment option for postmenopausal patients with ER +ve advanced/metastatic breast cancer. Estrogens are normally synthesized in the ovary in premenopausal women; following menopause, mean plasma estradiol (E2) levels fall from about 400–600 pmol/L to around 25–50 pmol/L. These residual estrogens come solely from peripheral aromatase conversion particularly in subcutaneous fat, and plasma E2 levels correlate with body mass index in postmenopausal women (31). The oral AIs anastrozole (Arimidex™), letrozole (Femara™), and exemestane (Aromasin™) all reduce serum estrogen levels in postmenopausal women by preventing the conversion of adrenal androgens into oestrogens (Fig. 70-3). Anastrozole and letrozole are third-generation nonsteroidal AIs that have similar pharmacokinetics with half-lives of approximately 48 hours, allowing a once-daily schedule (32,33). Exemestane is a steroidal aromatase inactivator with a half-life of 27 hours (Fig. 70-3) (34). All three compounds are orally active, and based on the clinical trials outlined below (Table 70-3) these drugs were licensed and approved as first-line endocrine treatment for postmenopausal women with ER+ve advanced breast cancer.

The first published data came from two parallel multicenter double-blind randomized controlled trials in which

TABLE 70-2

Studies Comparing Receptors Status in Primary versus Relapse

Change in receptor status	*Amir (n = 280) Prospective Reanalyzed*[10]	*Curigliano (n = 255) Retrospective Liver Only*[11]	*Karlsson (n = 470) Retrospective*[12]	*Lindstrom (n = 104-459) Retrospective*[13]
ER+ → ER–	12%	11%	36%	25%
ER– → ER+	13%	26%	22%	8%
HER2+ → HER2–	12%	32%	nr	7%
HER2– → HER2+	5%	6%	nr	5%

ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; n, number; nr, not reported.

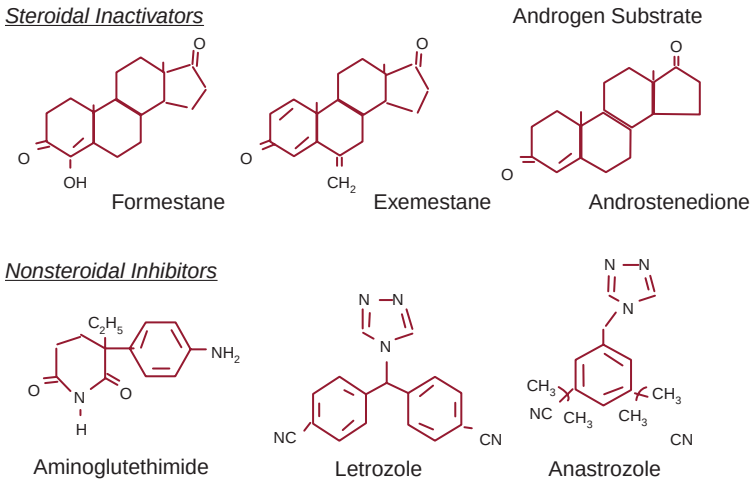

FIGURE 70-3 Chemical structures of some aromatase inhibitors.

anastrozole was compared with tamoxifen as first-line therapy in ER+ve breast cancer. The North American study in 353 women showed that anastrozole significantly prolonged the time to disease progression from 5.6 to 11.1 months (p = .005)(35), while in the larger global trial in 668 patients no difference was found between the treatments in terms of median time to progression (TTP) (8.2 months vs. 8.3 months), response rate (RR) (33% both arms), or clinical benefit rate (CBR) (36). The explanation for the different results may have involved a higher proportion of patients with unknown ER status in the second trial, and a subsequent combined analysis of women with just ER+ve disease from both trials confirmed a significant improvement in disease-free survival (8.5 months vs. 7.0 months) in favor of anastrozole (37). Short-term side effects such as hot flashes, vaginal dryness, and headaches were infrequent and similar in both trials in comparison with tamoxifen.

TABLE 70-3

Main Randomized Clinical Trials of Different Endocrine Therapies as First-line Treatment in MBC

Study/Arms	*n*	*ORR % (P value)*	*CBR % (P value)*	*Median TTP or PFS mo (P value)*	*Median OS mo (P value)*
		AI vs. Tamoxifen			
Anastrozole vs	171	21	59	11.1 (.005)	33
Tamoxifen[35]	182	17	46	5.6	32
Anastrozole vs	340	33	56	8.2	38
Tamoxifen[36]	328	33	55	8.3	42
Letrozole vs	453	32 (.0002)	50 (.0004)	9.4 (<.0001)	34
Tamoxifen[38,39]	454	21	38	6.0	30
Exemestane vs	182	46 (.05)	—	9.9 (.05)	37
Tamoxifen[40]	189	31	—	5.8	43
		Fulvestrant vs. Tamoxifen or AI			
Fulvestrant 250 mg monthly vs	313	31.6	54.3	6.8	36.9
Tamoxifen[51]	274	33.9	62	8.3	38.7
Fulvestrant 250 mg monthly vs	222	20.7	44.6	5.5	—
Anastrozole[52]	229	15.7	45.0	5.1	—
Fulvestrant 250 mg monthly vs	206	17.5	42.2	5.4	—
Anastrozole[53]	194	17.5	36.1	3.4	—
Fulvestrant LD + Anastrozole vs	258	31.8	55.0	10.8	37.8
Anastrozole[61]	256	33.6	55.1	10.2	38.2
Fulvestrant LD + Anastrozole vs	355	—	—	15 (<.007)	47.7 (.049)
Anastrozole[60]	352	—	—	13.5	41.3
Fulvestrant HD vs	102	36.0	72.5	23.4 (.01)	—
Anastrozole[56]	103	35.5	67.0	13.1	—

AI, aromatase inhibitors; CBR, clinical benefit rate; HD, high dose (500 mg i.m. at day 0 + 500 mg at days 14 and 28, thereafter 500 mg monthly until progression); LD, loading dose regimen (500 mg on day 0, 250 mg on days 14, 28, and 250 mg every 28 days thereafter); mo, months; n, number; ORR, objective response rate; OS, overall survival; Tam, tamoxifen; PFS, progression-free survival; TTP, time to progression.

The largest single trial was conducted with letrozole in comparison with tamoxifen in over 900 women with advanced breast cancer. Patients treated with letrozole had a significantly higher ORR, CBR, and prolonged TTP (Table 70-3) (38). Of particular note in this trial, nearly 20% patients had received prior tamoxifen in the adjuvant setting, although it had ceased a median of 3 years prior to development of metastatic disease—in this subgroup, retreatment with tamoxifen had a low response rate of 8% compared with a 32% response rate with letrozole. The improvements in clinical efficacy for letrozole resulted in an early improvement in survival during the first 2 years, although with longer follow-up this difference was lost (39). The explanation for this may relate to the high number (>50%) of patients who prospectively crossed over to the alternate treatment at the time of progression, because significantly more patients benefited from second-line letrozole after progression on tamoxifen than from second-line tamoxifen after letrozole.

Likewise, a European study in 383 patients compared the efficacy and tolerability of the steroidal aromatase inactivator exemestane with tamoxifen as first-line therapy (40). After a median follow-up of 29 months, there was an improvement in progression-free survival (PFS), together with a higher objective response rate with exemestane than tamoxifen (Table 70-3). A subsequent meta-analysis of 6 phase III prospective randomized clinical trials involving 2,787 women treated with second- or third-generation AI versus tamoxifen confirmed a significant advantage in ORR, TTP, and clinical benefit (CB = OR + SD), favoring AIs over tamoxifen (41). However, no difference was found in overall survival. Tamoxifen was associated with a significantly higher incidence of thromboembolic events and vaginal bleeding than the AIs. While some of the smaller trials were not always conducted with the academic rigor of large trials, they all consistently showed small but significant efficacy advantages of the AIs over tamoxifen.

All three drugs (anastrozole, letrozole, exemestane) are thus approved as first-line endocrine therapy options for postmenopausal women with ER+ve advanced breast cancer. It is not clear that one drug is significantly better than any other when direct comparisons have been made, although letrozole achieved greater aromatase inhibition than anastrozole in a crossover pharmaco-dynamic trial (42). Current clinical evidence suggests that there are unlikely to be major direct clinical differences between the different AIs in MBC (43). While there are no comparative data for exemestane with anastrozole or letrozole, further clinical responses have been reported for both exemestane and the second-generation steroidal inhibitor formestane in patients relapsing after anastrozole, letrozole, or the other nonsteroidal inhibitors, suggesting some partial non-cross resistance between the two types of inhibitors (44,45). In clinical practice, this has meant that exemestane is often used as a second-line option after prior first-line letrozole or anastrozole, as discussed further below.

Fulvestrant (alone or in combination with AI) as First-Line Therapy

Most postmenopausal women with metastatic ER+ve breast cancer have already received either an AI or tamoxifen in the adjuvant setting. Thus, the current clinical challenge is to establish an optimal first-line endocrine therapy for MBC given prior adjuvant endocrine therapy exposure. The ER down-regulator fulvestrant (Faslodex™) is a novel type of antagonist that, unlike tamoxifen, has no known agonist effects (46,47). Fulvestrant binds to the ER, but due to its steroidal structure and long side-chain, it induces a different conformational shape with the receptor to that achieved by the nonsteroidal antiestrogen tamoxifen. Because of this, fulvestrant prevents ER dimerisation and leads to the rapid degradation of the fulvestrant–ER complex, producing the loss of cellular ER (Fig. 70-4) (48). It has been shown that due to its unique mechanism of action, fulvestrant delays the emergence of acquired resistance compared with tamoxifen in an MCF-7 hormone-sensitive xenograft model (49), and that the lack of agonist effects means fulvestrant does not support the growth of tumors that became resistant to, and subsequently stimulated by, tamoxifen (50).

Early clinical studies showed that fulvestrant at the initially approved dose of 250 mg monthly by intramuscular injection (i.m.) had similar efficacy to tamoxifen as first-line treatment of hormone receptor MBC, with a median TTP of 6.8 and 8.3 months respectively (HR 1.18, 95% CI, 0.98–1.44; $p = .088$) and ORRs of 31.6% and 33.9% respectively (51). Given the widespread use of prior tamoxifen as adjuvant therapy, two separate phase III first-line trials compared fulvestrant with the AI anastrozole in postmenopausal women with locally advanced or metastatic breast carcinoma who had progressed after prior endocrine therapy (97% with tamoxifen, 56% as adjuvant therapy) (52,53). These trials were prospectively designed to allow combined analysis of data, and at a median follow-up of 15.1 months fulvestrant was at least as effective as anastrozole in terms of median time to progression (5.5 months vs. 4.1 months, respectively) and objective response (19% vs. 17%, respectively) (54). A subsequent survival analysis after a median follow-up of 27 months showed no significant difference in the median time to death between fulvestrant and anastrozole (27.4 months vs. 27.7 months, respectively) (55).

While these early first-line studies suggested that fulvestrant 250 mg was as effective as either tamoxifen or anastrozole in the first-line setting, more recent first-line studies with fulvestrant have investigated either different loading dose (LD) schedules (LD = 500 mg on day 1, then 250 mg on days 14, 28, and monthly thereafter) or a high dose (HD) schedule (HD = 500 mg on days 1, 14, 28, and monthly thereafter). A phase II trial (FIRST) compared fulvestrant HD with anastrozole as first-line treatment and showed a significantly longer TTP with HD fulvestrant (median TTP not reached versus 12.5 months; HR 0.63; 95% CI, 0.39–1.00; $p = .049$) (56). As discussed later, a randomized comparison of HD versus LD fulvestrant in the second-line setting (CONFIRM trial) has confirmed the better efficacy for the 500 mg HD schedule (57), resulting in an amendment to fulvestrant's new drug approval in 2010.

Preclinical evidence from two separate xenograft models suggested that fulvestrant could be significantly more effective when given in a low estrogen environment by combining it with an AI (58,59). Two randomized phase III trials tested the combination of anastrozole with fulvestrant (LD) versus anastrozole alone as first-line therapy in postmenopausal MBC patients (Table 70-3). SWOG S0226 demonstrated that fulvestrant plus anastrozole significantly improved median PFS (15.0 months vs. 13.5 months) and median OS (47.7 months vs. 41.3 months) compared to anastrozole alone (60). Safety and tolerability were similar between the two treatment arms. Conversely, the FACT trial reported no difference in the median PFS or median OS between the combination and the anastrozole arm (61). The main difference between these two trials was the proportion of endocrine therapy-naïve patients, 60% and 33% in the SWOG and FACT trial, respectively. Indeed, in an unplanned subgroup analysis of the endocrine-naïve subgroup in the SWOG trial, a significantly higher benefit was observed in the combination arm (median PFS 17.0 months versus 12.6 months), not observed in the smaller number of endocrine-naïve patients in the FACT trial. On the basis of this result, a currently active first-line phase III trial (FALCON, NCT01602380) is establishing whether fulvestrant (HD) and anastrozole is better than anastrozole alone in truly endocrine-therapy-naïve patients.

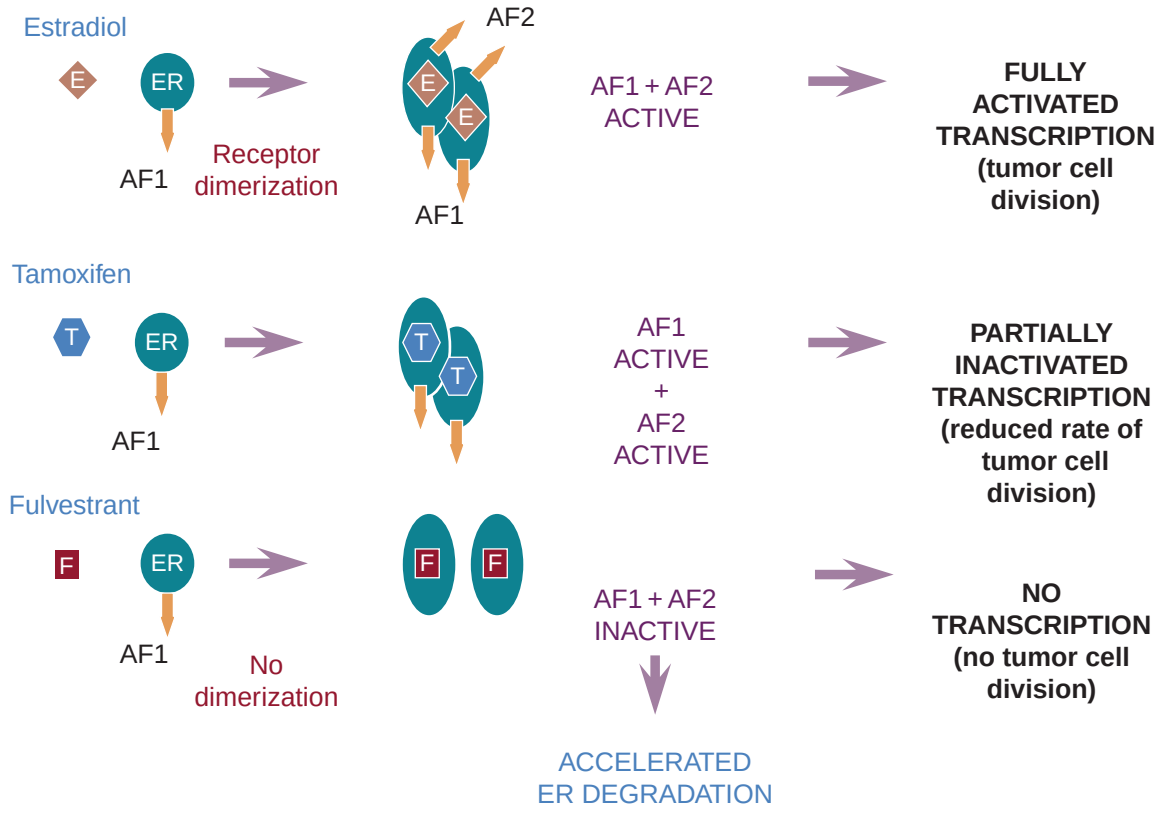

FIGURE 70-4 Diagram summarizing the different "mechanisms of action" of estradiol, tamoxifen, and fulvestrant via the estrogen receptor (ER) leading to different effects in transcription and ultimately tumor cell division.

To date, therefore, the nonsteroidal AIs remain the most effective first-line endocrine option for the majority of postmenopausal patients with MBC. In those with endocrine-sensitive disease, including those who are endocrine-therapy naïve, expected TTP are of the order between 10 to 15 months (Table 70-3). However, the influence of prior adjuvant endocrine therapy remains an important variable in the likelihood of success. While resistance to AIs inevitably develops, it does not preclude further endocrine responses, and effective second-line options are required for these patients.

SECOND-LINE/SEQUENTIAL ENDOCRINE THERAPY FOR POSTMENOPAUSAL MBC

Historically in the 1980s-1990s, tamoxifen was used as a first-line treatment for MBC followed by alternative endocrine therapies in the second-line setting such as the progestin megestrol acetate or the first-generation AI aminoglutethimide. When the third-generation AIs were first investigated as second-line therapy for postmenopausal women progressing after prior tamoxifen, in several RCTs they were shown to be superior in efficacy and/or side effects in this setting (Table 70-4) (62–69). However, given their subsequent improved efficacy in the first-line setting versus tamoxifen as discussed above, from 2001 onward the nonsteroidal AIs letrozole or anastrozole became the standard first-line therapy. Thus, it became important to know what the optimal endocrine therapy was in the second-line MBC setting following prior AI therapy, and in particular whether tamoxifen could be used, how effective the partially non-cross steroidal aromatase inactivator exemestane was, and what was the role of fulvestrant following prior AI therapy. The evidence for each is discussed below.

Tamoxifen

There are limited trials that have assessed the efficacy of tamoxifen after prior adjuvant AI therapy, and few prospective data show efficacy for tamoxifen where disease had progressed on a nonsteroidal AI (i.e., anastrozole or letrozole). The largest available data come from the letrozole versus tamoxifen study where over 50% of the patients prospectively crossed over to the alternative treatment at the time of progression (39). Median OS from the cross-over data was 19 months for patients who crossed to second-line tamoxifen from their AI, compared with 31 months for patients who crossed to second-line letrozole from tamoxifen. The only other data come from retrospective questionnaire data from the combined analysis of the two international phase III anastrozole versus tamoxifen TARGET trials. This analysis suggested that of 119 patients who went on the receive tamoxifen following progression on anastrozole, 58 patients (49%) derived clinical benefit and 12 patients (10%) had an objective response (70). A subsequent double-blind cross-over study by the Swiss centers in the TARGET Trial (SAKK 21/95 sub-trial) further investigated the clinical impact of the sequence anastrozole followed by tamoxifen and reported that 8/16 (50%) derived clinical benefit from tamoxifen (71).

A more contemporary source of data for the efficacy of tamoxifen after prior AI therapy (often in the adjuvant setting) has come from the phase II randomized TAMRAD study testing tamoxifen plus the mTOR inhibitor everolimus (RAD001) (n = 54) versus tamoxifen alone (n = 57) in postmenopausal patients with ER+ve MBC (72). Patients in

TABLE 70-4

Main Randomized Clinical Trials of Different Endocrine Therapies as Second-line Treatment or beyond in MBC

Study	*Arms*	*n*	*ORR % (P value)*	*Median TTP / PFS mo (P value)*	*Median OS mo (P value)*
		AI vs AG and Progestins			
Letrozole vs AG[66]	Letrozole 0.5 mg	192	16.7	3.3	21 (.04)[a]
	Letrozole 2.5 mg	185	19.5	3.4 (.008)[a]	28 (.002)[a]
	AG 250 mg × 2	178	12.4	3.2	20
Letrozole vs MA[65]	Letrozole 0.5 mg	188	12.8	5.1 (.02)	21.05 (.03)[a]
	Letrozole 2.5 mg	174	23.6 (.04)[a]	5.6 (.07)	25.3
	MA 160 mg	189	16.4	5.5	21.5
Letrozole vs MA[69]	Letrozole 0.5 mg	202	21	6.0 (.044)[a]	33
	Letrozole 2.5 mg	199	16	3.0	29
	MA 40 mg × 4	201	15	3.0	26
Anastrozole vs MA[64]	Anastrozole 1 mg	263	12.5	4.8	26.7 (.025)[a]
	Anastrozole 10 mg	248	12.5	5.3	25.5
	MA 40 mg × 4	253	12.3	4.6	22.5
Exemestane vs MA[68]	Exemestane 25 mg	366	15	4.7 (.037)[a]	- (.039)[a]
	MA 40 mg × 4	403	12.4	3.9	28.8
		Fulvestrant Trials			
CONFIRM[57,84]	Fulvestrant HD	362	9.1	6.5 (.006)	25.2
(2nd line) Phase III	Fulvestrant 250 mg monthly	374	10.2	5.5	22.8
EFECT[81]	Fulvestrant LD	351	7.4	3.7	nr
(3rd line or more) Phase III	Exemestane	342	6.7	3.7	nr
SOFEA[82] (acquired AI	Fulvestrant	243	7.4	4.4	20.2
resistance) Phase III	LD+Anastrozole	231	6.9	4.8	19.4
	Fulvestrant LD Exemestane	249	3.6	3.4	21.6

AG, aminoglutethimide; AI, aromatase inhibitor; HD, high dose (500 mg i.m. at day 0 + 500 mg at days 14 and 28, thereafter 500 mg monthly until progression); LD, loading dose regimen (500 mg on day 0, 250 mg on days 14, 28, and 250 mg every 28 days thereafter); MA, megestrol acetate; mo, months; n, number; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; TTP, time to progression.
[a]P vs MA (or AG).

the tamoxifen-alone arm had an ORR of 13%, a CBR of 42%, a median TTP of 4.5 months, and a median OS of 32.9 months. These limited data show that tamoxifen may have clinical benefit in almost 50% of patients relapsing on or after an AI, but relatively few obtain an objective response. Further details of this trial are described below.

Thus, tamoxifen may have some limited efficacy as second-line therapy after an AI although data are sparse to confidently determine the optimal sequence. However, preclinical studies (discussed later) suggest that tamoxifen may be an agonist in cells resistance to long-term estrogen deprivation, and that more effective endocrine/signaling strategies may exist for use following failure of first-line aromatase inhibitor therapy.

Exemestane

Steroidal AIs such as exemestane have an androgen structure and compete with the aromatase substrate androstenedione. They inactivate aromatase by irreversibly binding to its catalytic site, and additional aromatase must be produced before estrogen biosynthesis can resume. Early data suggested a lack of cross-resistance between steroidal AIs and nonsteroidal AIs and that steroidal AIs may be an option in nonsteroidal AI-resistant disease (73). In a phase II, open-label, multinational trial, 24% of patients overall achieved clinical benefit with exemestane following either aminoglutethimide (n = 136) or nonsteroidal AI treatment (n = 105) (45). The ORR and CBR were 8% and 27%, respectively, for patients who received prior aminoglutethimide, with 5% and 20%, respectively, for those who had previously received nonsteroidal AIs.

A separate retrospective analysis of 96 patients receiving exemestane, most of whom had received prior nonsteroidal AIs, reported that 39% experienced clinical benefit with exemestane (74). Lack of cross-resistance between exemestane and nonsteroidal AIs (NSAIs) was also reported in an open-label, exploratory trial comparing sequential treatment with exemestane and NSAIs in MBC (75). Exemestane showed activity in patients after relapse or lack of response to letrozole/anastrozole with an ORR of 8.7%, a CBR of 43.5%, a median TTP of 5.1 months, and a median OS 27.2 of months. As such, exemestane became a standard second-line treatment option for postmenopausal MBC after failure of first-line nonsteroidal AI therapy. As discussed below, exemestane was chosen as the control arm for two large phase III trials that assessed the steroidal antiestrogen fulvestrant in patients no longer responding to a NSAI.

Fulvestrant

Early clinical data with fulvestrant in advanced breast cancer following resistance to AIs came from several phase II studies that showed that fulvestrant 250 mg monthly produced clinical benefit in 20% to 52% patients who had received, and had progressed on, prior treatment with tamoxifen and a nonsteroidal AI (76–80). These results suggested that in addition to being effective after prior tamoxifen, disease progression after nonsteroidal AIs may not preclude subsequent treatment with fulvestrant. Two phase III studies have compared fulvestrant with exemestane, which is a recognized standard of care in this setting (Table 70-4).

The Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) compared the efficacy of fulvestrant 250 mg using the loading dose (LD) schedule versus exemestane in 693 patients in whom the disease had progressed on treatment with nonsteroidal AIs. Both therapies were equally effective and well tolerated, with a median TTP of 3.7 months for both arms and similar CBR (31.5% for exemestane and 32.2% for fulvestrant) (81). To note, 60% of patients had received at least two prior lines of endocrine therapy.

Given the pre-clinical data that suggested that the efficacy of fulvestrant, especially in the setting of endocrine resistance (i.e., post tamoxifen or AIs), may be more effective in a low background estrogen environment, this hypothesis was recently tested in a large UK phase III trial (82). The primary aim of the Study of Faslodex versus Exemestane with/without Arimidex (SoFEA) trial was to compare progression-free survival in patients who have progressed on a nonsteroidal AI following evidence of a prior endocrine response. In total, 736 patients with prior response to a NSAI in locally advanced/metastatic disease for more than 6 months (82%), or as adjuvant therapy for more than 12 months (18%) were enrolled in this partially blinded placebo-controlled study that compared fulvestrant (LD) plus continued anastrozole (n = 243), fulvestrant plus placebo (n = 231), or exemestane (n = 249). There was no significant difference in ORR, CBR, and OS (Table 70-4), and the median PFS was 4.4, 4.8, and 3.4 months, respectively. A longer PFS was positively correlated with duration of prior AI therapy, but no interaction with treatment was observed. These results confirmed the findings of EFECT trial in this setting, and a planned meta-analysis of the two studies confirmed no difference in efficacy between exemestane and fulvestrant (LD) (83).

Given the early data in the first-line setting suggesting that fulvestrant may be more effective if given in a high dose (HD) schedule, fulvestrant 250 mg monthly versus 500 mg monthly was compared in 736 patients with ER+ve MBC progressing after prior endocrine therapy in the CONFIRM trial (57). The objective response rates were similar in both arms (Table 70-4), although fulvestrant HD was associated with a significantly prolonged PFS compared to fulvestrant 250 mg (6.5 vs. 5.5 months, respectively; HR 0.80, 95% CI, 0.68–0.94; $p = .006$). The toxicity profile for both doses is similar, and fulvestrant HD has now become the approved dose for use in the United States and Europe. A final analysis showed a median OS of 26.4 versus 22.3 months in fulvestrant HD and 250 mg, respectively (HR 0.81, 95% CI, 0.69–0.96; $p = .016$), indicating that fulvestrant 500 mg is associated with a clinically relevant 4.1 month difference in median OS and 19% reduction in risk of death compared with fulvestrant 250 mg (84).

Progestins

Progesterone derivatives such as medroxyprogesterone (MPA) and megestrol acetate (MA) represent one choice of endocrine therapy in the treatment of MBC, although their exact mechanism of antitumor action is unclear (85). They suppress adrenal steroid synthesis and ER levels, altering tumor hormone metabolism and leading to consequent tumor cells death (85,86). Progestins have been demonstrated to have similar efficacy to tamoxifen (87,88), and therefore can represent a useful option in some patients, but they are associated with such significant side effects as weight gain, fluid retention, vaginal bleeding, and risk of thromboembolic events (89,90). Progestins may also act through the glucocorticoid receptor, androgen receptor, or progesterone receptor, and this activity seems to be maintained in patients resistant to steroidal AIs (86,90).

Anastrozole and exemestane have been shown to be marginally superior to MA in terms of survival in more recent randomized clinical trials (Table 70-4), but pooled analysis of nine phase III RCTs comparing AIs (both steroidal and nonsteroidal) versus MA in second-line for patients with MBC did not find any significant difference in terms of ORR and TTP (91). Unfortunately, the activity of MA after steroidal AIs failure has not been systematically studied because trials comparing steroidal AIs with MA have not employed a cross-over design (90).

Estrogens

In the 1940s, Haddow described the efficacy of the synthetic estrogen diethylstilbestrol (DES) in the treatment of breast cancer (92), discussing the paradox that certain organic compounds can both induce cancer and be used as antitumor therapy (93). The evidence of efficacy was restricted to postmenopausal women and suggested that the menopause-induced decline in estrogen levels may sensitize breast cancer cells to DES (94). To note, some patients have been treated with intermittent therapy, with repeated regressions upon reintroduction of DES (95). In the early 1980s a trial demonstrated no statistically significant difference in efficacy of tamoxifen and DES and tamoxifen became the preferred agent in view of its better toxicity profile (17).

On the basis of the antitumor effect of DES described above, it has been hypothesized that estrogen deprivation during AIs therapy paradoxically sensitize ER+ve breast cancer cells to low-dose estradiol therapy. In a phase II trial, 66 postmenopausal MBC patients treated with an AI with PFS (≥24 weeks) or relapse (after ≥2 years) of adjuvant AI use were randomized to low-dosage estradiol (6 mg, a level similar to that found in premenopausal women) versus 30 mg of oral estradiol (a level similar to that found in pregnant women) (96). A daily dose of 6 mg of estradiol provided a similar CBR as 30 mg (29% and 28%, respectively), with fewer serious adverse events (18% vs. 34% ≥ grade 3 toxicities). At disease progression, 7 patients with estradiol-sensitive disease were re-treated with AIs whose 2 had PR and 1 had SD, suggesting resensitization to estrogen deprivation. Therefore, the efficacy of 6 mg estradiol should be further examined in phase III clinical trials in MBC women with acquired resistance to AIs.

Abiraterone

AIs are structurally related to the natural substrate androstenedione, and they decrease circulating estrogen levels in postmenopausal women without affecting adrenal biosynthesis of corticosteroids, aldosterone, or other enzymes in the steroidogenic pathway. As cytochrome P450 (CYP)17 is upstream from aromatase in the steroid synthesis pathway, theoretically abiraterone acetate (AA), an irreversible inhibitor of cytochrome P450 (CYP)17, should be able to inhibit more completely the sex steroid synthesis (Fig. 70-5). In a phase I trial, AA demonstrated antitumor activity with manageable side effects, including hypokalemia and fluid retention (97). A currently ongoing randomized phase II trial, BCA2001, is comparing AA (plus low-dose prednisone)

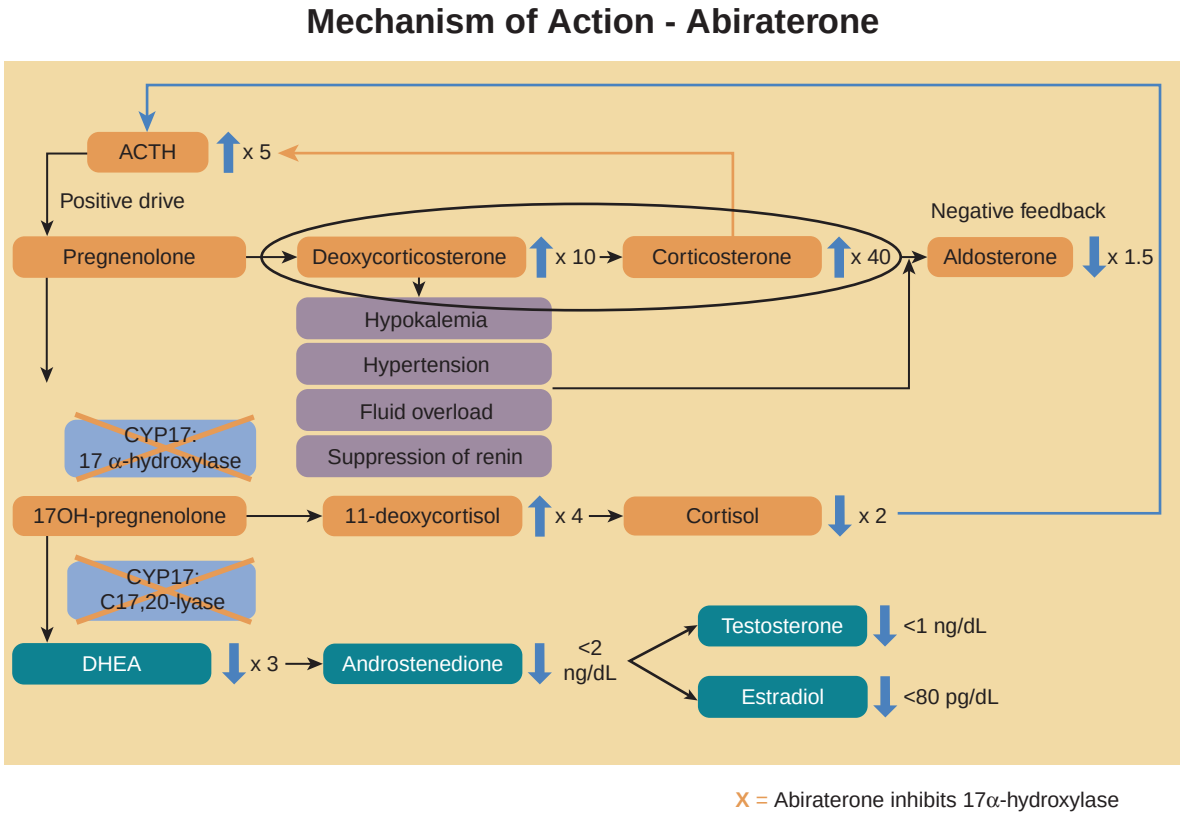

FIGURE 70-5 Mechanism of action of abiraterone acetate (AA), an irreversible inhibitor of cytochrome P450 (CYP)17, in the sex steroid synthesis pathway. (Modified with permission from Attard G, et al. *JCO* 2008;26:4563–4571.)

with or without exemestane versus exemestane alone (98). The hypothesis is that AA would reduce the production of adrenal androgens that may be converted to estrogens and would further suppress the production of estrogens peripherally by the addition of an AI (98). The BCA2001 study will evaluate whether ER signaling remains important to breast cancer growth in the setting of AI failure in postmenopausal women with ER+ve MBC. This study will also determine whether continued aromatase inhibition, through the use of exemestane, is required to maximally suppress estrogen biosynthesis when AA is used.

COMBINATION OF ENDOCRINE AND TARGETED THERAPIES

While there have been significant improvements in the efficacy of endocrine therapy for breast cancer, especially following the introduction of AIs (99), a major clinical issue with all endocrine therapies including estrogen deprivation is either primary lack of endocrine response in the tumor (de-novo resistance) or the subsequent failure of therapy following an initial endocrine response in the tumor (acquired resistance) (100). Understanding the basis for this resistance in advanced breast cancer is an important issue in helping determine what will be the most effective therapy options for the clinic.

Understanding Resistance to Aromatase Inhibitors

In the past much research has concentrated on mechanisms of resistance to tamoxifen. However, recent progress has been made in elucidating the basis for acquired resistance to long-term estrogen deprivation that may provide helpful clues as to prevention of resistance to AIs. It is now known that acquired (or secondary) endocrine resistance develops as consequence of a series of complex adaptive changes occurring in breast cancer cells during the selective pressure of long-term endocrine treatment (101). Activation of various pathways including PI3K/Akt/mTOR, EGFR/HER2, and FGFR leads to endocrine resistance in pre-clinical models, and increasing evidence suggests that targeting these could be a valid strategy to reverse resistance to endocrine therapy.

Laboratory research with ER+ve breast cancer cells into the mechanisms of resistance to long-term estrogen deprivation (LTED) has demonstrated that various growth factor pathways and oncogenes involved in the signal transduction cascade become activated and utilized by breast cancer cells to bypass normal endocrine responsiveness (102). Pre-clinical data indicate that exposure to LTED (analogous to that caused by AIs) and the subsequent development of acquired resistance is associated with adaptive increases in ER gene expression and intercellular signaling, resulting in hypersensitivity to low estradiol levels (103-106). There is evidence for increased "cross-talk" between various growth factor receptor signaling pathways and ER at the time of relapse on LTED (Fig. 70-6), with ER becoming activated and super-sensitized by a number of different intracellular kinases, including mitogen-activated protein kinases (MAPKs), epidermal growth factor receptor (EGFR) and HER2 / HER3 signaling, and the insulin-like growth factor (IGF)/AKT pathway (106-109). In cells that become resistant to long-term estrogen deprivation (LTED-R), ER-mediated gene transcription is

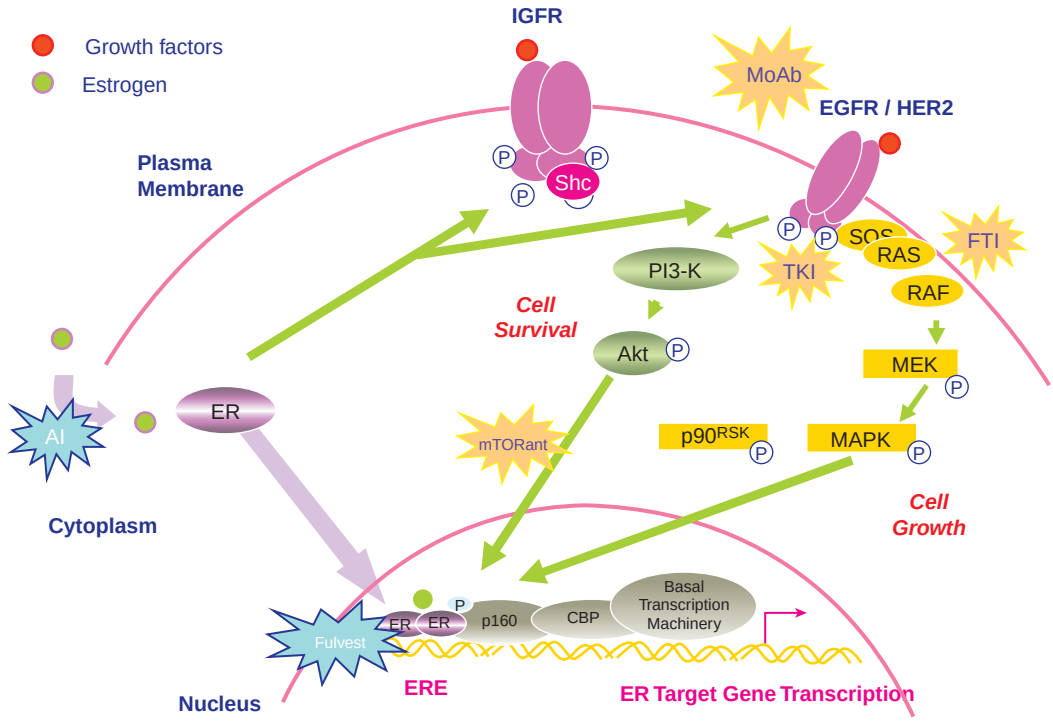

FIGURE 70-6 Cross-talk between various growth factor receptor signaling pathways and ER at the time of relapse on long-term estrogen deprivation (LTED), with ER becoming activated and super-sensitized by a number of different intracellular kinases, including mitogen-activated protein kinases (MAPKs), epidermal growth factor receptor (EGFR) and HER2/HER3 signalling, and the insulin-like growth factor (IGF)/AKT pathway. In cells that become resistant to LTED (LTED-R), ER-mediated gene transcription is enhanced 10-fold in these cells, but can be abrogated by a number of different approaches to interrupt upstream signalling including the EGFR tyrosine kinase inhibitor (TKI) gefitinib, MEK inhibitors, and the ER down-regulator fulvestrant that degrades ER protein.

enhanced 10-fold in these cells, but can be abrogated by a number of different approaches to interrupt upstream signaling including the EGFR tyrosine kinase inhibitor (TKI) gefitinib, MEK inhibitors, and the ER down-regulator fulvestrant, which degrades ER protein (104).

The ER can become involved with the PI3K/Akt/mTOR pathway in breast cancer cells, with both genomic and non-genomic "cross talk" between this signaling pathway and ER. Due to its role in cell survival, there is evidence that the pathway becomes activated in acquired hormone-resistant breast cancer and accounts for survival of cells despite the presence of continued endocrine blockade. Breast cancer cell lines with activated Akt (e.g., via loss of the regulatory PTEN tumor suppressor gene) have been shown to be especially sensitive to mTOR antagonism. Pre-clinical models of ER+ve hormone-sensitive and resistant breast cancer have been used to examine the effects of combining mTOR antagonists with endocrine therapy (110,111). Boulay et al. demonstrated that the estrogen-dependent growth of both wild-type MCF-7 and aromatase-expressing (MCF-7/Aro) breast cancer cells could be inhibited in a dose-dependent manner by the mTOR antagonist everolimus, suggesting that mTOR signaling is required for the estrogen-dependent proliferation of these cells (111). In subsequent experiments with the MCF-7/Aro cells, both the AI letrozole and the mTOR inhibitor everolimus inhibited androstenedione-induced cell proliferation. However, the combination of letrozole and everolimus produced maximal growth inhibition, with clear evidence for additive/synergistic effects. In particular increased activity of the letrozole-everolimus combination correlated with a greater effect on G1 progression and a significant decrease in cell viability and apoptosis.

Likewise, a separate group have shown that MCF-7 cells expressing a constitutively active Akt were able to proliferate under reduced estrogen conditions and were resistant to the growth inhibitory effects of tamoxifen, both *in vitro* as well as *in vivo* in xenograft models (110). However, co-treatment with temsirolimus inhibited mTOR activity and restored sensitivity to tamoxifen, primarily through induction of apoptosis, thus suggesting that Akt-induced tamoxifen resistance may in part be mediated by signaling through the mTOR pathway. These laboratory data therefore support a strategy for targeting a downstream element of the pathway such as mTOR, which has been shown to restore endocrine sensitivity in both cell lines and xenograft models and thus provides a rationale for combining endocrine therapy with mTOR inhibition. The main clinical issue is whether this benefit is confined to tumors that have developed endocrine resistance, or whether this could be an effective first-line treatment options that improves the efficacy of aromatase inhibition.

Thus, it would appear that the ER remains an integral part of signaling even following failure of AIs and that a possible successful approach could involve the use of various signal transduction inhibitors to abrogate activation of ER signaling (Fig. 70-6). As discussed below, clinical evidence is now emerging that such drugs may be more effective when

given in combination with endocrine therapy in an attempt to delay or reverse endocrine resistance.

Combinations with mTOR Antagonists

One of the first clinical studies to demonstrate a benefit for an endocrine-mTOR inhibitor combination was a randomized phase II study in 270 postmenopausal women with ER+ve primary operable breast cancer that evaluated the benefit of adding everolimus (10 mg/day) or placebo to neoadjuvant letrozole (2.5 mg/day) for 16 weeks preoperatively (112). The primary endpoint of the study was tumor response, with significantly greater response rates for the addition of everolimus to letrozole by both clinical (68.1% vs. 59.1%) and radiological assessments. A significantly greater reduction in cell proliferation measured by change in Ki-67 was seen in the letrozole/everolimus combination arm compared to letrozole, and associative correlative studies were also conducted to determine those tumors most likely to respond to combined mTOR antagonism and aromatase inhibition. Interestingly, specific mutations in PIK3CA were found to be associated with a greater likelihood of an anti-proliferative response to the combination of letrozole plus everolimus. In particular mutations in the allosteric helical domain of exon 9 were associated with a poor anti-proliferative response to letrozole alone but a good response to letrozole plus everolimus. This particular PIK3CA mutation has been associated with a worse prognosis in breast cancer, and a greater likelihood of response to the combination would support a role for the PI3K/Akt/mTOR pathway in endocrine resistance.

There have been two important studies in the metastatic setting that have evaluated the addition of everolimus to endocrine therapy for postmenopausal women with ER+ve MBC who have already received prior endocrine therapy (Table 70-5). Tamoxifen plus everolimus was compared with tamoxifen alone in patients with AI-resistant MBC in the small randomized phase II study TAMRAD (Tamoxifen plus Everolimus) (72). The combination therapy showed an improvement in TTP (8.6 months vs. 4.5 months), 6-month CBR (61% vs. 42%), and median overall survival compared with tamoxifen alone. Importantly, the trial design included stratification according to type of resistance to previous treatment with AIs, with primary resistance being defined as disease progression developing either during/within 6 months of completion of adjuvant AI therapy or within 6 months of starting AI therapy for MBC, while acquired secondary resistance was defined as those relapsing >6 months after stopping adjuvant AIs or responding for ≥6 months to AIs in the metastatic setting. An exploratory subgroup analysis showed that the greatest clinical benefit from the combination arm occurred in patients with acquired secondary resistance.

These clinical data from TAMRAD would support the hypothesis that tumors that initially respond and then develop resistance to AIs may utilize the PI3K/Akt/mTOR pathway and that this combined approach should be most effective in those patients with ER+ve advanced disease that progresses during or recurs after NSAI therapy (113). This was confirmed in the Breast Cancer Trials of Everolimus-2 (BOLERO-2) study, a large randomized phase III trial that assigned 724 postmenopausal patients with ER+ve MBC in a 2:1 ratio to either exemestane alone or the combination of exemestane and everolimus (114). All patients had progressed on a NSAI, and importantly 84% of them had demonstrated prior hormone-sensitive disease defined as "at least 24 months of endocrine therapy before recurrence in the adjuvant setting, or a response or stabilization for at least 24 weeks of endocrine therapy for advanced disease" (114). Furthermore, nearly 60% of patients had also received an antiestrogen (tamoxifen or fulvestrant), and approximately 80% had received their AI for MBC—as such, the study was predominantly one of second-line endocrine therapy in patients with evidence or prior endocrine sensitivity before developing acquired secondary resistance to their NSAI. In BOLERO-2 there was a statistically significant and clinically relevant improvement in PFS for the combination (median 7.8 months vs. 3.2 months, HR = 0.45; p <.0001) (115). The clinical benefit was primarily due to better control of the disease, although there was a significant improvement in tumor response rates from only 0.4% in the exemestane-alone group to 9.5% in the everolimus/exemestane group (p = .001)(114). OS results are expected to be mature in 2014. An increased incidence of side effects including stomatitis, fatigue, rash, diarrhea, non-infectious pneumonitis, and hyperglycemia was observed in both trials for the addition of everolimus, albeit the majority were grade 1 or 2 in severity (72,114). Given that many of these toxicities are not

TABLE 70-5

Main Studies Testing the Addition of mTOR Antagonists to Overcome Resistance to Endocrine Therapy in MBC

Study	*Phase*	*Arms*	*n*	*ORR % (P value)*	*CBR % (P value)*	*Median TTP or PFS mo (P value)*	*Median OS mo (P value)*
TAMRAD(72)	II RCT, with previous AI exposure[b]	Everolimus + Tamoxifen	54	–	61.1 (.045)[c]	8.6 (.0026)[c]	nr (.0019)[c]
		Tamoxifen	57	–	42.1	4.5	24.0
BOLERO-2 (114,115)	III RCT, progressed on NSAI[a]	Everolimus + Exemestane	485	9.5 (<.001)	79.6	7.8 (<.0001)	nr
		Exemestane	239	0.4	59.0	3.2	nr
HORIZON(116)	III RCT, AI-naive	Letrozole + Temsirolimus	555	27	44	8.9	nr
		Letrozole + Placebo	555	27	46	9.0	nr

AI, aromatase inhibitor; CBR, clinical benefit rate; nr, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RCT, randomized controlled trials; TTP, time to progression.

[a]> 50% of patients in each arm with ≥ 3 previous therapies, stratified by sensitivity to previous hormonal therapy, presence of visceral metastases; [b]Stratified by primary versus secondary hormone resistance: primary resistance: relapse during adjuvant AI therapy or progression during first 6 months of initiating AI for metastatic disease. Secondary resistance: late relapse (at or after 6 months) or previous response to AI therapy for metastatic breast cancer and subsequent progression; [c]Exploratory analysis;

observed with endocrine therapy alone, this may impact on treatment feasibility in clinical practice. However, the magnitude of benefit in PFS led to the approval of everolimus in combination with exemestane in the United States and Europe during 2012 as a new treatment option for ER+ve MBC previously treated with an AI.

A key question remains as to whether the combination of an mTOR inhibitor with endocrine therapy will only be effective for endocrine-resistant breast cancer, or whether this is a new option for endocrine-sensitive MBC in the first-line setting that could substantially delay or prevent endocrine resistance developing. A large first-line phase III study (HORIZON) has recently reported the efficacy of the oral mTOR antagonist temsirolimus (30 mg orally for 5 days every 2 weeks) in combination with letrozole versus letrozole/placebo in 1,112 patients with AI-naïve ER+ advanced breast cancer (Table 70-5) (116). In contrast to BOLERO-2, the population in this larger study was mainly totally endocrine therapy naïve (approximately 60%) and had received no prior AI therapy for locally advanced/metastatic disease. Temsirolimus had previously shown some efficacy using an iv formulation in heavily pretreated MBC (117), and in a small 3-arm randomized phase II study in combination with letrozole (118).

However, in HORIZON there was no improvement in PFS overall (median 9 months, HR = 0.90; p = .25) or in the 40% patient subset that had received prior adjuvant endocrine therapy. Toxicities such as rash, diarrhea, stomatitis, and asthenia were greater for the combination, and the study was terminated by the Independent Data Monitoring Committee after the second interim analysis. These data suggest that as first-line therapy the combination may not be any better than an AI alone.

Thus, it is becoming clear that improving endocrine therapy by the addition of an mTOR antagonist is not that simple (119). The significant efficacy for the combination of everolimus and exemestane in those patients refractory to prior AI therapy is a major advance in providing greater clinical benefit compared with the use of just further endocrine therapy alone for these patients, which may spare the use of palliative chemotherapy for a period of time. The up-regulation of the PI3K/Akt/mTOR pathways during the acquisition of resistance to long-term estrogen deprivation was already evident from pre-clinical studies and has now been confirmed in both the TAMRAD and BOLERO-2 trials. As for identifying untreated ER+ve MBC patients who would benefit from the combination in the first-line setting, this appears much trickier—it is possible that some ER+ve tumors are inherently primed to respond to the combination, as shown with the PIK3CA mutations in the neoadjuvant study. However, to date there is no proven biomarker that can be used as a true indicator of mTOR activation to identify patients with tumors dependent on this pathway, other than the clinical development of acquired secondary resistance to nsAI therapy, which is where this therapy should be used.

Combinations with EGFR / HER2 Therapies

Results from various pre-clinical studies of acquired endocrine resistance in ER+ breast cancer have consistently demonstrated that a functional ER signalling pathway persists that often cross-talks with enhanced peptide growth-factor-receptor signalling pathways (104,120). The clinical implication of these experimental data were that a combined approach utilizing hormonal agents combined with growth-factor-receptor targeted therapies could enhance efficacy and delay/prevent the emergence of endocrine resistance. In particular, a number of trials have been conducted with either the HER2 monoclonal antibody trastuzumab or the EGFR/HER2 tyrosine kinase inhibitors (TKIs) gefitinib, erlotinib, or lapatinib in combination with endocrine therapy (121). While some of these trials have included patients with established hormonal resistance where activated growth factor pathways may be operative, many of the trials were conducted in the first-line ER+ve hormone-sensitive setting in combination with an AI. In patients with established endocrine resistance, it was hoped that combined therapy could be more effective than another endocrine therapy, while in the first-line setting the expectation was that combined therapy might delay the time to disease progression by blocking a key resistance mechanism in ER+ve breast cancer cells (i.e., peptide growth factor signalling) from the outset.

Gefitinib and erlotinib are both small-molecule tyrosine kinase inhibitors of the ATP binding site of the epidermal growth factor receptor (EGFR) and have been shown to delay the development of tamoxifen resistance in vitro (122). Phase II monotherapy studies of gefitinib in unselected patients with advanced breast cancer were disappointing, and the only trial to report a reasonable number of responses included patients with ER+ve tamoxifen-resistant breast cancer (123), the setting in which pre-clinical models had shown the best evidence of activity for gefitinib. Subsequently, two small phase II studies explored the potential benefit for combining either gefitinib or erlotinib with an AI in unselected patients with ER+ve advanced breast cancer, but neither study showed significant clinical efficacy (124,125).

Two randomized phase II studies of HER family targeting have been reported to date in the first-line advanced breast cancer setting (Table 70-6). A double-blind placebo-controlled phase II trial of tamoxifen with/without gefitinib was conducted in 290 patients as first-line endocrine therapy in postmenopausal women with ER+ve metastatic breast cancer (126). This study set out to prove the pre-clinical concept that combination therapy could delay the onset of acquired resistance to endocrine therapy, as demonstrated both in xenograft models *in vivo* (120,127). The patient's disease was either endocrine naïve or had developed greater than a year after completion of adjuvant tamoxifen (Stratum 1, n = 206), or had developed during or after AI therapy (Stratum 2, n = 84). In the endocrine-naïve patients (Stratum 1) there was a numerical increase in progression-free survival from 8.8 to 10.9 months (HR 0.84, 95% CI, 0.59–1.18; p = .31), which met the predefined criterion of a 5% improvement in PFS. Patients who had been pre-exposed to AIs did not gain any benefit from the combination, suggesting that difference in patient populations is crucial in selecting an appropriate populations to test in these studies.

A second randomized trial of gefitinib and anastrozole versus anastrazole alone in a similar first-line patient population of women with ER+ve advanced breast cancer reported a significant prolongation of progression-free survival from a median of 8.2 months with anastrozole to 14.6 months with the combination (HR 0.55, 95% CI, 0.32–0.94) (128). Although the number of patients in this second study was only 93, a subsequent combined analysis suggested that the benefit for the combination was seen exclusively in those patients who were endocrine therapy naïve and had not received any prior endocrine therapy in the adjuvant setting. On the basis of these results, a prospective multicenter study (MINT, NCT 01151215) was set up with a novel tyrosine kinase inhibitor AZD8931, a potent inhibitor of EGFR, HER2, and HER3, to test the hypothesis that combined therapy of growth factor blockade together with anastrozole could delay time to progression compared with anastrozole alone in endocrine-therapy-naïve metastatic breast cancer. This study will be the definitive test of this concept.

TABLE 70-6

Main Studies Testing EFGF/HER2 Inhibitors Plus Endocrine Therapy to Overcome Endocrine Resistance in MBC

Study	*Phase*	*Arms*	*n*	*ORR%*	*Median TTP or PFS (mo)*	*Median OS (mo)*
Cristofanilli et al.[128]	II RCT	Anastrozole + Placebo	50	12	8.4	nr
		Anastrozole + Gefitinib	43	2	14.7	nr
Osborne et al.[126]	II RCT	Tamoxifen + Placebo	136	14.9	8.8	nr
		Tamoxifen + Gefitinib	153	12.4	10.9	nr
TAnDEM[132]	III RCT	Anastrozole	104	6.8	2.4	23.9
		Anastrozole + Trastuzumab	103	20.3[a]	4.8[a]	28.5
EGF30008[136]	III RCT	Letrozole + Placebo	108	15	3	32.3
		Letrozole + Lapatinib	111	28[a]	8.2[a]	33.3
eLEcTRA[133]	II RCT	Letrozole	31	13	3.3	nr
		Letrozole + Trastuzumab	26	27	14.1	nr

mo, months; nr, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival, RCT, randomized controlled trials; TTP, time-to-progression.
[a]Statistically significant difference.

Likewise, targeting HER2 in hormone receptor positive breast cancer has been explored as a means of improving endocrine responsiveness. This may involve re-expression of silenced ER as outlined in pre-clinical data (129). Indeed, clinical evidence exists that trastuzumab can restore both ER expression and endocrine responsiveness in a series of 10 patients with ER-ve HER2+ve advanced breast cancer who had serial biopsies during trastuzumab therapy (130). A phase II clinical trial of letrozole and the monoclonal antibody trastuzumab in patients with ER+ve/HER2+ve MBC revealed that the combination was well tolerated and had a CBR of 50% (131). Subsequently, a randomized phase II trial in 207 patients with known ER+ve/HER2+ve MBC (TAnDEM) reported a doubling of PFS with the addition of trastuzumab over anastrozole alone (4.8 months vs. 2.4 months; $p = .0016$), although there was no significant impact on OS (Table 70-6) (132). A small phase II study (eLEcTRA) showed a similar potential benefit for the addition of trastuzumab to letrozole as first-line treatment in ER+ve/HER2+ve MBC (133).

Subsequently, lapatinib, a potent oral tyrosine kinase inhibitor of both EGFR and HER2, has been explored in combination with endocrine therapy based on *in vitro* data have demonstrated that estrogen deprivation significantly enhances the anti-proliferative effects of lapatinib in HER2 amplified breast cancer cell lines (134). Likewise, preclinical evidence suggested that lapatinib could significantly enhance sensitivity to tamoxifen in cell lines with acquired tamoxifen resistance (135). Results from a phase III trial of 1,286 patients with metastatic ER+ breast cancer who were randomized to receive either letrozole alone or letrozole combined with lapatinib were recently reported (136). In patients with known ER+ve/HER2+ve tumors (n = 219), the addition of lapatinib to letrozole significantly reduced the risk of progression (HR 0.71, 95%CI, 0.53–0.96; $p = 0.019$), improving the median PFS from 3.0 months for letrozole to 8.2 months for the combination (Table 70-6). The clinical benefit was also significantly greater for the combination (48% vs. 29%; $p = .003$), and the combination became an approved treatment option in the United States and Europe from 2010 for ER+ HER2+ MBC in situations when chemotherapy was not indicated.

In the EGF30008 trial there were an additional 952 patients with ER+ve/HER2–ve tumors, where the hypothesis was that any development of acquired resistance to letrozole due to adaptive EGFR or HER2 up-regulation might be prevented/delayed by the combination. However, in the ER+ve/HER2–ve population overall there was no improvement in PFS, although potential benefit from the addition of lapatinib may exist for those subset of patients that relapsed during adjuvant tamoxifen therapy. This result is consistent with previous data relating to tamoxifen sensitizing to HER2 up-regulation in some cases, but also implies that in endocrine sensitive disease co-blockade of HER2 with estrogen deprivation from the outset cannot delay resistance. As such, combined endocrine therapy and growth factor targeting in only indicated for MBC that is proven to have both ER and HER2 amplification, and further research is indicated in the first-line setting in ER+ve/HER2–ve MBC to see whether combined therapy can further improve the efficacy of endocrine therapy—the first-line MINT study in endocrine naïve MBC will be the definitive test of this concept in clinical practice.

ENDOCRINE THERAPY FOR PREMENOPAUSAL PATIENTS WITH METASTATIC BREAST CANCER

For women with ER+ve MBC who are still premenopausal when they develop advanced disease, the available endocrine therapy options include ovarian ablation (via surgery, radiotherapy, or luteinizing hormone-releasing hormone analogues [LHRHa]), tamoxifen, or a combination of ovarian ablation with tamoxifen or with an AI (Fig. 70-7). While oophorectomy and ovarian irradiation induce permanent ovarian ablation, the most widely used method involves using an LHRHa to induce a potentially reversible medical ovarian ablation. Goserelin (Zoladex™) is the most widely used LHRHa in ER+ve advanced disease and is administered as a 3.6 mg subcutaneous monthly depot injection. The most common side effects are those of estrogen suppression, including hot flushes and less frequently reduced libido, vaginal dryness, headache. The local injection is well tolerated. A pooled analysis of several phase II studies that included 228 pre- and perimenopausal women with advanced breast cancer showed that 36% had an objective response to goserelin, with an additional 50% showing stabilization of their disease (137). The median duration of response was

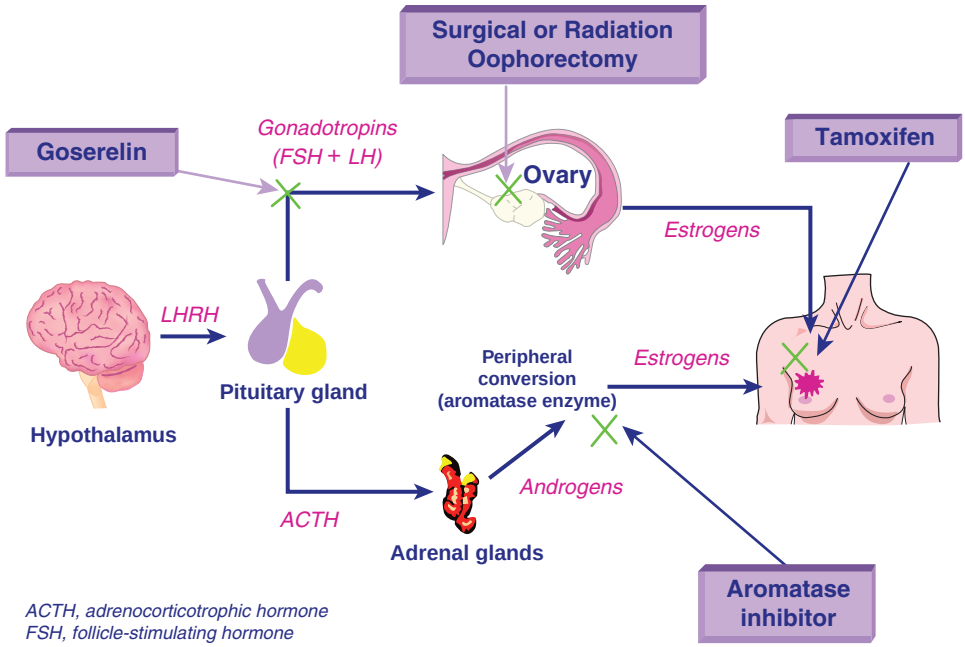

FIGURE 70-7 Available endocrine therapy options for women with ER+ve MBC developing advanced disease when they are still premenopausal: ovarian ablation (via surgery, radiotherapy, or luteinizing hormone-releasing hormone analogues [LHRHa]), tamoxifen, or a combination of ovarian ablation with tamoxifen or with an aromatase inhibitor (AI).

10 months, with an overall survival of 26 months. These results were comparable to previously published data with either tamoxifen or surgical oophorectomy in this group of premenopausal patients with advanced disease (25).

Combined therapy of goserelin plus tamoxifen has been compared with goserelin alone as first-line endocrine therapy in 318 pre- and perimenopausal women with advanced breast cancer (138). In this study objectives response rates were statistically similar (38% for goserelin + tamoxifen, 31% for goserelin), but there was a significant improvement in median TTP (6.5 months vs. 5.3 months). OS was similar (32 vs. 29 months), and there was no difference in tolerability for the combination. In another trial 161 premenopausal patients with advanced breast cancer were randomly assigned to treatment with the LHRHa buserelin, tamoxifen, or both (139). Combined treatment with buserelin and tamoxifen was superior to treatment with buserelin or tamoxifen alone by ORR (48% vs. 34% and 28%, respectively), median PFS (9.7 months vs. 6.3 months and 5.6 months, respectively, $p = 0.03$), and OS (3.7 years vs. 2.5 years and 2.9 years, respectively; $p = .01$).

Subsequently, there was a meta-analysis of four randomized trials of LHRHa + tamoxifen versus LHRHa alone, and significant benefits were found for the combination in terms of improved ORR (39% vs. 30%; $p = .03$), median PFS (8.7 months vs. 5.4 months, HR 1.31, $p < .001$), and most importantly OS (34.8 months vs. 30.0 months; $p = .02$) (140). Thus, standard practice is now to recommend LHRHa plus tamoxifen as first-line endocrine therapy in hormone-sensitive advanced breast cancer. Of note, some caveats need to be considered because there was no formal cross-over of patients who received the LHRH agonist alone to tamoxifen as second-line therapy in three of the four studies, and there was no detailed collection of toxicity or quality of life data (141). In a nonrandomized controlled study, fulvestrant 250 mg has also been combined with goserelin 3.6 mg every four weeks, with a CBR of 58% in 26 premenopausal patients (142).

Several unanswered questions remain in the endocrine therapy of premenopausal patients. In particular, it is unclear whether complete estrogen suppression using LHRHa and an AI will be superior to using LHRHa + tamoxifen as first-line endocrine therapy for advanced disease. Given the superiority of AI over tamoxifen in postmenopausal women, it is not unreasonable to suppose that LHRHa + AI could further enhance endocrine responsiveness over LHRHa + tamoxifen; however, there are no randomized data yet to answer this, and there are concerns that the hormonal toxicities of maximal estrogen blockade might outweigh the benefits. Likewise, it is unclear whether sequential estrogen suppression might not be a better long-term strategy compared with maximal estrogen suppression up front. In the past, further clinical benefit has been reported for premenopausal women with advanced breast cancer initially treated with goserelin, and then at progression given an AI combined with goserelin (143).

New randomized trials will be required to see if a sequential approach of LHRHa alone or LHRHa + tamoxifen followed by switch at progression to LHRHa + AI would produce overall greater disease control and improved survival than using LHRHa + AI up front. Unfortunately, the relatively small number of suitable patients for such trials makes them difficult to undertake, and answers to these clinical questions are unlikely to occur quickly.

NEW COMBINED STRATEGIES TO OVERCOME ENDOCRINE RESISTANCE

The emergence of endocrine resistance during prolonged therapy is complex, and it is unlikely that any single mechanism is operative. While the EGFR/HER2 and mTOR pathways have been studied extensively, numerous other signaling pathways may also be implicated. Both pre-clinical and early phase clinical research is now trying to identify various other strategies to overcome endocrine resistance, based on the availability of targeted therapeutics that can be combined with endocrine therapy. Some of the key areas are discussed below, together with a list of current randomized trials that are investigating various signal transduction inhibitors in combination with endocrine therapy in ER+ve advanced breast cancer (Table 70-7).

TABLE 70-7

Randomized Clinical Trials Investigating Signal Transduction Inhibitors (STIs) Plus Endocrine Agents in MBC

Target	*Agent*	*Stage and Study Number*	*Estimated Enrollment (n pts)*
PI3K/AKT/mTOR	XL147 (inhibitor of PI3K) or XL765 (dual inhibitor of PI3K and mTOR) Plus Letrozole	Phase I/II (NCT01082068)	99
	GDC-0941 + Fulvestrant or GDC-0980 + Fulvestrant or Placebo + Fulvestrant	Phase II (NCT01437566)	270
	BKM120 (pan-PI3K inhibitor) Plus Fulvestrant versus Placebo Plus Fulvestrant	Phase III (NCT01633060)	615
	MK-2206 (Akt inhibitor) Plus Anastrozole, or Letrozole, or Exemestane, or Fulvestrant	Phase I (NCT01344031)	54
Histone deacetylase (HDAC)	Entinostat (SNDX-275) Plus Exemestane versus Placebo Plus Exemestane	Phase II (NCT00676663)[149]	125
Vascular endothelial growth factor/ angiogenesis	Bevacizumab Plus Tamoxifen or Letrozole versus Tamoxifen or Letrozole alone	Phase III (NCT00601900)	502
	Bevacizumab Plus Letrozole or Fulvestrant versus Letrozole or Fulvestrant alone	Phase III (NCT00545077)[155]	378
	BMS-690514 (inhibitor of EGFR, HER2, and VEGF receptor kinases) Plus Letrozole versus Lapatinib Plus Letrozole	Phase II (NCT01068704)	140
Proteasome (NF-kB pathway)	Bortezomib plus Fulvestrant versus Fulvestrant alone	Phase II (NCT01142401)	118
Src kinase	Dasatinib Plus Fulvestrant versus Fulvestrant Alone	Phase II (NCT00754325)[166]	100
	Dasatinib Plus Exemestane versus Exemestane Alone	Phase II (NCT00767520)[167]	157
Fibroblast growth factor receptor (FGFR)	AZD4547 Plus Fulvestrant versus Fulvestrant Alone	Phase I/II (NCT01202591)	120
Insulin-like growth factor type I (IGF-I)	MEDI-573 (dual Dual IGF-I/II-neutralizing antibody) Plus AI versus AI Alone	Phase Ib/II (NCT01446159)	193
	BMS-754807 Plus Letrozole versus BMS-754807 Alone	Phase II (NCT01225172)	59
	MM-121 Plus Exemestane versus Exemestane Alone	Phase II (NCT01151046)	130
Cyclin dependent kinase (CDK) 4/6	PD-0332991 Plus Letrozole versus Letrozole alone	Phase I/II (NCT00721409)[174]	177
	PD-0332991 Plus Letrozole versus Placebo Plus Letrozole	Phase III (NCT01740427)	450
Epidermal growth factor family and HER2	Lapatinib or Trastuzumab or Both Plus AI	Phase III (NCT01160211)	525
	Pertuzumab Plus Trastuzumab Plus AI versus Trastuzumab Plus AI	Phase II (NCT01491737)	250

AI, aromatase inhibitor; HER2, human epidermal growth factor receptor 2; mTOR, mammalian target of rapamycin; n, number; PI3K, phosphatidylinositol-3-kinase; pts, patients.

Agents Targeting PI3K/AKT/mTOR Pathway

Several other drugs that target the PI3K/AKT pathway upstream of mTOR are currently being tested in phase I/II trials in patients with advanced ER+ve breast cancer in the hope that they may prove more specific and effective than current mTOR inhibitors. These include pan- or isoform-specific PI3K inhibitors, dual PI3K/mTOR inhibitors, and AKT inhibitors (Table 70-8) (101). For example, BKM120 is a potent oral pan-PI3K inhibitor that when given either continuously or intermittently in combination with letrozole in a phase I study has been demonstrated to be safe, with evidence of anti-tumor efficacy as assessed by FDG-PET scans (144). The combination of BKM120 with fulvestrant has also been investigated (145), and a randomized phase III study of BKM120 with fulvestrant in patients with HR+ve/HER2–ve locally advanced/metastatic breast cancer who have progressed

TABLE 70-8

Novel Agents Targeting PI3K/AKT/mTOR Pathway under Investigation

Target(s)	*Drug*	*Pharmaceutical Company*
PI3Kα	BYL719	Novartis
PI3Kα	GDC-0032	Genentech
PI3Kα	MLN-1117	Millenium
PI3Kd	CAL-101	Calistoga
Pan-PI3K	XL-147	Exelixis/Sanofi
Pan-PI3K	BKM120	Novartis
Pan-PI3K	GDC-0941	Genentech
Pan-PI3K	PKI-587	Pfizer
PI3K/mTOR	XL-765	Exelixis/Sanofi
PI3K/mTOR	BEZ235	Novartis
PI3K/mTOR	GDC-0980	Genentech
PI3K/mTOR	PF-4691502	Pfizer
TORC1/2	MLN-128	Millenium
TORC1/2	OSI-027	OSI Pharma
TORC1/2	AZD2014	AstraZeneca
AKT (catalytic)	AZD5363	AstraZeneca
AKT (allosteric)	MK-2206	Merck
AKT (catalytic)	GDC-0068	Genentech

after prior AI therapy (BELLE-2, NCT01610284) is recruiting a second-line patient population very similar to that in the BOLERO-2 trial. Given the likely increased use of everolimus in combination with exemestane in the second-line setting, a further trial will assess the role of BKM-120 with fulvestrant in patients who have progressed on or after mTOR inhibitors (BELLE-3) (NCT01633060).

Another approach is to develop drugs that target PI3K and mTOR together, and two pharmaceutical companies have set up studies comparing these dual inhibitors with pan-inhibitors of PI3K, both in combination with endocrine therapy versus endocrine therapy alone. For example, either XL147 (inhibitor of PI3K) or XL765 (dual inhibitor of PI3K and mTOR) are being combined with letrozole in a phase I/II trial (NCT01082068) in ER+ve advanced breast cancer. Likewise, FERGI is a multicenter, international, randomized, double-blinded, placebo-controlled phase II trial recruiting patients with advanced or MBC who have previously received treatment with an AI, randomized to receive either GDC-0941 (pan PI3K inhibitor) + fulvestrant or GDC-0980 (dual inhibitor of PI3K and mTOR) + fulvestrant, or placebo + fulvestrant (NCT01437566).

Whether these dual targeted drugs are more effective than pan-isoform PI3K inhibitors remains to be seen, together with early assessments of toxicities. Other therapeutics have been developed to target Akt (Table 70-8), which is an important regulator of the pathway, and a phase I trial of MK2206 in combination with anastrozole, letrozole, exemestane, or fulvestrant is currently recruiting postmenopausal women with ER+ve metastatic breast cancer (NCT01344031).

Histone Deacetylase Inhibitors (HDACI)

Another possible approach to reverse hormone resistance is the use of histone deacetylase inhibitors (HDACI) to resensitize breast cancer cells to hormone manipulation (146,147). It has been shown that in some breast cancers, expression of ER can be repressed/lost by epigenetic modifications such as methylation and histone deacetylation, and this could be a mechanism for endocrine resistance. Entinostat is an HDACI that has been shown to increase expression of both ER and the enzyme aromatase in a dose-dependent manner both *in vitro* and *in vivo*, which then sensitized breast cancer cells to estrogen and subsequent inhibition by the AI letrozole (148). Furthermore, in xenograft experiments the combination of letrozole plus entinostat was significantly more effective at inhibiting xenograft growth than either therapy alone. In a randomized phase II trial (ENCORE 301, NCT00676663), entinostat in combination with exemestane was compared to exemestane/placebo in patients who had received prior hormonal therapy (149). This trial showed prolongation of median PFS (4.3 months vs. 2.3 months) and extension of OS benefit (26.9 months vs. 19.8 months), and a randomized phase III trial is being planned. Similarly, a phase II study testing vorinostat and tamoxifen in 43 patients with ER+ve MBC progressing on endocrine therapy showed a ORR of 19% and a median response duration of 10.3 months (150). Correlative studies suggest that HDAC2 expression could be a predictive biomarker, and that histone hyperacetylation may be a valid pharmaco-dynamic marker for the efficacy of this combination.

Anti-angiogenic Agents

Pre-clinical data (151) and retrospective clinical data (152) suggest that high vascular endothelial growth factor (VEGF) levels in breast tumors are associated with a decreased response to endocrine therapy. Because several phase II studies had suggested the feasibility and activity of the combination of bevacizumab with endocrine agents (153,154), a randomized phase III study (LEA) was conducted to test the hypothesis that anti-VEGF treatment with bevacizumab could prevent resistance to hormone therapy (either letrozole 2.5 mg/day or fulvestrant 250 mg/4 weeks) given as first-line therapy in endocrine responsive advanced breast cancer (155). The PFS was better with the combination of bevacizumab plus endocrine therapy than with endocrine monotherapy (18.4 months vs. 13.8 months), but this was not statistically significant. The combination had a significantly higher incidence of hematologic and non-hematologic toxicities and does not appear to be a promising approach to enhance first-line therapy. The absence of a robust positive effect in the LEA trial together with negative data from the BEATRICE trial in women with triple-negative disease question the efficacy of angiogenesis inhibition in breast cancer (156). Results from another ongoing randomized phase III trial of endocrine therapy alone or endocrine therapy plus bevacizumab for women with hormone receptor-positive advanced breast cancer are also awaited (NCT00601900).

Growth factors and hormones are involved in the regulation of breast cancer cell proliferation, which requires activation of MAPK via Ras and Raf (157). Sorafenib is an oral multikinase inhibitor that inhibits tumor growth by acting on the tumor cells and tumor vasculature cells in preclinical models of human cancer, including breast cancer (158). It targets the MAPK pathway at the level of Raf kinase, induces tumor cell apoptosis, and potently inhibits VEGFR-1, VEGFR-2, VEGFR-3, and platelet-derived growth factor receptor (PDGFR)-β tyrosine kinase autophosphorylation (159). This suggested that sorafenib may be of potential benefit in the treatment of breast cancer, especially in patients who are resistant to hormone therapy. The rationale for evaluating the use of sorafenib in combination with hormonal therapies in patients with breast cancer in this setting has been investigated in a study of the combination of anastrozole and sorafenib in women with MBC where the combination demonstrated a 23% CBR in 35 patients with hormone receptor positive, AI-resistant MBC, which may be attributable to the restoration of sensitivity to AIs (160).

Another inhibitor of angiogenesis is BMS-690514, which is a potent and selective inhibitor of epidermal growth factor receptor (EGFR), HER2, and HER4, as well as the VEGF receptor kinases. When BMS-690514 was tested in a panel of breast tumor cell lines, there was a clear demarcation between cell lines that were sensitive and those that were resistant. Overexpression of HER2 seemed to be sufficient to predispose breast tumor cell lines to inhibition by BMS-690514, again underscoring its intrinsic potency to that receptor target (161). An open-label randomized, parallel, two-arm phase II study comparing BMS-690514 plus letrozole with lapatinib + letrozole in recurrent/metastatic breast cancer patients who are hormone receptor positive despite HER2 status and who relapsed while receiving or after completing adjuvant antiendocrine therapy has been recently completed and results are awaited (NCT01068704).

Proteasome Inhibitors

Several groups have now demonstrated that the PI3K/Akt pathway provides cancer cell survival signals, in part through activation of the nuclear factor kappa B (NF-κB) transcription factor, and that Akt activation of NF-κB may be an important mechanism in the development of tamoxifen-resistant breast cancer (162,163). Bortezomib is a proteasome inhibitor that blocks the NF-κB pathway. It was tested in a phase II study in combination with endocrine treatment (164). Despite effective target inhibition that was demonstrated in peripheral blood mononuclear cells and tumor samples, no objective anti-tumor responses were observed. Addition of a proteasome inhibitor to anti-hormonal therapy resulted in 22% CBR in a limited number of patients with endocrine resistant and progressive MBC. A randomized phase II study of fulvestrant versus fulvestrant in combination with bortezomib in women with ER+ve MBC is currently recruiting (NCT01142401) (Table 70-7).

Agents Targeting Src Kinase

Results from pre-clinical studies showed that the ER-Src kinase axis plays an important role in promoting hormonal resistance by proto-oncogenes such as HER2, PELP1, and that blocking this axis prevents the development of hormonal independence in vivo (165). Since PELP1, HER2, and Src kinase are commonly deregulated in breast cancers, combination therapies of Src inhibitors with endocrine agents may have better therapeutic effect by delaying the development of hormonal resistance. Dasatinib is a potent, broad-spectrum ATP-competitive inhibitor of Src tyrosine kinase. However, the addition of dasatinib to fulvestrant in a randomized phase II study in ER+ postmenopausal MBC patients who had progressed after a NSAI did not improve PFS, CBR, or OS (166). Similarly, 157 patients were randomized in a double-blind phase II trial (CA180-261) to receive dasatinib (100 mg daily) or matched placebo in combination with exemestane (25 mg daily). While the PFS difference was not significant in overall study population, a higher CBR in the dasatinib arm and higher PFS in patients with symptomatic bone metastasis (HR = 0.68) suggested that dasatinib may have efficacy in a subset of patients. The safety profile was consistent with previous dasatinib experience; AEs, including pleural effusion and diarrhea, were more common with dasatinib as compared with placebo (167).

Agents Targeting FGFR Pathway

Several studies have shown that the fibroblast growth factor receptor-1 gene (*FGFR1*) is amplified in approximately 10% of all breast cancers, correlating with increased *FGFR1* mRNA or protein expression (169). Amplification of *FGFR1* is uncommon in HER2-positive tumors, but is enriched in up to 20% of ER+ve breast cancers. Amplification and overexpression of *FGFR1* may be a major contributor to poor prognosis in luminal-type B breast cancers, driving anchorage-independent proliferation and endocrine therapy resistance (169). AZD4547 is a potent selective inhibitor of *FGFR-1, 2* and *3* receptor tyrosine kinases (enzyme and cellular phosphorylation endpoints) and has a significantly lower potency for inhibition of IGF1R and KDR (168). The co-administration of an FGFR inhibitor and exemestane has the potential to improve outcome for patients with aggressive disease or resistance to endocrine therapy. Therefore, GLOW is a randomized double-blind phase IIa study (with phase I combination safety run-in) designed to assess the safety and efficacy of AZD4547 in combination with exemestane versus exemestane alone in ER+ve breast cancer patients with FGFR1 Polysomy or Gene Amplification who have failed treatment with one prior endocrine therapy (adjuvant or first-line metastatic) (NCT01202591).

Agents Targeting Insulin-like Growth Factor Type I (IGF-I)

The role of the insulin-like growth factor (IGF) system in endocrine-resistant breast cancer has been studied, and inhibitors of this pathway are currently in clinical trials in ER+ve patients who have progressed on prior endocrine therapy. Early reports show no benefit for addition of IGF1R inhibitors to endocrine therapy in this setting, although pre-clinical research examining the effectiveness of IGF1R inhibitors in vitro by generating tamoxifen-resistant (TamR) cells shows that cells selected for tamoxifen resistance *in vitro* may have down-regulated IGF1R, making antibodies directed against this receptor ineffective (170). MEDI-573 is a dual-targeting human antibody that neutralizes IGF-I/-II ligands and inhibits insulin-like growth factor receptor 1 (IGF1R) and insulin receptor-A (IR-A) signaling pathways that play a role in breast and other epithelial cancers. By sparing insulin receptor-B (IR-B) and its hybrid receptors, MEDI-573 is expected to achieve antitumor activity without perturbing glucose homeostasis and has showed acceptable safety and favorable PK profiles without significant changes in glucose levels (171). A biomarker-rich phase Ib/II study of MEDI-573 with an AI in patients with advanced ER+ve breast cancer is ongoing (NCT01446159). Likewise, BMS-754807 is a small-molecule dual-kinase inhibitor targeting IGFIR and IR, and a phase II study of BMS-754807 combined with letrozole or BMS-754807 alone in hormone receptor-positive breast cancer subjects with acquired resistance to non-steroidal AIs (NCT01225172) is ongoing.

Inhibitor of Cyclin-dependent Kinase (CDK) 4/6

Modulating the cell cycle has always been an attractive therapeutic target in cancer, and previously published data have suggested that CDK 4/6 inhibition may play a key role in the treatment of subsets of breast cancers (172,173). PD 0332991 is a novel oral selective inhibitor of cyclin-dependent kinase (CDK) 4/6, which prevents cellular DNA synthesis by blocking cell cycle progression from G1 to S phase. Recently, it was reported that the combination of PD 0332991 and letrozole significantly improved median PFS in a randomized phase II study in patients with advanced ER+ve breast cancer, including those with identified cyclin D1 amplification and/or p16 loss in whom CDK 4/6 inhibition is expected to be most effective (174). In the first part of this two-part phase II study, 66 postmenopausal women with ER+ve MBC were randomly assigned to either the combination of PD 0332991 and letrozole or to letrozole alone. The second part of the study involved 99 patients with ER+ve

cancers possessing certain genomic alterations, specifically cyclin D1 amplification and/or p16 loss. A progression-free survival of 26.1 months was observed for patients in the combination arm versus 7.5 months for patients treated with letrozole alone. In patients with measurable disease, an improved response rate was seen (45% vs. 31%), and the toxicity profile for the combination was favorable with the most common adverse events being (uncomplicated) neutropenia, leukopenia, anemia, and fatigue.

On the basis of this extremely promising result, a randomized, multicenter, double-blind first-line study of PD-0332991 plus letrozole versus letrozole/placebo in postmenopausal women with ER+ve/HER-ve MBC who have not received any prior systemic anti-cancer treatment for advanced disease will open to recruitment soon (NCT01740427). As such, CDK 4/6 inhibition seems a very promising approach to enhance endocrine response in ER+ve endocrine sensitive breast cancer that could potentially produce that quantum leap in response to first-line endocrine therapy that to date has eluded this area of clinical research in ER+ve advanced breast cancer.

CONCLUSION

Enormous progress in endocrine therapy for ER+ve metastatic breast cancer has been made over the last three decades, as illustrated in this chapter. Tamoxifen is perhaps the best original example in oncology of a biologically targeted therapy, and it has subsequently had a major impact on improving survival in ER+ve early breast cancer. In the late 1990s the introduction of the third-generation AIs as first-line therapy for postmenopausal advanced disease heralded the next major improvement (Table 70-3), such that objective tumor response rates of >30% with progression-free intervals of 10 to 15 months and overall survival in excess of 3 years are now to be expected with endocrine therapy in this setting. This allows patients significant clinical benefit before the need for cytotoxic chemotherapy, allowing them to maintain a good quality of life with minimal toxicities from therapy. In the second-line setting, other endocrine therapies can still be effective, especially if good benefit was seen in the first-line setting, but as discussed above objective response rates are often <10% with progression-free intervals of only 3 to 4 months and overall survival less than 2 years (Table 70-4). More effective treatments following AIs are urgently needed.

Understanding the biology of ER+ve breast cancer and the mechanisms of resistance has been central to any attempts to improve further upon the current level of clinical efficacy achieved with various endocrine therapies in the advanced breast cancer setting. Undoubtedly, the recent significant efficacy for the combination of the mTOR antagonist everolimus and exemestane in those patients refractory to prior AI therapy is a major advance in providing greater clinical benefit compared with the use of just further endocrine therapy alone for these patients, which may spare the use of palliative chemotherapy for a period of time. This option is likely to become a new standard of care in the second-line setting for postmenopausal women with ER+ve advanced breast cancer who have been previously treated with a nonsteroidal AI. As indicated above, numerous other targeted approaches are also under investigation to see if they could be effective options in this second-line setting, and some may prove successful as it is unlikely that the mTOR pathway is the only relevant resistance mechanism.

Whether combinations of any signaling therapeutics and endocrine therapy will become a future option for the first-line hormone-sensitive setting is less clear. To date, any co-treatment of unselected hormone-sensitive ER+ve MBC with a given drug combination in the hope of delaying endocrine resistance and improving the benefit already obtained with first-line AI therapy does not appear to work. The challenge in daily clinical practice is to identify the relevant pathways that are operative in individual patients with ER+ve MBC, and in future all clinical studies in ER+ve advanced breast cancer should make a greater effort to enrich their trial population with the most appropriate patients. Genomic profiling in ER+ve breast cancer may help identify those more likely to develop resistance to endocrine therapy, or indeed the pathways that these tumors are most likely to utilize as escape mechanisms, which in turn may guide appropriate selection of target therapies to add in at the time of relapse. Selection of these ER+ve subgroups for future combination strategies may in turn yield answers faster than treating a more heterogeneous and unselected group of patients with ER+ve advanced breast cancer.

MANAGEMENT SUMMARY

- All patients with ER+ve metastatic disease should be considered for a trial of endocrine therapy, and sequential endocrine therapy should be given until the patient no longer responds.
- For patients with ER/PgR +ve breast cancer and a low risk of rapid progression of their advanced disease, endocrine therapy can be very effective in the treatment of their advanced/metastatic disease.
- The treatment-free interval since prior adjuvant endocrine therapy, together with quantitative levels of hormone receptors, determine the likelihood of benefit from further endocrine therapy in the metastatic setting.
- At the time of relapse, the majority of tumor cells retain estrogen receptor (ER), although levels of expression may fall and other signaling pathways that cross-talk with ER may be functional.
- For postmenopausal women with ER/PgR +ve advanced/metastatic breast cancer, aromatase inhibitors (AIs) are the treatment of choice—in the first-line setting, these therapies can give 10 to 15 months median progression free survival, depending on whether there has been exposure to prior adjuvant endocrine therapy.
- There is no proven benefit to combination endocrine therapy in postmenopausal patients with metastatic disease, although one trial in largely previously untreated patients did show a significant advantage for the combination of fulvestrant 500 mg plus an AI.
- In premenopausal advanced breast cancer, combined ovarian suppression and tamoxifen is more effective than either therapy alone. There are no data to show whether ovarian suppression and an AI is superior, and to date this is reserved as a second-line treatment option.
- Sequential endocrine therapy with other agents such as fulvestrant or exemestane can be effective in postmenopausal patients who have demonstrated prior endocrine responsiveness in the advanced setting, although response rates are low and overall the median progression free survival is only 3 to 5 months.

- The combination of the steroidal aromatase inactivator exemestane with the mTOR antagonist everolimus has become a new treatment option following progression on nonsteroidal AI, due to enhanced efficacy compared with exemestane alone. Additional toxicities need to be considered, and there is no role for this combination in the first-line endocrine naive setting.
- There is no proven role for the combination of growth factor receptor inhibitors and endocrine therapy in ER+ve/HER2-ve breast cancer.
- In postmenopausal women with known ER+ve/HER2+ve metastatic breast cancer, the combination of AIs and HER2 targeted therapy is an approved combination, and is more effective than endocrine therapy alone for those patients who do not require immediate chemotherapy.
- Improving outcomes for those patients with acquired endocrine resistance is an urgent issue. Ongoing research studies are investigating numerous different signaling inhibitors in combination with endocrine therapy based on pre-clinical evidence that these strategies could overcome endocrine resistance.

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CHAPTER 71

Treatment of Metastatic Breast Cancer: Chemotherapy

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CHAPTER CONTENTS

INTRODUCTION

In 2013, the United States had an estimated 232,340 new cases of breast cancer and 39,620 breast cancer-related deaths occurred in women (1). Survival has continually improved over the last six decades (1). In many developing countries, the incidence of breast cancer is rising sharply due to changes in lifestyle, reproductive factors and increased life expectancy (2). More than half of incident cases occur in the developing world, with the percentage of deaths in these countries double that in high-income countries (2). The treatment of advanced breast cancer is often more resource intensive and associated with worse outcomes, further taxing patient populations that may have fewer resources.

Access to screening programs has resulted in a higher proportion of women being diagnosed with earlier stages of disease which are imminently curable. However, approximately 6% to 10% of breast cancers are metastatic at presentation and systemic recurrence occurs in about 30% of early breast cancer cases, many beyond the first 5 years (3,4). Metastatic breast cancer (MBC) patients have a median survival of 2 to 3 years. Patients have a diverse clinical behavior driven by histological and molecular subtype (and increasingly by therapy) though historically fewer than 5% survive beyond 10 to 15 years (5–7). Patients with very limited disease, particularly if limited to soft tissue and/or bone, were the ones most likely to have long periods of progression-free survival (6). Newer therapies, particularly those targeting the estrogen receptor (ER) and the human epidermal growth factor receptor 2 (HER2) may have favorably altered the natural history of these breast cancer phenotypes (8).

CARE OF PATIENTS WITH METASTATIC DISEASE

MBC is by definition an incurable disease and most patients with metastatic disease will likely die from their disease. At the same time, the growing number of therapeutic options has changed the outcome for many patients, particularly for those with ER-positive and/or HER2-positive disease whose treatment backbone will center around the use of anti-estrogens and HER2-targeted therapies, respectively. Despite the lack of therapies targeting specific pathways, it is now well accepted that not all triple-negative breast cancers (TNBC) are the same, and there is a growing understanding that this nomenclature encompasses a spectrum of tumors with diverse clinical behavior (9). Patients with TNBC often will have durable and clinically meaningful

responses to conventional chemotherapy regimens, often given as single agents, and many are able to have prolonged progression-free survival (PFS) intervals.

Goals of Therapy

It is critical for patients and their doctors to establish early on the overall goals of therapy, which will primarily center around symptom control, prevention of complications, and in many cases prolongation of overall survival (OS). It is strongly recommended that members of the health team (especially physicians) discuss early on with patients and their family members and caregivers, including preliminarily when to discontinue chemotherapy and focus primarily on symptom management. Multidisciplinary care is key, and should include pain management, nutritional and psychosocial support, family therapy, and other medical specialists as needed. As discussed in greater detail in other chapters of this book, patients should be referred early on for a palliative care evaluation.

Disease Monitoring

A growing body of evidence suggests a role for maintenance chemotherapy in patients with MBC (10). It is often simple to assess if patients are benefiting from systemic therapy or not. At the same time, there is great interest in identifying early on if the treatment started will help them or not. Tumor markers like CA27.29/CA15-3 and CEA are often used to monitor disease status, but oncologists are strongly discouraged from making therapy changes exclusively based on a test result, especially if patients are clinically stable without worsening of symptoms or evident disease progression by imaging studies. Enumeration of circulating tumor cells (CTCs) has been a topic of great interest, and a commercial assay has been available since the mid-2000s based on evidence suggesting an early prognostic role for progression-free and OS in patients starting a new systemic regimen (11). Unfortunately, the enumeration assay detects circulating tumor cells in only 30% of patients with MBC. A recently completed trial (SWOG S0500, NCT00382018) is now examining whether treatment decision-making to continue or change therapy based on blood levels of CTCs in women with MBC lead to an improved clinical outcome (clinical utility).

In the meantime, more specific measures of circulating tumor DNA are now being tested with potential implications for surveillance in the adjuvant setting, monitoring of disease in the metastatic setting, and characterization of disease biology. Proof of concept studies have now shown that these assays are feasible, albeit costly if dependent on whole-genome sequencing approaches, and must now be prospectively tested (12,13). Other groups have tested more selective approaches that targeted the detection of circulating tumor DNA of more commonly observed somatic genomic abnormalities like mutations in PIK3CA (14).

Patients with Small Volume of Metastatic Disease

Improvements in staging imaging studies have also caused stage migration and a growing number of patients are now diagnosed with limited or oligometastatic disease (15). These patients, specially those presenting with locally advanced disease and small volume isolated systemic metastases may often benefit from combine modality therapy, including surgery and radiation therapy for local control and/or for resection of focal sites of systemic disease. The role of systemic therapy for patients who become free of macroscopic disease with no evidence of disease (NED) remains controversial.

In late 2012, investigators reported on the role of chemotherapy as adjuvant therapy for patients with locally recurrent breast cancer (the CALOR trial, NCT00074152). Unfortunately, the study was closed due to slow accrual after 162 eligible patients were randomized to ER and/or HER2-targeted therapy, with or without chemotherapy, but after 8 years of follow-up, a 5-year improvement in OS (88% vs. 76%) favored those also given chemotherapy. There was also a striking difference in disease-free survival (DFS) rate between the ER-negative population who received chemotherapy and those who did not (67% vs. 35%), but this was less pronounced in the ER-positive population (70% vs. 69%), suggesting that the majority of benefit was in ER-negative tumors. In view of the challenge of mounting a definitive study, the data suggest that combined multimodality therapy is a reasonable approach for a select group of patients.

PRINCIPLES OF CHEMOTHERAPY

Breast cancer is generally considered to be a chemosensitive disease. The short term aims of chemotherapy in MBC are to increase response rates and maximize symptom control; the medium term end points are to anticipate complications and extend PFS; and the long term goals are to attempt to improve OS while minimizing therapy toxicity or disruption of quality of life (QOL). Chemotherapy treatment is individualized based on disease and patient-related factors such as endocrine responsiveness and HER2 expression, tumor-related symptoms, disease-free interval, extent and sites of metastatic disease, organ function, comorbidities, age, and performance status. Treatment-related issues such as drug efficacy, side effect profile, previous systemic therapy, quality of life considerations, costs, and patient preferences have also to be taken into account. Tailoring chemotherapy options is made complex by a myriad of tumor and patient-related factors that must be considered, the large number of chemotherapy regimens available without specific predictive markers of benefit, and the likelihood of disease progression that will force patients to go through a sequence of treatment regimens. Therefore, early on it is critical to discuss with patients and their caregivers the overall goals of therapy, the limitations of existing regimens, the concept of palliative care, and limitations of active therapy.

Prospective trials comparing chemotherapy to best supportive care have not been pursued to a greater extent due to the number of therapy options with clinical efficacy in the adjuvant and advanced settings. Although there have been numerous trials in MBC, the higher response rates and longer PFS seen in certain regimens over others have not translated into survival benefits in most trials in part due to tumor biology, small sample sizes, study designs allowing crossover to the investigational agent, and the increasing availability of newer more efficacious therapeutic regimens.

Endocrine therapy must be the initial consideration in ER-positive MBC with a less aggressive phenotype, such as those with a long disease-free interval and predominantly bone and soft-tissue disease. Chemotherapy is meant for ER-negative disease or ER-positive disease that has become endocrine-resistant or that displays higher risk features such as the often discussed but infrequently observed visceral crisis and/or a short disease-free interval. Visceral crises are uncommon but could be defined as presence of symptomatic lymphangitic lung metastases, bone marrow replacement, carcinomatous meningitis, or symptomatic liver metastases (16). Small volume lung or liver metastases (especially if minimally symptomatic) must not be considered a definitive indication for chemotherapy if endocrine therapy is suitable.

A meta-analysis of published and unpublished trials comparing endocrine therapy or chemotherapy treatment in advanced breast cancer revealed no significant difference in OS (hazard ratio [HR] 0.94, 95% confidence interval [CI], 0.79–1.12, p = .5) (17). Notably, over 50% of women in these trials had visceral disease, which is often seen as an indicator for chemotherapy use. A pooled estimate of reported response rates (8 trials; n = 817) showed a significant advantage for chemotherapy over endocrine therapy (relative risk [RR] 1.25, 95% CI, 1.01–1.54, p = .04), but the two largest trials showed results in opposite directions with a significant test for heterogeneity (p = .0018), thus questioning this observation (18,19). Six of the seven fully published trials reported increased toxicity with chemotherapy, in particular nausea, vomiting, and alopecia. The shortcomings of these analyses were that the trials were from 1963 to 1995, and contained ER-negative or unknown tumors. These trials used endocrine agents which are not commonly used as first-line choices today and also had outdated chemotherapy regimens. Hence, the role of more contemporary chemotherapy agents in comparison to endocrine therapy remains uncertain. Clinical trials have failed to show a survival benefit of combined chemo endocrine therapy over either modality used separately (20).

Biopsy of metastatic sites of disease is always encouraged as this may impact subsequent treatment decisions, first to confirm the development of metastatic disease and second to retest ER and HER2, especially for tumors that may have tested negative when first diagnosed but the clinical behavior (e.g., long DFS) might suggest otherwise. Discordance in receptor results may occur due to tumor heterogeneity missed by the limited tissue sampling of a needle biopsy, limited reproducibility and concordance of assays especially when testing of the primary tumor and metastatic sites done years apart, or true biologic change over time (21,22).

Single versus Combination Chemotherapy

The active classes of chemotherapy drugs are the anthracyclines, taxanes, vinca alkaloids, antimetabolites, alkylating agents, epothilones, and other antimicrotubule agents such as eribulin. Randomized trials comparing combination versus sequential single agent chemotherapy have shown combination regimens give better response rates and tumor time to progression (TTP) or PFS, but survival benefit tend to be observed in studies that did not allow crossover from the single-agent arm to the new investigational drug upon progression (see Table 71-1). Well-defined comparisons of combination versus the same agents used in sequence (a registration strategy less favored by the pharmaceutical industry) are unavailable, hence the true impact on survival outcomes is not known.

In an early systemic review of 15 trials (n = 2,442) comparing polychemotherapy to single agents in MBC treatment, the complete and partial responses for polychemotherapy were significantly better than that associated with single agents (20). Survival data from 12 trials (n = 1,986) also favored polychemotherapy regimens (HR 0.82, 95% CI, 0.75–0.90), translating into an 18% reduction in risk of death (20). The limitations of this meta-analysis were its usage of published material instead of individualized patient data, trials from the pretaxane era consisting of outdated regimens, small sample sizes, poorly designed studies, heterogeneity of patients and their previous treatments, and a lack of data on exposure to adjuvant therapy, and prior treatment for metastatic disease. Its modest total number of patients (n = 996) only slightly exceeded that of an important randomized ECOG study comparing combination versus sequential single-agent therapy which is discussed later (23).

A Cochrane meta-analysis of 43 trials consisting of 9,742 women of whom 55% were receiving first-line chemotherapy for metastatic disease showed a statistically significant advantage for the combination regimens in terms of OS (HR 0.88; p < .00001), TTP (HR 0.78; p < .00001), and response rates (RR 1.29; p < .0001) (24). They were however associated with more leukopenia, nausea, vomiting, and alopecia.

Clinical trial designs have incorporated comparisons of (i) a particular agent versus combination regimens consisting of completely different agents, or (ii) a particular drug versus a regimen containing that same drug in addition to other agents. With regards to the first trial design, taxanes as single agents have shown superiority in terms of survival over older regimens such as cyclophosphamide/methotrexate/5-fluorouracil/prednisone (CMFP) or mitomycin/vinblastine (25,26). Capecitabine was reported to have comparable TTP and OS compared with intravenous (IV) cyclophosphamide/methotrexate/5-fluorouracil (CMF) (27). As for study design (2), the seminal Eastern Cooperative Oncology Group (ECOG) trial E1193 assigned 739 patients with MBC to doxorubicin alone, paclitaxel alone, or the combination, with crossover allowed for the single agent therapy arms (23). Combination therapy demonstrated significantly higher complete and partial responses compared to the single-agent doxorubicin or paclitaxel arms (47% vs. 36% vs. 34%), and median time-to-treatment failure (TTF) (8 months vs. 5.8 months vs. 6 months), although median survivals were similar (22 months vs. 18.9 months vs. 22.2 months). Responses were seen in 20% of patients crossing from doxorubicin to paclitaxel and 22% of patients crossing from paclitaxel to doxorubicin (p = not significant). Global QOL measurements from on-study to week 16 were similar in all three groups. While this is the largest randomized trial to address this issue, it remains a relatively small study with limited statistical power.

Other trials of similar design comparing concomitant epirubicin and paclitaxel versus sequential therapy in MBC (28), or capecitabine and taxanes in sequence or combination (29), did not show a survival benefit. Other combinations such as vinorelbine/doxorubicin and gemcitabine/vinorelbine have found no difference in OS between the combinations versus single agents doxorubicin or vinorelbine respectively (30,31). Two important trials have demonstrated a survival benefit of taxane-containing combinations over the taxane itself and will be discussed in detail later in the chapter (32,33). One of them showed that the docetaxel/capecitabine combination had significantly superior RRs, TTP, and OS over single-agent docetaxel, while the other showed that the gemcitabine/paclitaxel regimen had superior RRs, TTP, and OS compared to paclitaxel, although there was a lack of a planned crossover design in both studies.

In general, sequential single agents have a more favorable toxicity profile and a better QOL without compromising crucial end points such as OS and TTP. Hence, sequential therapy is useful in the metastatic setting where efficacy should be balanced with a good QOL. This sequential single-agent strategy is also useful in patients with less aggressive disease, those who are older, or with a poorer performance status. However, in cases where rapid tumor shrinkage is needed due to symptomatic disease, combination therapy is preferred.

Intermittent versus Continuous Chemotherapy

The issue of chemotherapy duration in the metastatic setting remains an unresolved issue. Several randomized trials have attempted to address the potential benefits of continuous chemotherapy versus chemotherapy for a fixed

TABLE 71-1

Selected Clinical Trials of Single versus Combination Chemotherapy

Author (Reference)	*Regimen*	*Sample No. (n)*	*Median Follow-Up (months)*	*RR*	*TTP/PFS (months)*	*OS (months)*
Comparison of a Particular Agent versus Combination Regimens of Completely Different Agents						
Bishop et al., 1999 (25)	Pac vs. CMFP	209	26	29% vs. 35% (p = .37)	5.3 vs. 6.4 (p = .25)	17.3 vs. 13.9 (p = .068)
Nabholtz et al., 1999 (26)	Doc vs. MV	392	19	30% vs. 11.6% (p <.0001)	19 wks vs. 11 wks (p = .001)	11.4 vs. 8.7 (p = .0097)
O'Shaughnessy et al., 2001 (27)	Cap vs. IV CMF	93	Not stated	30% vs. 16% (study not designed to determine statistical difference)	4.1 vs. 3.0	19.6 vs. 17.2
Comparison of a Particular Agent versus Combination Regimens which Contain that Particular Agent						
Conte et al., 2004 (28)	Epi × 4 cycles → Pac × 4 cycles vs. Epi + Pac	198	Not stated	53% vs. 62% (p = .23)	10.8 vs. 11 (p = ns)	26 vs. 20 (p = ns)
Soto et al., 2006 (29)	Cap → Pac/Doc vs. Cap + Pac vs. Cap + Doc	277	15.5	46% vs. 65% vs. 74%	6.3 vs. 6.5 vs. 8.5	31.5 vs. 33.1 vs. 28.6
Norris et al., 2000 (30)	Dox vs. Dox/VNB	289	29	30% vs. 38% (p = .2)	6.1 vs. 6.2 (p = .5)	14.4 vs. 13.8 (p = .4)
Martin et al., 2007 (31)	VNB vs. VNB/Gem	251	Not stated	26% vs. 36% (p = .093)	4 vs. 6 (p = .0028)	16.4 vs. 15.9 (p = .805)
O'Shaughnessy et al., 2002 (32)	Doc/Cap vs. Doc	511	15 (minimal follow-up)	42% vs. 30% (p = .006)	6.1 vs. 4.2 (p = .0001)	14.5 vs. 11.5 (p = .0126)
Albain et al., 2008 (33)	Pac vs. Pac/Gem	529	Not stated	26.2% vs. 41.1% (p = .0002)	3.98 vs. 6.94 (p = .0002)	15.8 vs. 18.6 (p = .0489)

Cap, capecitabine; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; CMFP, cyclophosphamide, methotrexate, 5-fluorouracil, prednisone; Doc, docetaxel; Epi, epirubicin; Gem, gemcitabine; IV, intravenous; MV, mitomycin, vinblastine; OS, overall survival; Pac, paclitaxel; PFS, progression-free survival; RR, response rate; TTP, time to progression; VNB, vinorelbine.

number of cycles, and then resumption only upon disease progression. Trial designs have varied with regards to the maintenance treatment with some continuing the same chemotherapeutic agents while others have utilized different regimens (see Table 71-2). However, earlier studies in the pretaxane era comparing shorter versus longer chemotherapy durations were hampered by insufficient sample sizes, chemotherapy drugs considered obsolete, nonstandard chemotherapy schedules, and limited durations in the control arms. More recent trials with newer agents have been carried out. A recent meta-analysis of 11 randomized controlled trials (RCTs) (n = 2,269) demonstrated that longer first-line chemotherapy had a marginally improved OS (HR 0.91, 95% CI, 0.84–0.99; p = .046) and substantially longer PFS (HR 0.64, 95% CI, 0.55–0.76; p < .001) (34). No statistically significant variation in effects on OS and PFS were seen when trials were stratified according to timing of randomization, study design, number of cycles in the control arm, and concomitant endocrine therapy. Lengthening PFS is considered clinically beneficial as this may improve QOL by delaying symptoms of progressive disease that may be perceived as valuable by the patient. Unfortunately, only the study by Coates et al. (35) in this meta-analysis evaluated this issue, reporting that QOL was indeed better in the extended chemotherapy arm. Shortcomings of this analysis were lack of individualized patient data, no quality control on original records and analyses, limitation of subgroup analyses to those only on trial, moderate number of trials and sample numbers, outdated chemotherapeutic agents, and heterogeneity of study designs, chemotherapy regimens and publication status. There were three studies in the meta-analysis which included more recent agents like paclitaxel and liposomal doxorubicin, none of which demonstrated a survival benefit with maintenance therapy as well (36–38). In the Spanish Breast Cancer Research Group (GEICAM) 2001–01 study, patients without disease progression after three cycles of doxorubicin followed by three cycles of docetaxel were randomized to pegylated liposomal doxorubicin (PLD) for six cycles or to observation (38). PLD significantly prolonged the primary end point of TTP by 3.3 months compared to observation although OS was not significantly prolonged. PLD toxicities were manageable with up to 5% experiencing fatigue, mucositis, and palmar-plantar erythrodysesthesia.

OS seems not to be influenced by continuing chemotherapy indefinitely, with the benefit primarily in PFS. Thus, patients who need to stop treatment due to drug-related toxicities can be reassured that this is not detrimental to their survival. In those who have symptomatic disease and

TABLE 71-2

Selected Clinical Trials Comparing Maintenance versus Intermittent Chemotherapy

Author (Reference)	*Sample No. (n)*	*Exp Arm*	*Control Arm*	*Median TTP/ PFS (months) Exp Arm*	*Median TTP/ PFS (months) Control Arm*	*Median Survival (months) Exp Arm*	*Median Survival (months) Control arm*	*Median Follow-Up*
Coates et al., 1987 (35)	305	Continuous AC or oral CMFP	AC or oral CMFP × 3 cycles → AC or CMFP × 3 cycles on PD	6	4 (p = sig)	10.7	9.4 (p = .19)	Not stated
Harris et al., 1990 (303)	43	Continuous mitoxantrone	Mitoxantrone × 4 cycles	5.5	6.5 (p = ns)	12	13 (p = ns)	Not stated
Muss et al., 1991 (304)	145	CAF × 6 cycles → oral CMF × 12 cycles or 1 year	CAF × 6 cycles → oral CMF × 12 cycles or 1 year on PD	9.4	3.2 (p < .001)	21.1	19.6 (p = .67)	36.1 mos
Ejlertsen et al., 1993 (305)	318	Tamoxifen + CEF × 24 cycles or until PD	Tamoxifen + CEF × 8 cycles or until PD → CEF × 16 cycles or until subsequent PD	14	10 (p = .00003)	23	18 (p = .03)	Not stated
Gregory et al., 1997 (306)	100	VAC, VEC or MMM × 12 cycles	VAC, VEC or MMM × 6 cycles	10	7 (p = .01)	13	10.5 (p = .3)	Not stated
Falkson et al., 1998 (307)	141	Doxorubicin-containing chemotherapy × 6 cycles → CMF(P)TH	Doxorubicin-containing chemotherapy × 6 cycles	18.7	7.8 (p < .0001)	32.2	28.7 (p = .74)	50 mos
French Epirubicin Study Group (55)	392	A: FEC 75 × 11 cycles B: FEC 100 × 4 cycles → FEC 50 × 8 cycles	C: FEC 100 × 4 cycles → FEC 100 × 4 cycles on PD	10.3 vs. 8.3 (p = .38; A vs. B)	6.2 (p < .001; A + B vs. C)	17.9 18.9	16.3 (p = .49)	41 mos
Nooij et al., 2003 (308)	196	Continuous oral CMF	Oral CMF × 6 cycles → CMF on PD	5.2	3.5 (p = .011)	14	14.4 (p = .77)	Not stated
Gennari et al., 2006 (36)	238	Epirubicin or doxorubicin + paclitaxel × 6–8 cycles → paclitaxel × 8 cycles	Epirubicin or doxorubicin + paclitaxel × 6–8 cycles	8	9 (p = .817)	28	29 (p = .547)	Not stated
Mayordomo et al., 2009 (37)	180	Epirubicin × 3 cycles → paclitaxel × 3 cycles → weekly paclitaxel until PD	Epirubicin × 3 cycles → paclitaxel × 3 cycles	12	8 (p = .1)	24	24	24 mos
Alba et al., 2010 (38)	155	Doxorubicin × 3 cycles → docetaxel × 3 cycles → PLD × 6 cycles	Doxorubicin × 3 cycles → docetaxel × 3 cycles	8.4	5.1	24.8	22	20 mos

AC, doxorubicin, cyclophosphamide; CAF, cyclophosphamide, doxorubicin, 5-fluorouracil; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; CMFP, cyclophosphamide, methotrexate, 5-fluorouracil, prednisone; CMF(P)TH, cyclophosphamide, methotrexate, 5-fluorouracil, prednisone, tamoxifen, halotestin; EXP, experimental; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; MMM, mitoxantrone, mitomycin C, methotrexate; PD, progressive disease; PLD, pegylated liposomal doxorubicin; PFS, progression-free survival; TTP, time to progression; VAC, vincristine, doxorubicin, cyclophosphamide; VEC, vincristine, epirubicin, cyclophosphamide.

remain responsive to chemotherapy, continuing therapy can be a favorable option to prolong time to disease progression. In clinical practice, no predefined number of courses of chemotherapy must be delivered, and factors such as treatment tolerability and disease response in terms of disease stabilization as opposed to tumor shrinkage must be taken into account. If the patient shows improvement after two to three cycles, then the same regimen is continued for another two to three cycles before further reassessment. The duration of treatment in patients who have stable disease or who continue to respond is controversial. Although there is limited evidence for maintenance chemotherapy long-term, chemotherapy can be continued beyond six to eight cycles for PFS benefit, and only ceased upon disease progression or intolerable toxicities. Endocrine therapy could be used as maintenance therapy in ER-positive disease, or the patient closely monitored for recurrence without any systemic therapy if ER-negative disease and a therapy holiday is being considered. However, the targeted therapy such as trastuzumab should be continued if HER2-positive disease, either alone or with endocrine therapy in endocrine responsive disease. For those who progress while on one line of treatment or during the chemotherapy-free period, they are generally switched to an alternative agent or regimen based upon their performance status, previous chemotherapy exposure, and potential for further treatment response.

Chemotherapy Scheduling

The impact of chemotherapy scheduling has been less well studied. The Norton-Simon hypothesis derived from clinical and laboratory observations states that "therapy results in a rate of regression in tumor volume that is proportional to the rate of growth that would be expected for an unperturbed tumor of that size" (39). This hypothesis has led to the dose-dense approach to breast cancer chemotherapy, thus short circuiting the Gompertzian growth curve before tumor regrowth achieves its mathematically greatest gains. This has been illustrated by the Cancer and Leukemia Group-B (CALGB) 9741 adjuvant trial, which confirmed the clinical efficacy in terms of DFS and OS of a dose-dense 2-weekly schedule of sequential doxorubicin/cyclophosphamide and paclitaxel for four cycles each with colony stimulating support over an identical regimen but administered in a 3-weekly fashion (40). The use of dose-density as strictly defined has not been shown to be effective in the metastatic setting.

Weekly scheduling attempts to maximize frequency and cumulative doses with a more favorable toxicity profile. A weekly scheduling at a lower chemotherapy dose with regards to taxanes has been shown to be superior to the 3-weekly regimen. In the CALGB 9840 trial, a higher response rate and TTP favoring weekly paclitaxel over the 3-weekly schedule has been demonstrated (41).

Oral CMF (cyclophosphamide for 14 days, methotrexate and 5-FU on days 1 and 8) every 28 days has been shown to be better than IV CMF every 3 weeks with respect to response rates (48% vs. 29%; $p = .003$) and OS (17 months vs. 12 months; $p = .016$) possibly due to scheduling leading to a higher dose intensity achieved (42).

Trials exploring other scheduling approaches such as theoretically non-cross-resistant agents utilized in a sequential fashion, or adding on additional different agents have not shown any remarkable clinical significance (43–45). In summary, the trials in general do not demonstrate any major survival benefit from using dose-dense chemotherapy, sequential non-cross resistant regimens or "intensified" regimens whereby new agents are added on, and appear to support simpler single-agent regimens to minimize therapy-related toxicities. At the same time, weekly regimens (e.g., paclitaxel) or even daily regimens (e.g., oral etoposide) appear to be more efficacious with less side effects.

CHEMOTHERAPY OPTIONS (SINGLE AGENT AND COMBINATIONS)

In view of the lack of specific biomarkers that predict differential responsiveness to conventional chemotherapy regimens according to the established phenotypes, the regimens discussed below in principle equally apply to patients with TNBC and those with ER-positive/HER2-negative disease that has become endocrine-resistant. Later in this chapter we discuss strategies that may potentially apply more specifically to TNBC, especially in tumors that might have basal-like features.

Meaningful improvements in survival have been seen with the advent of newer therapeutic options and better supportive medical care. Median OS is about 18 to 24 months, with a range of a few months to many years, according to tumor subtype as well as sites and burden of metastatic disease. Several favorable prognostic factors include ER-positivity, a longer relapse-free interval of more than 2 years and metastases involving the chest wall, bones, or lymph nodes. Weight loss, poor performance status, elevated serum lactate dehydrogenase, and less than 35 years old are poor prognostic factors.

The goals of treatment are alleviation of symptoms, prolongation of survival, and improvement in QOL. OS in MBC trials is the gold standard although this end point requires prolonged follow-up and is now frequently diluted by increasingly more effective subsequent treatment options.

There is no standardized treatment regimen sequence to be utilized in MBC although anthracyclines and taxanes are the mainstay of initial treatment. Eighty reports of 63 trials were identified from the Cochrane Breast Cancer Group (CBCG) and abstracts from the American Society of Clinical Oncology (ASCO) annual scientific meeting (2000–2007) (46). There was little evidence from trials reported from 2000 to 2007 that major survival differences existed between many commonly employed chemotherapy regimens.

Combination chemotherapy versus sequential single agent use depends on disease characteristics and patient-related factors. For those with rapidly progressive symptomatic disease or a visceral crisis, combination therapy would be the preferred choice particularly in the first-line setting. Once disease stability is achieved (usually six to eight cycles), a switch to maintenance therapy should be considered. In the absence of rapid clinical progression or life-threatening visceral metastases, sequential single agent chemotherapy is recommended for most patients with low risk disease such as no multi-organ involvement and a longer disease-free interval, with consideration also given to endocrine therapy to this group if ER-positive. Single-agent therapy given in weekly schedules is also preferable for those with visceral impairment or bone marrow suppression due to metastatic disease where dose-reduced single agents may attempt to control the disease at first. For those with asymptomatic or minimally symptomatic disease and/or without visceral involvement, endocrine therapy can be used upfront. If PFS is short or the disease becomes more symptomatic, then switch of treatment to chemotherapy may be considered before another line of endocrine therapy.

Single-Agent Chemotherapy

Single agents include anthracyclines, taxanes, antimetabolites and other microtubule inhibitors. Response rates range

from 25% to 45% and PFS 5 months to 8 as first-line therapy; 15% to 30% and 2 months to 5 respectively as second-line therapy; and 0% to 2% and 1 to 4 months respectively as third-line therapy (47). From fourth-line therapy and beyond, data are scant, although chemotherapy is often continued with further lines of treatment. While worth considering in patients with good performance status and whose disease might have responded to earlier lines of chemotherapy, there is little or no evidence to support pursuing this in patients with poor performance status or whose disease is refractory to earlier lines of therapy. Rather, palliative care measures aiming at reducing symptoms and improving QOL should take primacy over a simple switch to another chemotherapy drug.

Lack of response to first-line chemotherapy treatment or a short progression-free period portends a poorer response to subsequent lines of treatment. The drug of choice for first-line therapy would depend on the disease-free interval since the end of adjuvant chemotherapy. Those whose disease recurs in <12 months would reflect a degree of resistance to the previous regimen. Sequential single agents may have lower response rates but also lower toxicities and no compromise in survival.

Anthracyclines

Since their introduction in the 1980s, anthracyclines have remained one of the most active agents for breast cancer. In an overview of randomized trials, inclusion of anthracyclines—such as doxorubicin—were found to confer a benefit in RR, TTF, and OS over nonanthracycline containing regimens (48). Anthracyclines have response rates of 35% to 50% for those who are anthracycline-naïve, or those who develop metastases after 12 months after anthracycline-based adjuvant therapy (23,30,49), but their efficacy in those with an anthracycline-free interval of <12 months is uncertain. Common dosing schedules are doxorubicin 60–75 mg/m^2 3-weekly or 20 mg/m^2 weekly; or epirubicin 75–100 mg/m^2 3-weekly or 20–30 mg/m^2 weekly. The risk of congestive heart failure is dose-related and rises from about 5% at a cumulative doxorubicin dose of 400 mg/m^2 to 16% at cumulative doses of more than 500 mg/m^2 (50). The use of anthracyclines in the metastatic setting is limited by acute toxicities such as nausea, vomiting, myelotoxicity, alopecia, and long-term issues such as leukemogenic risks and cardiotoxicity.

Liposome-encapsulated and PLD have comparable efficacy to doxorubicin but with reduced cardiotoxicity. Women with MBC who were randomized to receive either first-line PLD 50 mg/m^2 every 4 weeks or doxorubicin 60 mg/m^2 every 3 weeks showed comparable objective RR (33% vs. 38%), PFS (6.9 months vs. 7.8 months) and OS (21 months vs. 22 months), but there was significantly higher risk of cardiotoxicity with doxorubicin (RR = 3.16, 95% CI, 1.58–6.31; $p < .001$) (51). PLD caused less alopecia (20% vs. 66%), nausea (37% vs. 53%), vomiting (19% vs. 31%), and neutropenia (4% vs. 10%), but had more palmar-plantar erythrodysesthesia (48% vs. 2%), stomatitis (22% vs. 15%), mucositis (23% vs. 13%), and infusion reactions (13% vs. 3%).

Using PLD as salvage therapy has been shown to have comparable efficacy to that of common salvage regimens such as vinorelbine in taxane-refractory MBC (52). In women whose disease progressed after first or second-line taxane-containing chemotherapy for MBC, PLD 50 mg/m^2 every 28 days compared to vinorelbine 30 mg/m^2 weekly or mitomycin 10 mg/m^2 on day 1 every 28 days plus vinblastine 5 mg/m^2 on days 1, 14, 28, 42 every 6 to 8 weeks demonstrated similar PFS (HR 1.26; $p = .11$) and OS (HR 1.05; $p = .71$) (52). In anthracycline-naive patients, PLD had a significantly longer PFS compared to the comparator arms (HR 2.4; $p = .01$), although those patients on PLD had more palmar-plantar erythrodysesthesia (37% vs. <1%) and stomatitis. These results suggest that liposomal doxorubicin may offer an alternative therapeutic option for those who are at increased cardiac risk such as elderly patients, those who have cardiac risk factors, and those previously exposed to anthracyclines.

In patients previously treated with adjuvant anthracyclines, the combination of liposomal doxorubicin with docetaxel compared to docetaxel alone showed an improved RR and PFS but not OS (53). However, this combination was not granted regulatory approval because of excessive palmar-plantar erythrodysesthesia. Nonetheless, rechallenging patients with liposomal doxorubicin either singly or in combination with other agents remains an option for those previously treated with adjuvant anthracyclines if more than 12 months have elapsed since their completion (54).

Anthracycline Combinations

Data have shown that anthracycline-based regimens have improved response rates and PFS compared to regimens that do not contain doxorubicin (20,48,49), with some showing a survival benefit (48). Anthracycline-based combination regimens like doxorubicin/cyclophosphamide (AC), epirubicin/cyclophosphamide (EC), cyclophosphamide/doxorubicin/5-FU (FAC or CAF), or 5-FU/epirubicin/cyclophosphamide (FEC) are more active than single-agent anthracyclines but also have more toxicities, mainly myelosuppression, gastrointestinal toxicity, cardiotoxicity, and alopecia. They have not demonstrated a survival benefit over monotherapy. For example, the French Epirubicin Study Group comparing first-line epirubicin 75 mg/m^2 alone with fluorouracil 500 mg/m^2, epirubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2 (FEC 50), and 5-FU 500 mg/m^2, epirubicin 75 mg/m^2, cyclophosphamide 500 mg/m^2 (FEC 75) as first-line treatment for advanced breast cancer patients found superior response rates for the combination regimen compared to single-agent therapy (FEC 50 [44.6%] and FEC 75 [44.7%] vs. epirubicin [30.6%] [$p = .04$ and $p = .0006$]) (55). The epirubicin alone group showed better tolerability than the two combination groups, which did not differ significantly. PFS and OS were not significantly different among the three groups but more early relapses occurred in the epirubicin and FEC 50 groups.

Another randomized prospective study comparing sequential monotherapy versus sequential combination regimens as first and second-line therapies: weekly epirubicin (E) 20 mg/m^2 until progression or until cumulative dose of 1,000 mg/m^2 followed by mitomycin (M) 8 mg/m^2 every 4 weeks (n = 153) versus combination cyclophosphamide 500 mg/m^2, epirubicin 60 mg/m^2, and fluorouracil 500 mg/m^2 every three weeks (CEF) followed by mitomycin 8 mg/m^2 plus vinblastine (V) 6 mg/m^2 every 4 weeks (n = 150) found higher objective response rates for the anthracycline regimens (CEF 55%, E 48%, M 16%, MV 7%) (56). Between the two anthracycline regimens, the combination gave longer response durations (CEF 12 months vs. E 10.5 months) but there was no difference in PFS or OS between the two treatment arms. Toxicities were less and QOL was better in the single-agent arm.

Rechallenging with Anthracyclines/Liposomal Doxorubicin

Rechallenging with anthracycline-based chemotherapy up to cumulative doses of doxorubicin 450–550 mg/m^2 and epirubicin 800–900 mg/m^2 is acceptable. Retrospective studies

have examined the feasibility of rechallenging with anthracyclines in the first-line setting for patients who have been exposed to anthracyclines in the adjuvant setting (57–60). All studies had a similar schema comprising a chemo-naive group, others who had received CMF or CMF-like regimens, or anthracyclines. There was a trend towards a worse clinical outcome (response rates and survival) for those with prior adjuvant chemotherapy, and this was statistically significant in two studies (58,59). However, there was no difference between CMF and anthracycline-based adjuvant regimens with regards to impact on first-line anthracycline therapy outcomes.

A small randomized phase III study compared rechallenging with epirubicin/docetaxel versus docetaxel alone as first-line chemotherapy in patients exposed to adjuvant or neoadjuvant epirubicin, and found similar antitumor efficacy in the two arms with more leukopenia, nausea and stomatitis in the epirubicin/docetaxel arm (61). Hence, the use if anthracyclines as first-line treatment for those already exposed to adjuvant anthracyclines is generally not recommended. In this case, taxane-based therapy is usually considered instead.

Liposomal doxorubicin is active in MBC patients who have been previously treated with conventional anthracyclines, with an overall clinical benefit rate of 24% (62). In a study conducted on behalf of the Spanish Breast Cancer Research Group, patients who did not have progression after three cycles of doxorubicin 75 mg/m^2 followed by three cycles of docetaxel 100 mg/m^2 administered 3-weekly were then randomized to liposomal doxorubicin 40 mg/m^2 once every 28 days for six cycles or observation (38). At a median follow-up of 20 months, liposomal doxorubicin significantly improved TTP (8.4 months vs. 5.1 months; HR = 0.54; p = .0002) compared to the control arm, although OS was not significantly prolonged (24.8 months vs. 22 months, HR = 0.86; p = .44). Liposomal doxorubicin was well tolerated with only 5% experiencing grade 3 or 4 fatigue, mucositis or palmar-plantar erythrodysesthesia. Hematologic toxicities were slightly greater with 12% experiencing neutropenia but only two with febrile neutropenia. However, non-cross-resistance between conventional and liposomal doxorubicin and the appropriateness of treating patients who have progressed on conventional doxorubicin with liposomal doxorubicin cannot be assessed from this study.

Data pooled from two prospective randomized phase III clinical trials comparing non-PLD or conventional doxorubicin combined with cyclophosphamide or liposomal doxorubicin versus conventional doxorubicin as monotherapy in patients previously treated with anthracyclines revealed significant differences for overall RR and median TTP in favor of liposomal doxorubicin, although there was no difference in OS (63–65). Moreover, there was less cardiotoxicity for the liposomal doxorubicin formulation.

In summary, data suggest that a greater benefit is achieved when rechallenging with non-PLD than conventional doxorubicin, either as monotherapy or in combination with other agents. Hence, patients who were exposed to adjuvant anthracyclines may remain responsive to liposomal formulations of anthracyclines.

Epirubicin versus Doxorubicin

In order to compare the efficacy of epirubicin to doxorubicin in the treatment of MBC, 13 randomized controlled trials (11 published reports and 2 reports in abstract form) were reviewed (66). No significant differences in response rates or median survival were observed at equal doses of epirubicin and doxorubicin. Although higher RRs were observed for higher epirubicin doses, this did not translate into a survival advantage. However, epirubicin was associated with less nausea, vomiting, neutropenia, and cardiotoxicity. A recent meta-analysis however failed to demonstrate a significant difference in congestive heart failure (CHF) risk between epirubicin and doxorubicin, although there was a suggestion of a lower rate of clinical heart failure for patients treated with epirubicin (67).

Taxanes

Until the development of taxanes in the 1990s, treatment options were much more limited. In a systematic review of taxane-containing chemotherapy compared with nontaxane regimens, taxane-based regimens showed a higher RR (odds ratio [OR] 1.34; p < .001), TTP (HR 0.92; p = .02), and OS (HR 0.93; p = .05), although there was significant heterogeneity in the trials, partially due to varying efficacy of the comparator regimens (68). The conclusion was that taxane-containing regimens were more effective than some, but not all nontaxane regimens. Taxanes have been studied in two main groups of patients; those who are anthracycline-naive and those who have been anthracycline pretreated.

Anthracycline-Naive Patients

In the TAX 303 phase III study evaluating docetaxel 100 mg/m^2 versus doxorubicin 75 mg/m^2 every 3 weeks for a maximum of seven cycles in MBC patients who had previous alkylating agent chemotherapy, docetaxel was significantly better than doxorubicin in terms of RR (48% vs. 33%; p = .008), even in those with poor prognostic factors such as visceral metastases and resistance to prior chemotherapy (69). Median TTP was longer in the docetaxel (26 weeks vs. 21 weeks) although the difference was not significant, and median OS was similar in the two groups (15 months vs. 14 months). Febrile neutropenia was more prevalent in the doxorubicin group, including cardiotoxicity, nausea, vomiting and stomatitis, whereas there was more diarrhea, neuropathy, fluid retention, skin and nail changes with docetaxel.

In an European Organisation for Research and Treatment of Cancer (EORTC) study (n = 331) for MBC comparing first-line doxorubicin 75 mg/m^2 with paclitaxel 200 mg/m^2 both once every 3 weeks, with a crossover design incorporated, doxorubicin was significantly better than paclitaxel for objective response rates (41% vs. 25%; p = .003), median PFS (7.5 months vs. 3.9 months; p < .001), but not in OS (18.3 months vs. 15.6 months; p = .38) (49). At crossover to doxorubicin or paclitaxel during second-line therapy, response rates were 30% and 16%, respectively. The doxorubicin arm was more toxic than paclitaxel in terms of hematologic, gastrointestinal, and cardiac side effects, but counterbalanced by better symptom control. There was no difference in QOL between the two treatment groups.

In the ECOG trial described previously, first-line paclitaxel 175 mg/m^2 versus doxorubicin 60 mg/m^2 produced equivalent outcomes in terms of RRs, TTF, and median survival, although this may be attributable to the lower dose of doxorubicin at 60 mg/m^2 used (23).

Paclitaxel 200 mg/m^2 every 3 weeks when compared to oral CMF plus prednisone (CMFP) every 28 days in untreated patients with MBC, had a significantly longer OS after adjustment for prognostic factors without a difference in overall response rate (ORR) and TTP (25). CMFP had more leukopenia, thrombocytopenia, nausea, and vomiting, but overall QOL assessments were similar in the two treatment arms. However, the dose of paclitaxel used in practice is usually 175 mg/m^2 as higher doses have greater toxicities but have not demonstrated a better efficacy (70).

In conclusion, the evidence does not indicate a clear superiority of an anthracycline or taxane in anthracycline-naive patients, and either agent can be used as first-line therapy after taking into account previous adjuvant therapy exposure, tolerability, and side effect profile.

Anthracycline Pretreated Patients

Taxanes have been compared to older nonanthracycline regimens in MBC patients with prior anthracycline exposure and found to be superior in terms of ORR, TTP, and OS in some instances. Docetaxel 100 mg/m^2 every 3 weeks compared to methotrexate/fluorouracil after anthracycline failure in advanced breast cancer had a significantly higher ORR (42% vs. 21%) and median TTP (6.3 months vs. 3 months), but no significant difference in OS although notably crossover was allowed upon progression (71). The same dose of docetaxel has also been shown to be significantly better to mitomycin plus vinblastine in MBC progressing after previous anthracycline therapy in terms of RR (30% vs. 11.6%; $p < .0001$), median TTP (19 weeks vs. 11 week; $p = .001$) and OS (11.4 months vs. 8.7 months; $p = .0097$) (26). Docetaxel 100 mg/m^2 every 3 weeks was found to be equivalent in terms of TTP and OS when compared to a regimen of vinorelbine and continuous infusional fluorouracil in MBC patients who had been exposed to anthracyclines in the adjuvant, neoadjuvant, or palliative setting (72).

Paclitaxel monotherapy is also active in those who have been exposed to anthracyclines. Paclitaxel 175 mg/m^2 every 3 weeks was found to be inferior to 3-weekly cisplatin/oral etoposide in patients with advanced breast cancer pretreated with anthracyclines (73). The cisplatin/etoposide arm was superior to paclitaxel with respect to RR (36.3% vs. 22.2%; $p = .038$), TTP (5.5 months vs. 3.9 months; $p = .003$), and median OS (14 months vs. 9.5 months; $p = .039$).

In the TAX-311 multicenter open-label phase III study (n = 449) comparing docetaxel 100 mg/m^2 versus paclitaxel 175 mg/m^2 in patients with advanced breast cancer that had progressed after an anthracycline-containing chemotherapy regimen, docetaxel demonstrated significantly superior median OS (15.4 months vs. 12.7 months, HR 1.41; $p = .03$) and TTP (5.7 months vs. 3.6 months, HR 1.64; $p < .0001$), with a higher ORR which did not reach statistical significance (32% vs. 25%; $p = .10$) (74). Both hematologic and nonhematologic toxicities were greater for docetaxel but QOL scores were not significantly different between the groups over time. Another trial directly comparing second-line docetaxel 100 mg/m^2 or paclitaxel 175 mg/m^2 after failure of anthracyclines, confirmed that TTP and OS were significantly better for docetaxel (75).

Inference from the available data suggests that docetaxel may be superior to 3-weekly paclitaxel. However, docetaxel maintenance therapy is often limited by hematologic toxicities, peripheral neuropathy, fatigue, nail changes, and fluid retention. Notably, docetaxel has not been compared to the more commonly used weekly paclitaxel schedule, which has demonstrated a survival advantage over the 3-weekly regimen.

In the CALGB 9840 trial for MBC patients who had received up to one line of prior chemotherapy in the metastatic setting, weekly paclitaxel was compared to 3-weekly paclitaxel 175 mg/m^2 (41). Owing to a 30% incidence of grade 3 sensory neuropathy, the starting dose of weekly paclitaxel was amended from 100 mg/m^2 to 80 mg/m^2. The weekly regimen was superior to the 3-weekly regimen in terms of RR (42% vs. 29%; $p = .0004$), TTP (9 months vs. 5 months; $p < .0001$), and OS (24 months vs. 12 months; $p = .0092$). The statistical validity may have been reduced by inclusion of 158 patients who received paclitaxel 175 mg/m^2 from the CALGB 9342 study evaluating three doses of single-agent paclitaxel (76). Although grade 3 or more neutropenia was more frequent with the 3-weekly compared to weekly regimen (15% vs. 9%), febrile neutropenia requiring hospitalization remained infrequent in both arms (4% vs. 3%). Grade 3 neuropathy was a treatment-limiting toxicity more common with the weekly regimen (24% vs. 12%; $p = .0003$).

These results were confirmed by the Anglo–Celtic study, which showed a better response rate for the weekly paclitaxel 90 mg/m^2 for 12 cycles compared to 3-weekly paclitaxel 175 mg/m^2 for four cycles (42% vs. 27%; $p = .002$) (77). Although the TTP was not significantly different, it was thought that the mismatch in treatment duration may have accounted for this.

A meta-analysis of randomized controlled trials comparing weekly and 3-weekly taxanes in advanced breast cancer reported that weekly paclitaxel 80–100 mg/m^2 had an OS survival benefit over 3-weekly paclitaxel 175 mg/m^2 therapy (5 studies, 1,471 patients, HR 0.78, 95% CI, 0.67–0.89; $p = .001$), but with worse sensory neuropathy (78). In contrast, no difference between weekly docetaxel 35–40 mg/m^2 and 3-weekly docetaxel 100 mg/m^2 was reported for ORR, PFS, and OS, the only advantage being significantly less neutropenia or neutropenic fever in the weekly docetaxel schedule. On the contrary, nail changes and epiphora were significantly lower in the 3-weekly docetaxel schedule. Limitations of this meta-analysis were small sample sizes with none of the trials designed to measure OS as a primary end point, lack of individualized patient data with only published trials used, and considerable heterogeneity in design, modes of treatment, and response rates.

Docetaxel 100 mg/m^2 as approved for MBC treatment in the U.S. and Europe is not a tolerable dose in Asian patients due to increased toxicities. In a study examining three different doses of second-line docetaxel at 60 mg/m^2, 75 mg/m^2 and 100 mg/m^2 for at least six cycles in pretreated MBC patients, significantly higher ORRs (22.1% vs. 23.3% vs. 36%; $p = .007$) and TTP (13.7, 13.9, 18.6 weeks; $p = .014$) were obtained with higher doses in the assessable population, but there was no difference in OS in the intent-to-treat population at a median follow-up of 30 months (79). About 80% of patients were exposed to prior anthracyclines in each arm. Most hematologic and nonhematologic toxicities were related to increasing doses, including those of febrile neutropenia rates (4.7% vs. 7.4% vs. 14.1%). Hence, lower doses of docetaxel must be considered for those who are more frail or who have tolerability issues. As a consequence, in clinical practice we usually use weekly paclitaxel 80 mg/m^2 or 3-weekly docetaxel 60–100 mg/m^2.

Cross-resistance between the Taxanes

There is evidence of an incomplete cross-resistance between paclitaxel and docetaxel, since modest responses are still seen in those exposed to the alternate taxane (80,81). However, using a taxane after progression on the other may be best reserved for patients who relapse more than 12 months after adjuvant taxane-containing therapy or who had previous clinical response to taxanes with a reasonable time lapse of at least a year. In a small retrospective study (n = 44) of patients with docetaxel-resistant MBC, paclitaxel 80 mg/m^2 weekly obtained objective responses in 14 of 44 women (31.8%, 95% CI, 17.5–46.1), seven of which had primary resistance to docetaxel (82). The median duration of response and time to progression were 6.1 months and 5 months respectively (82). In another larger retrospective study of weekly paclitaxel 80 mg/m^2 in 82 patients with docetaxel-resistant MBC, the patients were classified into those with primary or secondary resistance (short interval ≤120 days, long interval >120 days) (83). The response rate

to paclitaxel for those with primary docetaxel resistance (n = 24) was 8.3%, and those with secondary resistance (n = 58) was 24.1% (short interval [n = 39] 17.9%, long interval [*n* = 19] 36.8%), the differences in response rates being statistically significant (p = .0247). Conversely, docetaxel every 3 weeks was reported to have a response rate of about 18% to 25% in paclitaxel-refractory MBC (81,84).

The data suggest that treatment with an alternative taxane can result in objective responses. Studies support the notion that there is only partial cross-resistance between paclitaxel and docetaxel. However, it should be noted that there was wide variation in extent of prior anthracycline and/or taxane exposure in these studies, as well as the dose and schedule of taxanes used.

Nab-paclitaxel

Nab-paclitaxel is a Cremophor-free, albumin-bound formulation designed to distribute into tumor tissue more rapidly and at higher concentrations than conventional paclitaxel, thus possibly improving drug delivery and reducing toxicity. It is FDA-approved for MBC as monotherapy after failure of anthracycline-based combination chemotherapy for MBC, or after relapse within 6 months of adjuvant anthracyclines. It allows higher doses of paclitaxel infusion, over a shorter duration of 30 minutes, with no need for antihistamine or corticosteroid premedications.

It has been compared to docetaxel and paclitaxel, both as 3-weekly regimens. In a phase III trial comparing 3-weekly nab-paclitaxel 260 mg/m^2 without premedication versus paclitaxel 175 mg/m^2 with premedication in women with MBC (majority of whom had ≤1 prior MBC chemotherapy regimen not including a taxane) (85), nab-paclitaxel had significantly superior RRs (33% vs. 19%; p = .001) and TTP (23.0 weeks vs. 16.9 weeks, HR = 0.75; p = .006) compared with standard paclitaxel, but no difference in OS. OS was significantly longer in the subgroup who received nab-paclitaxel compared with paclitaxel as second-line or greater therapy (56.4 weeks vs. 46.7 weeks, HR 0.73; p = .024). Grade 4 neutropenia was significantly lower for nab-paclitaxel compared with standard paclitaxel (9% vs. 22%, respectively; p < .001) despite a 49% higher paclitaxel dose. Grade 3 sensory neuropathy was more common with nab-paclitaxel (10% vs. 2%, respectively; p < .001), lasting for a median of 22 days. No hypersensitivity reactions occurred with nab-paclitaxel despite the absence of premedication.

In another phase II trial (n = 302) comparing first-line nab-paclitaxel 300 mg/m^2 3-weekly, 100 mg/m^2 weekly or 150 mg/m^2 weekly, versus docetaxel 100 mg/m^2 3-weekly, there was a significant prolongation of PFS (>5 months) in patients receiving nab-paclitaxel 150 mg/m^2 weekly compared with docetaxel 100 mg/m^2 q3w (86). Nab-paclitaxel 150 mg/m^2 weekly showed a significantly longer PFS than docetaxel by independent radiologist assessment (12.9 months vs. 7.5 months, respectively; p = .0065). Both 150 mg/m^2 (49%) and 100 mg/m^2 (45%) weekly of nab-paclitaxel demonstrated a higher ORR than docetaxel (35%), but this did not reach statistical significance. Nab-paclitaxel 3-weekly versus docetaxel was not different for PFS or ORR. Disease control rate (stable disease ≥16 weeks or confirmed overall complete or partial response) was significantly higher for patients receiving either dose of weekly nab-paclitaxel compared with docetaxel, but survival data were not mature at the point of this publication. Grade 3 or 4 fatigue, neutropenia, and febrile neutropenia were less frequent in the nab-paclitaxel arms, whereas the frequency and grade of peripheral neuropathy were similar in all arms.

Nab-paclitaxel has also shown activity, albeit limited, in taxane-resistant MBC patients (87), with a tolerable toxicity profile of only about 17% grade 1 or 2 sensory neuropathy in taxane-pretreated MBC patients (88). In general, nab-paclitaxel demonstrated better response rates and PFS compared to 3-weekly paclitaxel or docetaxel. However, nab-paclitaxel (and ixabepilone) failed to demonstrate superior efficacy compared to standard weekly paclitaxel in the three-arm phase III open-label randomized trial CALGB 40502/NCCTG N063H study (NCT00785291) comparing the three therapies given in a weekly fashion with bevacizumab (which became optional subsequently) as first-line for metastatic breast cancer patients (89). The PFS for ixabepilone was found to be significantly inferior to paclitaxel, while nab-paclitaxel was not superior to paclitaxel. There was no difference in OS for all treatment arms and unfortunately the investigational arms were more toxic (e.g., peripheral neuropathy) than the conventional weekly paclitaxel arm.

The higher cost of nab-paclitaxel may compare favorably to the cost of docetaxel (90). However, the lack of meaningful clinical efficacy when compared to conventional paclitaxel suggest that the extra cost associated with the use of nab-paclitaxel can only be justified in patients who cannot tolerate use of steroids needed in most patients treated with paclitaxel.

Anthracyclines versus Taxanes

In a meta-analysis of individualized patient data on three single-agent trials comparing taxanes with anthracyclines (n = 919), taxanes fared significantly worse for PFS (5.1 months vs. 7.2 months, HR1.19; p = .011), although response rates for taxanes versus anthracyclines (38% vs. 33%; p = .08), and survival (19.5 months vs. 18.6 months, HR 1.01; p = .9) were similar (91).

Single-agent anthracyclines may be used for first-line therapy of MBC if the patient is anthracycline-naive. Re-using anthracyclines in the metastatic setting after adjuvant exposure is not usually preferred due to the presence of dose-limiting cardiotoxicity and the availability of multiple other drug options. A taxane may also be used as first-line treatment for those who are taxane-naive or who have an adjuvant taxane-free interval of more than 12 months. In the latter scenario, an alternative taxane (docetaxel or paclitaxel) to that used in the adjuvant setting may be preferred. Both are reasonable options in the first-line setting with neither being definitively superior to the other. Resistance to anthracyclines and taxanes has been defined as disease recurrence occurring within 6 to 12 months of an adjuvant, neoadjuvant or first-line metastatic regimen or while on active treatment.

Anthracycline Combined with Taxanes

It is not clear if the combination of the two most active agents anthracyclines and taxanes are more beneficial compared to sequential use of these agents in the treatment of MBC. This has been compared in several phase III studies evaluating a paclitaxel-based or docetaxel-based combination (23,92).

ECOG 1193 trial compared doxorubicin 60 mg/m^2, paclitaxel 175 mg/m^2 over 24 hours, and the combination of doxorubicin 50 mg/m^2 followed 3 hours later by paclitaxel 150 mg/m^2 over 24 hours, the latter plus granulocyte colony-stimulating factor, as first-line therapy in 739 women with MBC (23). Although complete and partial responses, and PFS were significantly higher in the combination arm compared to either the doxorubicin or paclitaxel arms, there was no significant difference in median OS as well as QOL measurements. Cardiac toxicity was equivalent in patients receiving single-agent doxorubicin and combination therapy perhaps due to the dose and administration schedule of the combination arm.

A Spanish Breast Cancer Research Group (GEICAM-9903) phase III study evaluated three cycles of doxorubicin 75 mg/m^2 followed by three cycles of docetaxel 100 mg/m^2, both every 21 days or six cycles of the combination doxorubicin 50 mg/m^2 and docetaxel 75 mg/m^2 every 21 days, to determine if sequential therapy could reduce the incidence of hematological toxicity especially febrile neutropenia (primary end point) while maintaining antitumoral activity (secondary end point) (92). Febrile neutropenia was significantly less common in the sequential compared to the combination arm (29.3% vs. 47.8%), and so were other toxicities like asthenia, diarrhea, and fever. There were no significant differences between the sequential versus the combination arms in terms of ORRs (61% vs. 51%), median duration of response (8.7 months vs. 7.6 months), median TTP (10.5 months vs. 9.2 months), and median OS (22.3 months vs. 21.8 months).

The ERASME 3 study compared docetaxel/doxorubicin or paclitaxel/doxorubicin every 3 weeks for four cycles followed by docetaxel or paclitaxel respectively for four cycles as first-line therapy in MBC (93). At a median follow-up of 50.2 months, there was no significant difference in QOL scores (measured after the first four cycles), ORR, PFS, and OS between the two treatment arms. However, hematologic toxicity and asthenia were significantly increased in the docetaxel arm and neuropathy in the paclitaxel arm.

The therapeutic benefit of anthracycline/taxane combinations compared to nontaxane anthracycline combinations has been studied as first-line therapy in several studies (94–99). Only a few studies have demonstrated an OS advantage for the anthracycline/taxane combination over anthracycline-based regimens (97,99). An Eastern European phase III trial of doxorubicin 50 mg/m^2 followed 24 hours later by paclitaxel 220 mg/m^2 over 3 hours versus 5-FU 500 mg/m^2 IV, doxorubicin 50 mg/m^2 IV, and cyclophosphamide 500 mg/m^2 (FAC) showed an overall RR (68% vs. 55%; p = .032), median TTP (8.3 vs. 6.2 months; p = .034), and OS (23.3 vs. 18.3 months; p = .013) significantly in favor of the doxorubicin/paclitaxel arm (97). The percentages of second-line therapy were similar in both arms except that taxane use was more prevalent in the FAC arm (24% vs. 2%). The grade 4 neutropenia rate was significantly higher in the doxorubicin/paclitaxel arm (89% vs. 65%; p < .001), although the incidences of fever, infection, and cardiotoxicity were low. QOL measurements were similar in the two arms.

In another Dutch study (n = 216), first-line doxorubicin 50 mg/m^2 followed one hour later by docetaxel 75 mg/m^2 compared with FAC showed a significantly higher objective RR (58% vs. 37%; p = .003), TTP (8 vs. 6.6 mo; p = .004), and OS (22.6 vs. 16.2 mo; p = .019) (99). Although febrile neutropenia rates were significantly higher in the doxorubicin/docetaxel arm (33% vs. 9%; p < .001), with two toxic deaths, the congestive heart failure rate was similarly low in both arms (3% vs. 6%). Additional taxanes as second-line therapy was administered to 67% and 23% of patients in the FAC and doxorubicin/docetaxel arms respectively. It should be noted that OS was not a primary study end point, there was a small sample size and the survival on the anthracycline-based arm was particularly poor.

An EORTC study looked at combinations of doxorubicin/paclitaxel versus doxorubicin/cyclophosphamide did not reveal any benefit in terms of RR, PFS, and OS although there was a significantly increased febrile neutropenia rate in the doxorubicin/paclitaxel arm (32% vs. 9%) (95). The doxorubicin/docetaxel combination was also compared to AC in the TAX 306 multicenter, multinational randomized phase III trial (n = 429) and showed a significantly higher RR (59%, CR 10%, PR 49%) than for those taking AC (47%, CR 7%, PR 39% [p = .009]) and TTP (37.3 vs. 31.9 weeks; p = .014), but no OS benefit and similar QOL measurements (98). Some 29% in the AC group received additional treatment with docetaxel compared with only 6% in the doxorubicin/docetaxel group. There was also a higher febrile neutropenia rate in the doxorubicin/docetaxel arm (33% vs. 10%; p < .001), although cardiotoxicity was similarly low in both arms (CHF 3% in doxorubicin/docetaxel and 4% in the AC arms).

In a phase III study comparing 3-weekly docetaxel/doxorubicin/cyclophosphamide (TAC) (75/50/500 mg/m^2) to FAC (500/50/500 mg/m^2) as first-line in MBC, TAC demonstrated a significantly higher RR (55% vs. 44%; p = .02), but there were no improvements in TTP or OS compared with FAC (94). A significantly higher incidence of grade 3 and 4 hematologic and nonhematologic toxicities, including more cardiotoxicity, was found in the TAC arm. A higher percentage in the FAC group received crossover docetaxel treatment than the TAC group (38% vs. 11%).

In a U.K.-driven trial assessing the combination of epirubicin/paclitaxel versus epirubicin/cyclophosphamide, a significantly better response rate (65% vs. 55%; p = .015) for the epirubicin/paclitaxel arm was demonstrated, although there were no differences in TTP and OS (96). Comparing epirubicin/docetaxel versus epirubicin/cyclophosphamide also did not yield any differences in the efficacy end points of ORR, PFS, and OS in a German study (100).

Two pooled analyses have not found an OS advantage for the anthracycline/taxane combination although there was a better response rate and TTP (91,101).

In a combined pooled analysis and literature-based meta-analysis of seven phase III prospective randomized trials (three published and found abstracts; n = 2,805), a significant difference was found in favor of anthracycline/taxane combinations over standard anthracycline regimens for ORR (RR 1.21; p < .001), a borderline significance for TTP (RR 1.10; p = .05), but no significant OS difference (101). The neutropenia and febrile neutropenia rates were significantly higher in the anthracycline/taxane arms. This analysis has been hampered by incomplete and non-definitive abstract data, heterogeneity in median follow-up which could have affected survival analysis, and a lack of individualized patient data.

In another analysis consisting of individualized patient data collected on eight randomized combination trials (n = 3,034), there was a significant benefit of anthracycline/taxane combinations over nontaxane anthracycline-based regimens, in terms of response rate and PFS, with no significant difference in OS (91).

On the basis of these results, anthracycline/taxane combinations should not routinely replace anthracycline-based regimens in clinical practice. There was limited statistical power in these trials to detect an OS benefit. Meta-analyses confirmed a better response rate and PFS, but not OS. The disappointing results of the anthracycline/taxane combinations are not completely unexpected as there is no preclinical evidence of synergy between them and both have overlapping and limiting hematological toxicities. These regimens should be reserved for only those patients with good performance status and life-threatening disease.

Other Taxane Combinations

After progression on anthracyclines, taxane combinations may sometimes be used if a higher response rate is required. Certain combinations have shown a survival benefit compared to single-agent taxanes such as docetaxel/capecitabine and paclitaxel/gemcitabine (32,33). However, there was no planned crossover in the studies, a third arm with single-agent capecitabine or gemcitabine were missing, and these combinations have been associated with increased toxicities.

Based on data from these trials, the FDA approved both combination regimens for treatment of MBC pretreated with anthracyclines: the capecitabine/docetaxel combination indicated for anthracycline and/or taxane-failed disease and the gemcitabine/paclitaxel combination as first-line therapy after failure of prior anthracycline-based adjuvant chemotherapy.

The capecitabine/docetaxel combination capitalizes on the synergistic antitumor activity of these two drugs observed in xenograft models (102). Capecitabine generates 5-FU preferentially in tumor tissue mimicking continuous 5-FU infusion, this tumor selectivity achieved because of the higher activity of thymidine phosphorylase in human tumor tissue compared with healthy tissue (103,104). Docetaxel also causes upregulation of thymidine phosphorylase and Bcl-2 downregulation (105). Both drugs also capitalize on their nonoverlapping toxicities as docetaxel is myelosuppressive, but capecitabine has a low incidence of myelosuppression. An international phase III trial of 511 patients with unresectable locally advanced or metastatic disease previously exposed to anthracyclines in the neoadjuvant, adjuvant or metastatic setting were randomized to capecitabine 1,250 mg/m^2 twice daily for 14 out of 21 days and docetaxel 75 mg/m^2 on day 1 every 21 days (n = 255) compared to docetaxel 100 mg/m^2 every 21 days (n = 256) (32). In addition, more than 90% of patients had received previous alkylating agents and 5-FU had been administered to about three-quarters of patients. The capecitabine/docetaxel arm demonstrated superior TTP (HR 0.652; p = .0001, 6.1 months vs. 4.2 months), OS (HR 0.775; p = .0126, 14.5 months vs. 11.5 months), and objective tumor response (42% vs. 30%; p = .006). Of note, approximately 30% of patients in each arm were ER-negative which indicates activity of the treatment in this subgroup. More grade 3 adverse events (AEs) in the capecitabine/docetaxel arm necessitated treatment interruption or dose reduction (71% vs. 49%), due largely to hand-foot syndrome. The frequency of grade 3/4 neutropenia and neutropenic fever was 24% versus 28% in the combination versus docetaxel arms. Approximately 65% patients in the combination arm required dose reduction of capecitabine alone (4%), docetaxel alone (10%), or both drugs (51%) for AEs, while only 36% required dose reduction for the docetaxel arm. Myalgia, arthralgia, neutropenic fever and sepsis were more common with docetaxel, while hand-foot syndrome, diarrhea and stomatitis were more frequent with docetaxel/capecitabine, although there was no significant difference in QOL scores. A high proportion of patients received post-study treatment in both arms (70% and 63% in combination and single-agent docetaxel arms respectively), with similar proportions in each arm receiving post-study 5-FU, vinorelbine, anthracyclines, trastuzumab and paclitaxel. Post-study docetaxel was administered in 20% and 7% of the combination and single-agent docetaxel arm respectively; and the use of post-study capecitabine was more common in the monotherapy compared to the combination arm (27% vs. 4%). As no crossover was planned and only a small proportion of patients on docetaxel subsequently received capecitabine, no definitive conclusions can be made regarding the relative merits of combination over sequential single-agent therapy (106). Lower doses of capecitabine and docetaxel may retain the efficacy while reducing the concomitant toxic effects as has been suggested by a retrospective analysis of this trial (107), which is important to consider when dealing with otherwise incurable disease and a primary goal of palliation.

Of interest, in a Mexican Oncology Study Group (MOSG) randomized phase III trial evaluating sequential capecitabine followed by a taxane versus combination capecitabine/paclitaxel or capecitabine/docetaxel, the response rate was higher for the combination arms, but there was a lack of PFS or OS benefit (29). On the contrary, another trial having a similar design of sequential docetaxel followed by capecitabine on progression versus combination capecitabine/docetaxel, but using different capecitabine doses and drug sequence, reported a higher ORR, TTP, and OS for the combination arm (108).

A randomized multicenter phase III trial by the AGO Breast Cancer Study Group was designed to show noninferiority of capecitabine/paclitaxel (XP) to epirubicin/paclitaxel (EP) as first-line in MBC with the primary end point PFS showing equivalence (12.3 months vs. 11.8 months,; p not significant), and the secondary end points of response rates and OS being comparable (109). The toxicity was relatively low for XP compared to other nonanthracycline containing combination therapies, with febrile neutropenia in only one patient and skin toxicities in five patients. Four patients stopped treatment for gastrointestinal reasons in the XP arm. This suggests that XP is an efficacious and more tolerable regimen compared to capecitabine/docetaxel.

A phase III global study which supported the approval of gemcitabine in MBC compared the efficacy of gemcitabine 1,250 mg/m^2 on days 1 and 8 plus paclitaxel 175 mg/m^2 on day 1 (GT) (n = 266) to paclitaxel 175 mg/m^2 on day 1 (n = 263) in 21-day cycles for patients who had relapsed after neoadjuvant or adjuvant anthracyclines (33). The GT arm was significantly better in terms of median OS (18.6 months vs. 15.8 months; p = .0489), TTP (6.14 months vs. 3.98 months; p = .0002) and ORR (41.4% vs. 26.2%; p = .0002). Grade 3 and 4 neutropenia (47.9% vs. 11.5%), febrile neutropenia (5% vs. 1.2%) and grades 2 to 4 fatigue and neuropathy were increased in the GT arm. As there was no preplanned crossover design and only 15.6% of patients on paclitaxel received subsequent gemcitabine as post-study treatment, there are no definite conclusions regarding the advantage of the combination over sequential therapy. As the standard comparator arm consisted of 3-weekly paclitaxel, there can also be no conclusions drawn regarding the superiority of the combination over other paclitaxel schedules such as weekly regimens which have been used more commonly nowadays. Notably, there is no evidence of synergy between gemcitabine and paclitaxel preclinically.

In a phase III trial, gemcitabine 1,000 mg/m^2 days 1,8/docetaxel 75 mg/m^2 on day 1 (GD) every 21 days was compared to capecitabine 1,250 mg/m^2 twice daily every 21 days/docetaxel 75 mg/m^2 (CD); one prior anthracycline regimen in the neoadjuvant, adjuvant, or first-line metastatic setting being required (110). No differences were found in PFS (8.05 months vs. 7.98 months; p = .121), ORR (32% both arms), and OS (19.29 months vs. 21.45 months; p = .983), although TTF was longer in the GD arm (4.24 months vs. 4.07 months; p = .059). Post-study treatment was administered in 71% and 73% of patients in the GD and CD arms respectively. Hematologic toxicities were similar between the arms except for grade 3 and 4 leukopenia (78% vs. 66%; p = .025). Erythropoietin and granulocyte colony-stimulating factor were administered to 18% and 30% of patients, respectively, in the GD arm and to7% and 25%, in the CD arm, with more patients in the GD arm requiring transfusions (17% vs. 7%; p = .0051). Several nonhematologic grades 3 to 4 toxicities were significantly higher in the CD arm that included diarrhea (8% vs. 18%; p = .009), hand-foot syndrome (0% vs. 26%; p < .001), and mucositis (4% vs. 15%; p < .001). Fewer patients in the GD arm discontinued treatment as a result of drug-related AEs (13% vs. 27%, respectively; p = .002), which could be related to the high doses of both drugs used in the capecitabine/docetaxel arm.

In another more recent phase III trial of GD versus CD with planned crossover to the alternate single agent (capecitabine or gemcitabine) on progression, the two combination arms

had similar efficacy and toxicities consistent with prior clinical experience (111). Exploratory analysis suggested that the GD to C crossover sequence may provide a benefit in TTP and OS compared to the CD to G arm although this was not significant.

In a phase III Central European Cooperative Oncology Group (CECOG) trial of MBC patients who had one prior anthracycline regimen in either early or late stage disease, randomized to 21-day schedules of either 8 cycles of combination gemcitabine 1,000 mg/m^2 days 1 and 8/docetaxel 75 mg/m^2 on day 8 or sequential docetaxel 100 mg/m^2 for 4 cycles followed by gemcitabine 1,250 mg/m^2 on days 1 and 8, there was no significant difference in TTP, ORR, response duration, and OS (112). A significantly larger proportion of patients in the sequential arm experienced greater leukopenia (68% vs. 29%; $p < .001$), neutropenia (83% vs. 49%; $p < .001$), but significantly more in the combination arm experienced anemia ($p = .003$). The increased neutropenia seen contrarily in the sequential arm was due to the use of docetaxel 100 mg/m^2 without granulocyte colony stimulating factor (GCSF) support.

However, weekly paclitaxel has been found to have significantly greater OS compared with docetaxel/gemcitabine. In a Hellenic Cooperative Oncology Group study ($n = 416$), patients were randomized to first-line paclitaxel 175 mg/m^2/carboplatin AUC6 (PCb) 3-weekly for six cycles, docetaxel 75 mg/m^2 on day 8/gemcitabine 1,000 mg/m^2 on days 1, 8 (GDoc) 3-weekly for six cycles or weekly paclitaxel 80 mg/m^2 for 12 weeks (Pw) (113). Those who had HER2-positive disease were allowed trastuzumab. The primary end point OS was superior for the weekly paclitaxel group compared to the other two groups (median survival: Pw 41 months vs. PCb 29.9 months vs. GDoc 26.9 months; $p = .037$), while there was no significant difference in TTP. In multivariate Cox model analysis adjusting for performance status (PS 1 vs. 0), the survival difference was statistically significant in favor of Pw compared with PCb for PS 1 patients, while the survival advantage for Pw over GDoc was not affected by PS. Those in the GDoc arm experienced more hematologic toxicities, while those in the paclitaxel containing arms had more sensory neuropathy. Febrile neutropenia occurred rarely in all three arms. Severe mucositis and alopecia were more prevalent in the GDoc and PCb arms compared to the Pw arm. The weekly paclitaxel arm was well-tolerated in all age groups, which suggests that it is a safe regimen for the older patient population. QOL was comparable in all treatment groups while weekly paclitaxel had the greatest cost effectiveness.

Although the above combinations have shown effective clinical responses, they are not often used due to associated toxicities, and the equivalent efficacies of sequential agents.

Capecitabine

Capecitabine is the first oral fluoropyrimidine approved by the FDA for MBC patients after failure of anthracyclines and taxanes. It has excellent tolerability with limited alopecia and bone marrow suppression. It received accelerated approval based on an ORR of 25.6% in a single arm trial in 162 patients with refractory breast cancer (114). Capecitabine 1,250 mg/m^2 twice daily for 14 days every 21 days has RRs of about 30% in first-line therapy (27) and about 15% to 30% in anthracycline and taxane pretreated patients (115–118). The lower dose capecitabine 1,000 mg/m^2 twice daily has a superior therapeutic index and comparable efficacy, and may help in alleviating the side effects such as palmar-plantar erythrodysesthesia, diarrhea, and nausea (119,120). Other schedules have also been attempted with reduced toxicity and apparent similar efficacy; such as, fixed, lower starting doses, or shorter week on/week off schedules (121,122).

Gemcitabine

Gemcitabine is a nucleoside metabolic inhibitor that targets DNA synthesis indicated for first-line treatment of MBC in combination with paclitaxel after failure of prior anthracycline-containing adjuvant chemotherapy, unless anthracyclines were clinically contraindicated (33).

As a single agent, gemcitabine is well-tolerated and results in objective ORRs of about 14% to 24% in the first-line setting and 12% to 30% in anthracycline and/or taxane pretreated patients (123–125). Thrombocytopenia can be dose-limiting especially in those who have been heavily pretreated. In a randomized phase III study comparing first-line gemcitabine 1,200 mg/m^2 or epirubicin 35 mg/m^2 on days 1, 8, and 15 of a 28-day cycle in anthracycline-naive MBC patients ≥60 years (median 68 years), epirubicin (n = 199) compared to gemcitabine (n = 198) demonstrated statistically significant superiority in TTP (6.1 months vs. 3.4 months; $p = .0001$) and overall survival (19.1 months vs. 11.8 months; $p = .0004$) (126). The ORRs for epirubicin versus gemcitabine was 40.3% and 16.4% in 186 and 183 evaluable patients respectively ($p < .001$). Common hematological grade 3 and 4 toxicities for gemcitabine versus epirubicin were neutropenia (25.3% and 17.9%), leukopenia (14.3% and 19.3%), and thrombocytopenia (9% vs. 1.5%). This confirms the greater efficacy of anthracyclines in the first-line setting but also illustrates that gemcitabine is an active drug in older population. In clinical practice, gemcitabine as a single agent or in combination with carboplatin is often used as subsequent salvage therapy in MBC after anthracyclines and taxanes have failed.

Vinorelbine

Vinorelbine is a vinca alkaloid which interferes with microtubule assembly, inducing cell cycle arrest at mitosis. Single agent weekly vinorelbine 30 mg/m^2 has objective RRs of about 15% to 40% depending on whether it is used as first-line, or in heavily pretreated patients (31,127,128). Single agent oral vinorelbine has shown ORR of 26% to 42% depending on line of treatment in several phase II trials (129–131). Vinorelbine is a good option for the older population and its main side effects are neutropenia, peripheral neuropathy, constipation, and less commonly paralytic ileus, with alopecia being rare. In clinical practice, its main use is reserved usually for the second or third-line settings after anthracyclines and/or taxanes have been utilized.

Phase III trials of IV vinorelbine/5-FU compared to docetaxel in anthracycline pretreated patients or IV vinorelbine/doxorubicin versus doxorubicin failed to show any benefit of the combination arms over their comparison monotherapy arms (30,72).

In the pivotal study of 64 patients with locally advanced or MBC (61% had visceral disease and 73% had at least 2 organs involved), oral vinorelbine given on a weekly basis for 8 weeks (60 mg/m^2 for first 3 cycles, then 80 mg/m^2 subsequently) resulted in a 31% response rate (24.1% PR, 6.9% CR), median PFS 17.4 weeks, and a safety profile comparable with intravenous vinorelbine (132).

Oral vinorelbine combined with capecitabine is an active combination which has been found to have comparable efficacy to the intravenous equivalent. Its toxicities are predictable and manageable, with a low rate of alopecia which may be viewed favorably by patients. In a pivotal phase II study evaluating this combination of 3-weekly oral vinorelbine 80 mg/m^2 (after cycle 1 at 60 mg/m^2) on days 1 and 8, plus capecitabine 1,000 mg/m^2 (750 mg/m^2 if ≥65 years) twice daily on days 1 to 14 as first-line therapy in women with HER2-negative MBC, the objective RR was 51% (complete response 4%), the clinical benefit rate was 63% (response or

SD for ≥6 months), median duration of response 7.2 months, median PFS 8.4 months, and median OS 29.2 months, with similar efficacy in those with visceral metastases (133). The toxicities were predictable and manageable with the main grade 3 and 4 toxicity being neutropenia (49%); two patients experiencing febrile neutropenia and three patients having a neutropenic infection (including one septic death). A particularly low rate of alopecia (9%) was observed.

This regimen was also evaluated in those resistant or refractory to anthracyclines and taxanes in two phase II studies (134). The study by Jones et al. consisting of 40 patients (75% refractory/resistant to anthracyclines/taxanes) receiving oral vinorelbine 60 mg/m^2 on days 1, 8, and 15 plus capecitabine 1,000 mg/m^2 bid on days 1 through 14 every 3 weeks, showed a RR 23.5%, median PFS 3.4 months, and median OS 11.3 months (134). In another small Italian phase II study (n = 38) administering oral vinorelbine 60 mg/m^2 on days 1 and 8 plus capecitabine 1,000 mg/m^2 bid on days 2 to 7, 9 to 16 every 3 weeks in MBC patients refractory to anthracyclines and taxanes, there was a RR of 39%, a median TTP 4.5 months, median duration of response 7 months and median OS 10 months (135).

Of interest, a randomized 3-arm phase II study of HER2-negative MBC patients previously exposed to neo- or adjuvant anthracyclines, comparing oral vinorelbine 80 mg/m^2 (after the first cycle at 60 mg/m^2) on days 1 and 8 plus capecitabine 1,000 mg/m^2 bid on days 1 through 14 every 21 days, the same drugs alternating every 3 cycles, and docetaxel 75 mg/m^2 plus capecitabine 1,000 mg/m^2 bid on days 1 to 14 every 3 weeks, showed a similar efficacy (RR, OFS, OS) for the combination arms, while the all oral combination induced less neutropenia, infection, hand-foot syndrome, fatigue/asthenia, and alopecia, and the docetaxel/capecitabine combination less gastrointestinal toxicity (136). The third arm evaluating sequential therapy was inferior although this could have been due to the higher prevalence of visceral disease in this arm.

In a retrospective observational study comprising patients from 13 centers and 7 countries between 2006 and 2008 (n = 216) who had received oral vinorelbine alone (54%) or in combination with capecitabine (46%) either as first (56%) or second-line (44%), disease control was achieved in 77% of patients; 74% as single-agent, 81% in combination, 82% in first-line, 71% in second-line (137). Median PFS was 9.7 months and 6.6 months in first- and second-line therapy respectively. These oral regimens were described by caregivers as convenient (81%), well-tolerated (84%), and had a good compliance by patients (76%). Because data from every-day practice matched that obtained from previous clinical trials in efficacy and tolerability, this is an attractive oral formulation to use.

The combination of alternating intravenous and oral vinorelbine has been combined with other agents such as epirubicin or docetaxel in phase II trials in the first-line setting, using an intravenous schedule on day 1 and an oral schedule on either day 8 or 15, with promising ORR of about 50% (138,139). Other chemotherapy agents have been evaluated via phase I and II trials in combination with oral vinorelbine, such as gemcitabine (140), paclitaxel (141), docetaxel (142), liposomal doxorubicin (143), and temozolomide (144), although none have been used commonly in clinical practice. Both oral and IV vinorelbine formulations have been used in treatment of MBC and have similar efficacy.

Vinflunine

Vinflunine is a novel microtubule inhibitor of the vinca alkaloid family which has shown activity in a phase II trial of anthracycline and taxane pretreated MBC patients with an ORR of 14%, median PFS of 2.6 months and a median OS of 11.4 months (145). In another phase II study of vinflunine used as second line treatment after anthracycline/taxane therapy, the ORR was 30%, median duration of response was 4.8 months, median PFS was 3.7 months, and OS 14.3 months (146). Several phase III trials have been set up in view of these promising phase II results.

CMF

CMF remains a viable option for MBC treatment but is often used later in the treatment sequence after the more commonly used agents such as anthracyclines, taxanes, capecitabine, vinorelbine, and gemcitabine. Although first-line CEF (cyclophosphamide 400 mg/m^2, epirubicin 50 mg/m^2, and fluorouracil 500 mg/m^2 on days 1 and 8) has demonstrated higher response rates (57% vs. 46%; p = .01), longer TTP (8.9 months vs. 6.3 months; p = .0064), and TTF (6.2 months vs. 5 months; p = .01) compared with IV CMF (cyclophosphamide 500 mg/m^2, methotrexate 40 mg/m^2, and fluorouracil 600 mg/m^2 on days 1 and 8), OS (20.1 months vs. 18.2 months;, p = .23) was reported to be similar (147). In practice, oral CMF is used more commonly and has been shown to be superior to the equivalent IV formulation (42).

Other Combinations

Various other combinations have shown activity in pretreated MBC in phase II or phase III studies. These include gemcitabine/cisplatin (RR 30% to 50%) (148–150), gemcitabine/vinorelbine (RR 30% to 40%) (31,151), and gemcitabine/epirubicin/paclitaxel (RR 62%) (152). Cisplatin has been combined with vinorelbine in patients previously treated with anthracyclines and docetaxel with a RR of about 50% (153). Other platinum combinations include cisplatin/docetaxel in anthracycline-resistant advanced breast cancer (RR 36%) (154), carboplatin/paclitaxel as first-line therapy (RR 41%) (155), cisplatin/capecitabine in anthracycline and taxane pretreated patients (RR 36%) (156), or cisplatin/oral etoposide in anthracycline pretreated patients (RR 36%) (73). Less common combinations of vinorelbine with doxorubicin or epirubicin have also shown promising activity (30,157). None of these regimens have shown an OS advantage over other more traditional regimens or single agents (30,152,157,158).

Ixabepilone

Increased use of anthracyclines and taxanes in the neo- or adjuvant settings limits treatment options for patients upon relapse. Nonanthracycline, nontaxane combinations have higher response rates but have not shown a survival benefit over single agents and other combination treatment regimens, hence the necessity for new drug developments.

Epothilones are naturally occurring macrolide antibiotics derived from the myxobacterium *Sorangium cellulosum*. Ixabepilone is an epothilone, belonging to a class of nontaxane tubulin polymerizing agents that have activity in taxane-resistant patients. It is approved by the United States FDA as monotherapy for patients who have tumors which are resistant to anthracyclines, taxanes, and capecitabine and in combination with capecitabine for MBC or locally advanced breast cancer resistant to anthracyclines and taxanes, or for those who are taxane resistant and further anthracyclines are contraindicated. It has however been refused marketing authorization by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use in 2008 due to its marginal benefits and concerning side effects such as significant peripheral neuropathy.

In a pivotal multicenter phase II study, patients with tumor progression after anthracyclines, taxanes, and capecitabine were given ixabepilone 40 mg/m^2 once every 21 days (159). In this heavily pretreated population (n = 113, 88% had received at least two prior lines), ORR was 11.5% and 18.3% in independent and investigator-related assessments. Median duration of response, PFS and OS were 5.7 months, 3.1 months, and 8.6 months respectively, 50% of which achieved SD. Grade 3 and 4 toxicities included peripheral sensory neuropathy (14%), fatigue/asthenia (13%), myalgia (8%), and stomatitis/mucositis (6%); with resolution of peripheral sensory neuropathy after a median of 5.4 weeks. In a separate phase II study of patients with MBC exposed to taxanes in the adjuvant, neoadjuvant or metastatic setting, the RR of 22% was slightly better, the main side effects being neutropenia, febrile neutropenia, fatigue, and diarrhea (160).

In a pivotal phase III registration trial (BMS 046), ixabepilone 40 mg/m^2 on day 1 plus capecitabine 1,000 mg/m^2 twice a day for 14 days every 21 days versus capecitabine 1,250 mg/m^2 for 14 days every 21 days in 752 women with locally advanced or MBC pretreated with or resistant to an anthracycline and resistant to a taxane demonstrated prolonged PFS (5.8 months vs. 4.2 months), a 25% reduction in risk of disease progression (HR 0.75; p = .0003), and increased response rates (35% vs. 14%; p < .0001) for the combination arm, but not OS (161,162). However, there was a clinically meaningful increase in OS in KPS 70–80 patients receiving combination therapy (HR 0.75; 95%CI 0.58–0.98) in a later analysis of OS (163). Majority of patients (65%) had ≥3 metastatic sites, and nearly half had received ≥2 prior regimens. Grade 3 and 4 toxicities were more frequent in the combination arm such as sensory neuropathy (21% vs. 0), fatigue (9% vs. 3%), and neutropenia (68% vs. 11%), as well as death related to toxicity especially in those with ≥ grade 2 liver dysfunction (3% vs. 1%). This study did not incorporate a crossover design from monotherapy capecitabine to ixabepilone, limiting interpretation of the optimal use of combination compared to sequential single-agent therapy.

In a larger confirmatory phase III study (BMS 048) using identical comparison arms of ixabepilone/capecitabine versus capecitabine, in 1,221 women with MBC previously treated with anthracyclines and taxanes but not necessarily resistant to them (about 25% and 74% of patients in both arms respectively received prior anthracyclines and taxanes) there were increased response rates (43% vs. 29%; p < .0001) and PFS (6.2 months vs. 4.2 months, HR 0.79; p = .0005) in the ixabepilone/capecitabine arm, but no significant difference in OS (16.4 months vs. 15.6 months, HR 0.90; p = .1162), although on adjusting for prognostic factors (i.e., performance status, age, number of organ sites, visceral disease, and ER status), an OS benefit was observed (HR 0.85; p = .0231) (163a). Of note, nearly a quarter of those in the ixabepilone-containing arm experienced grade 3 and 4 reversible peripheral neuropathy. The patients in BMS 046 all met strict resistance criteria in the pretreatment phase, whereas only half of the population in BMS 048 met the resistance criteria stipulated in BMS 046. A preplanned subset analysis of patients with TNBC suggested activity of this combination for this subgroup in terms of PFS (164). The data suggest a clinical benefit associated with addition of ixabepilone to capecitabine in TNBCs that had progressed after prior anthracycline and a taxane therapy as outlined below in the TNBC section. The combination of ixabepilone and capecitabine appears moderately well-tolerated with minimal overlapping toxicities. However, ixabepilone and its combinations are best reserved for patients with aggressive disease and limited treatment options.

However, in the previously described CALGB 40502/NCCTG N063H trial, the ixabepilone arm was closed early after the first interim analysis when the comparison of ixabepilone to paclitaxel crossed the futility boundary (89).

Eribulin

Eribulin mesylate is a structurally simplified, synthetic analog of halichondrin B, derived from the marine sponge *Halichondria okadai*. It is a nontaxane microtubule inhibitor with a unique end-poisoning mechanism by binding to the microtubule ends or inducing tubulin aggregates, which compete with soluble tubulin for addition to the growing ends of the microtubule (165). Specifically, eribulin sequesters alpha and beta tubulin into nonfunctional aggregates, causing a decreased ability for polymerization, an irreversible mitotic block, and cell cycle arrest at the G2/M phase with resulting apoptosis (166).

A phase III open-label Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389 (EMBRACE) trial randomized 762 women with locally recurrent or metastatic breast cancer in a 2:1 fashion to eribulin mesilate (1~4 mg/m^2 on days 1 and 8 of a 21-day cycle) or treatment of physician's choice (TPC) (167). Approximately 96% on the TPC arm received chemotherapy including vinorelbine (25%), gemcitabine (19%), capecitabine (18%), taxanes (15%), anthracyclines (10%), and other chemotherapies (10%) representing practical clinical decisions at that time (2006–2008), with only 4% receiving hormonal therapy. Nine patients received hormonal therapy and none received biologic therapy or best supportive care only. Patients had received two to five previous lines of chemotherapy (≥2 for advanced disease), including an anthracycline and a taxane, unless contraindicated. A median of four chemotherapy regimens were administered in both arms, 16% were HER-positive, about 25% were triple-negative and 50% had more than two organs involved. The primary end point median survival was significantly longer for eribulin compared to TPC (13.1 months vs. 10.6 months, HR 0.81; p = .041) and so was objective response rates (12% vs. 5%; p = .002). However, eribulin was not significantly different from TPC for median PFS (3.7 months vs. 2.2 months, HR 0.87; p = .137). The most common AEs in both groups for all grades were fatigue or asthenia (270 [54%] of 503 patients on eribulin and 98 [40%] of 247 patients on TPC), neutropenia (260 [52%] patients receiving eribulin and 73 [30%] of those on TPC), and nausea (174 [35%] of patients on eribulin and 70 [28%] of those on TPC). Peripheral neuropathy was the most common AE (35%, grade 3/4 approximately 8%) which led to discontinuation of eribulin in 5% of patients. A predefined exploratory subgroup analysis also demonstrated significant improvement in favor of eribulin for estrogen receptor, progesterone receptor, HER2, triple-negativity, number of organs involved, sites of disease, and prior capecitabine therapy (168). EMBRACE has been the only phase III study in MBC to define OS as the primary end point and meet it with a clear 3 month survival benefit. Furthermore, no study in MBC has included such a heavily pretreated population. The results of this study led to the FDA regulatory approval of eribulin in 2010 as third-line treatment of MBC after anthracycline and taxane failure in the adjuvant or metastatic setting, and at least two prior lines of metastatic chemotherapy regimens. Eribulin is a CYP3A4 substrate, and although phase II trials prohibited use of drugs metabolized by CYP3A4 and anticoagulant therapy, details of the EMBRACE study regarding use of CYP3A inhibitors were not described. Results are being awaited for a phase III E301 study for MBC in which eribulin

is being compared to capecitabine as second-line therapy, the primary objectives being to assess OS and PFS (169).

Platinums

Cisplatin and carboplatin have limited activity as single agents in MBC treatment. However, they have been combined with many different cytotoxics in the first- and second-line setting with some success. In the first-line setting, platinum agents with taxanes or vinorelbine have achieved RRs of up to 60% (170). In pretreated MBC patients, platinums with taxanes, vinorelbine or gemcitabine have yielded RRs of 40% to 50%. Cisplatin has demonstrable activity as a single agent as first-line therapy in MBC (171). The Translational Breast Cancer Research Consortium recently reported on encouraging preliminary results of trial TBCRC 009 (NCT00483223) with single-agent carboplatin and cisplatin in patients with TNBC and no more than one prior chemotherapy regimens for MBC. The role of platinum agents along or in combination with inhibitors of the enzyme poly ADP ribose polymerase (PARP) is an area of active research, especially among TNBC patients who also carry germline mutations in *BRCA1* or *BRCA2*.

Newer Agents

Several newer agents are in development and undergoing early phase clinical trial testing. Novel taxoids such as larotaxel, cabazitaxel and tesetaxel which may have activity in taxane resistant patients are undergoing phase II trials (172–175). Etirinotecan pegol (NKTR-102) is a topoisomerase I inhibitor-polymer conjugate that has shown activity in anthracycline-taxane and anthracycline-taxane plus capecitabine pretreated MBC including those with triple-negative disease (176). Liposomal cisplatin is a nontoxic form of cisplatin and its combination with vinorelbine in the first-line treatment of MBC resulted in a 53% response rate, a clinical benefit response of 90% and TTP of 8 months (177). Side effects included nausea and vomiting (14%), anemia (11%), and neutropenia (44%), but there were no neuropathy or nephrotoxicity events.

Summary on Chemotherapy Options (Single Agent and Combinations)

Sequential single agents may have lower response rates but also less toxicity and no compromise on OS when compared to combination chemotherapy. They are most appropriate for frail or elderly patients, or those with more indolent tumors. Anthracyclines and taxanes are the most active agents and are usually utilized alternately as first or second-line regimens for metastatic disease, depending on previous chemotherapy exposure in the adjuvant setting. However, with the wider use of anthracyclines and taxanes in the adjuvant and neoadjuvant setting, alternative agents need to be sought. Other active agents which are used include vinorelbine, gemcitabine, eribulin, and ixabepilone. Oral capecitabine is also a convenient oral formulation with a tolerable side effect profile. However regional differences in fluoropyrimidine tolerability exist, with more toxicities reported in the U.S. compared to Asian and European populations (178). This could be due to a possibly higher dietary folate intake in the U.S. or intrinsic genetic polymorphisms.

Combination therapy with its attendant higher response rates and better TTP may be more appropriate for symptomatic patients or for those with a visceral crisis, but at the cost of greater toxicity. In addition, its higher response rates do not translate into a superior survival outcome. A further disadvantage is that upon tumor progression, the disease is presumed to be resistant to both agents thus reducing the number of active agents available for use subsequently.

Although regulatory approvals consider OS as the gold standard, few phase III trials have the ability to detect OS differences especially in the first-line setting. Crossovers or subsequent therapies with newer more effective agents may attenuate OS differences. Few studies in the past have incorporated a crossover plan in their analysis and those that did failed to show an improvement in TTP or OS.

The recommendation is to use combination therapy for more aggressive disease and bulky visceral involvement, especially for those patients with a good performance status and minimal comorbidities. None of the combination regimens are established as standard first-line agents. Anthracyclines and taxanes-based combinations are the most commonly used although the former is limited by cumulative cardiotoxicity depending on prior exposure. Common anthracycline regimens include doxorubicin/cyclophosphamide, epirubicin/cyclophosphamide, doxorubicin/cyclophosphamide/fluorouracil, or epirubicin/cyclophosphamide/fluorouracil. Anthracycline/taxane combinations are not often used due to their significant hematologic toxicity and the lack of survival advantage over sequential single agents and other drug combinations. These other active combinations include the more commonly used anthracycline combinations, platinum/taxane, platinum/gemcitabine and platinum/vinorelbine regimens, cyclophosphamide/methotrexate/5-FU or others like capecitabine/docetaxel, gemcitabine/paclitaxel and ixabepilone/capecitabine which are less commonly utilized.

TRIPLE-NEGATIVE DISEASE

TNBC accounts for 6% to 28% of breast cancers (179). It possesses distinct epidemiological, histological, and clinical behavior features. Its prevalence is significantly higher among premenopausal women of African American or Hispanic descent, occurs at a younger age, and has a poorer survival when compared to other breast cancer subtypes (180,181). The risk factors are younger age (<26 years) at first full-term pregnancy, higher parity, absence of (or shorter duration of) breast-feeding, lower number of breast-fed children, younger age at menarche, use of medications to suppress lactation and high BMI (181,182). TNBCs are known to have an early recurrence peak within the first 3 years after diagnosis followed by a sharp decrease in subsequent years with virtually no relapse after 8 years (183). In a retrospective analysis, a greater proportion of TNBCs had visceral metastases as the site of first recurrence within the first 5 years compared to other subtypes of breast cancer (HR 4.0, 95% CI, 2.7–5.9; $p < .0001$) (184). However with longer follow-up, the subset of patients with ER-positive breast cancer (proliferative subset) had the same incidence of visceral metastases as TNBC (185). It seems to have a predilection for the lung and brain and less for the bone, which may be due to its propensity for hematogenous rather than lymphatic spread (186).

Triple-negative metastatic disease has a shorter median survival of 7 to 13 months with a limited duration of response to successive lines of chemotherapy of about 12 weeks to first-line, 9 weeks to second-line, and 4 weeks to third-line therapy (187). The poor prognosis of TNBC is independent of tumor grade, lymph node status, tumor size, and treatment (188). The majority of TNBCs are invasive ductal carcinomas; the less common histological subtypes include medullary, adenoid cystic, and metaplastic cancers. TNBCs can include other molecular subtypes that are difficult to characterize using standard markers available in clinical practice, such as claudin-low tumors, the interferon-rich, and the normal-breast-like subgroup (189). The risks for

TNBCs as a whole cannot be generalized to certain subtypes which may have inherently more favorable outcomes such as adenoid cystic or medullary carcinomas (190,191).

The definition of TNBC hinges on IHC-based negativity of estrogen, progesterone, and HER2 receptors. About 65% to 85% of TNBCs are of the basal-like subtype, the remaining of which includes a subset of poorly differentiated, highly proliferative breast cancer phenotype. Some 23% of basal-like cancers do not have the triple-negative (TN) phenotype, while about 30% of TNBC lack a basal phenotype (192). Basal-like breast cancers have no standard panel of IHC markers limiting their applicability in clinical practice. While IHC markers like ER/PR/HER2-negativity, presence of CK5/6, CK14, CK17, EGFR, and C-kit cave been used to try to identify the basal subtype, the reconciliation between phenotypes described based on microarray studies and those able to be defined using standard IHC assays in clinic remain suboptimal (193). Consequently, while most TNBCs appear to have a worse clinical outcome, despite greater initial responsiveness to chemotherapy, it remains not possible in most cases in usual clinical practice to identify the small subset of patients who on occasion present with a more indolent course.

Platinums

Treatment of TNBC is challenging due to the lack of standardized therapies. Approximately 70% to 90% of *BRCA1*-associated tumors have a TN and/or basal phenotype (194). In vitro studies of *BRCA1*-associated breast cancers have shown sensitivity to mitomycin-C (195), and platinum drugs (196); agents that cause interstrand cross-links, etoposide and bleomycin that cause double-strand breaks, whereas resistance to mitotic-spindle poisons such as taxanes and vinca alkaloids have been reported (197).

Small studies that did not select patients for triple-negativity showed single-agent platinum activity of 42% to 54% in MBC, but response rates were even lower at 0% to 9% for those who were pretreated (198). Platinum agents bind directly to DNA, forming DNA adducts leading to inter- and intra-strand crosslinks and resulting double-strand breaks (199). The *BRCA1* gene maintains genomic stability by promoting repair of these DNA double-strand breaks, particularly at the arrested replications forks (200). In preclinical models, cells with *BRCA1* mutations are unable to repair platinum-induced DNA damage and are thus postulated to be more susceptible to these agents (201). Two percent of breast cancers may be *BRCA1*-positive, whereas it may be as high as 10% with TNBCs (202). In addition to decreased *BRCA1* expression conferring subsets of TNBCs with more sensitivity to platinum agents, epigenetic alterations in *BRCA1* may also demonstrate this increased sensitivity (203).

The activity of platinum agents in *BRCA1*-mutant TNBCs is best observed in the neoadjuvant setting. High pathologic complete response rates of 70% to 90% have been observed when using cisplatin monotherapy for *BRCA1* mutants in several small neoadjuvant studies (204–206). A retrospective analysis of the clinical outcomes in Korean patients with metastatic breast cancer who received platinum-containing chemotherapy as first- or second-line treatment, focusing on the TN phenotype, found that the ORR of the TN phenotype was 38.8% and the disease control rate was 67.2%, which did not show statistical difference from those of other phenotypes (207). However, TN group showed shorter OS after platinum-containing chemotherapy (p = .005) than other phenotypes of breast cancers. Furthermore, OS from the relapse of TN group was poorer than others (p = .002).

A smaller French retrospective analysis (n = 143) of MBC patients treated with platinum-based chemotherapy reported a higher response rate for the TN subgroup versus the non-TNBC group (33.3% vs. 22%), but there was no difference in PFS and OS (208). A small retrospective study (n = 36) specifically examining cisplatin/gemcitabine chemotherapy in MBC (17 TNBC, 19 non-TNBC) reported a higher median PFS (5.3 months vs. 1.7 months; p = .058) for the TN subgroup, with a reduction of 47% in rate of progression for the TN compared to the non-TN patients (HR 0.53; p = .071) after adjusting for age, race, and menopause status (209).

A small trial (n = 15) using cisplatin in MBC patients who had received between zero and two chemotherapy regimens including prior anthracycline exposure, reported impressive response rates of 72% (CR 46%, PR 26%) (210). Sirohi et al. examined patients from a prospectively maintained breast unit database treated with platinum-based chemotherapy in the neoadjuvant, adjuvant and metastatic setting (211). . The regimen administered in the advanced setting was mitomycin/vinblastine/cisplatin or carboplatin. The ORR (CR + PR) was higher for TN metastatic patients (41% [14 of 34, 95% CI, 25%–58%] versus 31% (38 of 121, 95% CI, 23%–40%; p = .3), the median PFS was significantly longer (6 months vs. 4 months; p = .05) although OS was not significantly different (11 months vs. 7 months; p = .1) (211). However, the superior RR was not confirmed in another retrospective study consisting of a TN MBC patient population receiving platinum/taxane chemotherapy, although the time to death and OS were similarly poorer (212).

Currently, there is no clear indication as to whether platinums demonstrate superiority compared to other chemotherapeutic agents in an unselected TN population. There is insufficient data to recommend its use over standard regimens in early lines of chemotherapy, except perhaps in *BRCA* mutation carriers. A U.K.-driven phase III TNBC trial for metastatic TNBCs comparing carboplatin versus docetaxel with crossover at progression should shed further light on the efficacy of platinums in this breast cancer subtype (NCT00532727). Potential biomarkers have been identified but have not gained clinical utility. A nonrandomized phase II study designed to evaluate carboplatin or ciplatin as first- or second-line therapy in metastatic TNBC and to also study the expression of p63/p73 as biomarkers of response has been done (213). Preliminary results have shown an overall RR rate of 30.2% including four complete responses. The median PFS was about 3 months and about a third remained on study for more than 6 mos.

Taxanes

The efficacy of taxanes in TNBCs has been demonstrated in the adjuvant setting in both retrospective and prospective trials (214,215). Hence, there is much interest in their specific use in the metastatic setting. In an exploratory retrospective subset analysis of the CALGB 9342 trial which tested three doses of paclitaxel 170 mg/m^2, 210 mg/m^2 and 250 mg/m^2 in MBC, the triple-negative tumors (n = 44) were not found to differ significantly in terms of RRs and TTF from other tumor subtypes (n = 92), although the OS was significantly reduced (8.7 months vs. 12.9 months; p = .008) (216). There have been some data suggesting resistance of *BRCA1* mutation carriers to docetaxel such as a retrospective study of 175 patients with MBC treated with docetaxel-based regimens and demonstrating 19 patients with primary resistance, of which five were *BRCA1* mutation carriers and were TN (217). A U.K.-based *BRCA*-trial similar to the TN trial comparing first-line carboplatin and docetaxel in MBC patients who are *BRCA* carriers is also underway and will be able to answer the question of whether *BRCA* mutations confer resistance to docetaxel.

Nab-paclitaxel may represent a more effective TN treatment option. Paclitaxel-albumin-bound particles were demonstrated to have a higher efficacy, less toxicity, shorter infusion schedules, and higher intracellular drug delivery across endothelial cells compared to paclitaxel (85). Caveolin-1 encodes a protein which is a component of the caveolar membranes responsible for transcytosis of nab-paclitaxel into tumor cells. Caveolin-1 was strongly associated with high grade tumors, ER-negativity, and expression of basal cytokeratins, p63 and p-cadherin. CAV1 and CAV2 expression is also significantly associated with the basal-like phenotype (218). However, the evidence comparing it against paclitaxel remain scarce.

Antitubulin Agents

Ixabepilone is a novel class of agents that bind to β-tubulin, promoting microtubule stabilization, and causing cell cycle arrest in the G2/M phase and apoptosis (219). It can overcome or circumvent primary mechanisms of resistance to taxanes such as MDR P-glycoprotein or mutations in the class III isoform of β-tubulin (220). A pooled analysis (n = 1,973) of two large phase III clinical trials comparing ixabepilone/capecitabine with capecitabine in patients with MBC either resistant to (BMS 046) or pretreated with anthracyclines and taxanes (BMS 048) demonstrated increases in PFS in the combination compared to capecitabine arm (4.2 months vs. 1.7 months) and ORR (31% vs. 15%), with a trend to improved OS (10.3 months vs. 9 months) in the TN population (n = 443) (221). Although the ORR and PFS for the capecitabine arm in the overall population was 25% and 4.2 months respectively, the TNBC subgroup showed only a 15% ORR and 1.7 months PFS in those receiving capecitabine only.

EGFR Inhibitors

Currently, studies are focusing on the role of cytotoxics in combination with targeted therapies. TNBCs and basal-like breast cancers express EGFR in up to 72%, although activating mutations are rare (222). EGFR monoclonal antibody inhibitors have been explored given the relatively high expression of EGFR in this setting but have yet to gain a foothold in the therapeutic armamentarium.

Cetuximab has low activity as a single agent and shows only modest efficacy with chemotherapy. Cetuximab/carboplatin versus cetuximab alone has shown objective response rates of 18% versus 6%, and clinical benefit response rates (partial response or stable disease for ≥6 months) of 27% versus 10% in the Translational Breast Cancer Research Consortium (TBCRC) 001 multicenter randomized phase II study (n = 102) (223). The combination was deemed worthy of further evaluation. However notably, this was essentially a comparison of an anti-EGFR drug with or without carboplatin. The treatment effects could have been a reflection of the lack of a platinum rather than the presence of cetuximab per se.

A larger phase II study BALI-1 (n = 173) compared cisplatin/cetuximab versus cisplatin with conversion to cetuximab/cisplatin upon progression in TN MBCs who received less than one prior chemotherapy regimen (224). The best ORR was 20% (95% CI, 13.1%–28.5%; p = .5 for testing ORR >20%), with cetuximab/cisplatin and 10.3% (95% CI, 3.9%–21.2%), with cisplatin (OR 2.126, 95% CI, 0.809–5.591; p = .11). The median PFS was improved with the addition of cetuximab (3.7 months vs. 1.5 months, HR 0.675; p = .032), although it did not meet prespecified end points for significance. Grade 3 and 4 AEs occurring in more than 5% of patients in either arm included acne-like rash, neutropenia, fatigue, and dyspnea. In a subset of the U.S. Oncology 225200 trial, carboplatin/irinotecan and/or cetuximab (n = 78) showed a higher ORR (49% vs. 30%) but minimal difference in PFS (5.1 months vs. 4.7 months) with the cetuximab-containing arm (225).

The combination of ixabepilone with or without cetuximab as first-line treatment for TN locally advanced or MBC is currently being investigated in a randomized phase II trial (NCT00633464). Other EGFR inhibitors are also being evaluated in TNBCs such as panitumumab (NCT00894504) and erlotinib (NCT00739063), the latter trial being terminated because of poor accrual.

The evidence for EGFR playing a crucial role in TNBC oncogenesis has not been strong so far. Perhaps multiple downstream and parallel signaling pathways after EGFR activation may require multitargeted therapeutics. Samples from patients enrolled in two trials outlined above are currently being used to evaluate biomarkers of response (223,225,226).

PARP Inhibitors

PARPs constitute a large family of 18 proteins, in which PARP1, the founding member, and PARP2 activity are involved in single-stranded DNA base excision repair and replication fork repair by homologous recombination (227,228). PARP1 is also involved in histone modification and chromatin remodeling, allowing access of DNA repair proteins to the necessary sites (229). DNA repair is done via homologous recombination in normal cells, a process in which *BRCA* is integral. Cells that are deficient in *BRCA1* or *BRCA2* are more dependent on PARP1 to maintain genomic stability and hence the inhibition of PARP is potentially lethal.

PARP inhibition is likely to be highly specific for tumors that are deficient in *BRCA1* or *BRCA2* (230,231), while adding chemotherapy to PARP inhibitors may improve the efficacy in non-*BRCA* forms of TNBCs (232). In a proof-of-concept clinical trial, olaparib was shown to be effective in *BRCA1* and *BRCA2* mutation carriers, with almost doubling of the ORR at the oral 400 mg bid compared to the 100 mg bid dose (41% vs. 22%), prolongation of the median PFS (5.7 months vs. 3.8 months) with well-tolerated side effects of nausea, vomiting, fatigue, and anemia, although 30% required dose reductions or delays (233). Olaparib 200 mg bid was reported to be too myelosuppressive when used together with weekly paclitaxel 90 mg/m^2 for 3 out of 4 weeks despite growth factor support (234).

Iniparib is not a bona fide PARP inhibitor (235). It has been proposed to act via nonselective modification of various proteins by nonspecific adducts which alters stability, activity, and/or localization of the proteins resulting in a cellular insult capable of inducing various cellular responses including apoptosis, stress, cell-cycle perturbation, or DNA damage (235). An open-label phase II study (n = 123) compared carboplatin (C) AUC2 on days 1 and 8, and gemcitabine (G) 1,000 mg/m^2 on days 1 and 8, with or without iniparib (I) 5.6 mg/kg on days 1, 4, 8, 11 administered in 21-day cycles, in patients with metastatic TNBC who had received not more than two prior lines of treatment for metastatic disease (236). They found that the primary objective clinical benefit response (CR/PR/SD for ≥6 months) improved from 34% to 56% (p = .01) (236). Additional end points also improved such as overall response (52% vs. 32%; p = .02), median PFS (5.9 months vs. 3.6 months, HR 0.59; p = .01) and OS (12.3 months vs. 7.7 months, HR 0.57; p = .01). There was no significant difference in side effects such as neutropenia, thrombocytopenia, anemia, fatigue, and increased alanine aminotransferase between the groups. However, this was not confirmed in a larger phase III study (n = 519) with a similar TN patient population which did not meet the prespecified criteria for the co-primary end points of PFS (HR 0.79; p = .027) and OS (HR 0.88;

p = .28) (237). Some 152 of 258 GC pts (59%) crossed over to receive GCI following disease progression. Exploratory analysis showed that PFS and OS benefit was restricted to the prespecified stratification subgroup receiving the treatment in the second- and third-line setting compared to the first-line setting. This could be hypothesized to be due to the imbalance in baseline characteristics, increased disease severity for the first-line therapy subgroup, and exposure to taxanes in the first-line setting which could have caused increased susceptibility to DNA damaging agents thereafter. In multivariate analysis, the difference in treatment effects between the two exploratory first-line versus second-line and third-line subgroups were less pronounced. The toxicity profile was similar to that in the phase II study. We have a relatively limited knowledge of the mechanism of action of iniparib currently which compounds the issue.

The oral PARP1 inhibitor veliparib (ABT-888) is another drug that has shown some activity in *BRCA1* and *BRCA2* mutation carriers when given in combination with temozolomide, the main toxicity observed being thrombocytopenia managed by dose reduction (238). The ORR observed was 37.5%, the clinical benefit rate was 62.5% and the median PFS was 5.5 months in *BRCA*-carriers (as compared to 1.8 months in noncarriers).

Although PARP inhibitors have demonstrated impressive results in the treatment of *BRCA*-associated breast cancers, its effectiveness in the population of TNBCs without *BRCA* mutations is still lacking. An intriguing issue is whether PARP inhibitors are also beneficial in other non-triple negative subtypes. Genomic instability and defects in DNA repair mechanisms are not only restricted to TNBCs (239). A higher PARP expression has been detected in non-TN subtypes and linked to increased pathologic complete response rates to neoadjuvant taxane-anthracyclines regimens (240). Homologous DNA recombination impairment caused by PTEN deficiency has also been reported to cause increased susceptibility to PARP inhibition both *in vitro* and *in vivo* (241), and PTEN mutation or loss is present in about 50% of breast cancers (242). PARP inhibitors lack robust biomarkers to guide their usage apart from *BRCA* mutations. We have yet to refine their use with optimal chemotherapy regimens. More translational work will need to be done in this area to evaluate their clinical utility.

Src Inhibitors

Expression of the tyrosine kinase c-Src is frequently increased in breast cancer and promotes cellular motility and invasion (243). Current data on single-agent dasatinib, a dual abl/Src kinase inhibitor reports poor ORR 4.7% in heavily pretreated TNBCs, with a median PFS of 8.3 weeks (95% CI, 7.3–15.3) (244).

Androgen Receptor Targets

A subset of ER-negative tumors with paradoxical expression of genes known to be either direct targets of ER, responsive to estrogen, or typically expressed in ER-positive breast cancers was identified (245). *In vitro* studies demonstrated a proliferative response to androgens in an androgen receptor (AR) dependent and ER-independent manner (245). This particular subset of breast cancers could potentially be targeted by inhibitors of the androgen signaling pathway. In clinical practice, about 10% of TNBC patients have AR-positivity, which would represent about 2% of the entire breast cancer cohort assuming a TNBC rate of 20% (246). Hence, this drug would potentially cater only to a very small group of patients. A phase II feasibility study is currently underway (NCT00468715) evaluating the utility of bicalutamide, a nonsteroidal anti-androgen, in ER/PR-negative and AR-positive MBC patients.

Summary on Treatment in Triple-Negative Disease

Chemotherapy remains the backbone of treatment for TNBCs due to the lack of specific targeted therapies. In the St. Gallen 2011 and NCCN (version 3.2012) guidelines, there were no specific recommendations on the type of agents to use in unselected TNBCs (247). There are also no specific drug recommendations in this subpopulation by ASCO or ESMO to date. The profile of disease aggressiveness, young age, visceral metastases, and TN status seems to favor combination over single-agent chemotherapy. Anthracyclines (i.e., doxorubicin, epirubicin, and PLD) and taxanes (i.e., paclitaxel, docetaxel, and albumin-bound paclitaxel) remain important agents in this setting as in ER-positive breast cancers. However, in patients with visceral relapse within one year after anthracycline/taxane chemotherapy, other alternative agents should be used. These include the antimetabolites (i.e., capecitabine and gemcitabine) and microtubule inhibitors and/or stabilizers (i.e., vinorelbine, eribulin, and ixabepilone). Combination regimens that have activity include carboplatin/gemcitabine, platinum/vinorelbine, ixabepilone/capecitabine, capecitabine/vinorelbine, paclitaxel/gemcitabine, and docetaxel/capecitabine. As there is no standard first-line agent or regimen, therapy should be individualized for each patient and enrollment into clinical trials is encouraged. Although they demonstrate a better response to chemotherapy compared to ER-positive subtypes, the ultimate prognosis remains poor. Research into other modalities of treatment involving various tyrosine kinase inhibitors and inhibitors of FGFR receptors, mTOR, PI3K and MEK are ongoing.

CHEMOTHERAPY AFTER LOCAL THERAPY IN OLIGOMETASTATIC DISEASE

Oligometastatic disease is characterized by solitary or a few detectable metastatic lesions limited to a single organ such as the lung, liver, or bone. This population of more favorable stage IV disease is estimated to be present in about 1% to 10% of newly diagnosed MBC patients (248). For such individuals, combined local and systemic therapies with surgery, radiotherapy, regional, and systemic chemotherapy may result in long-term survival.

Assessment of the suitability of such treatment modalities depends on the biology of the tumor such as its disease-free interval, its extent of disease involvement, the feasibility of complete resection of the metastases, the performance status of the patient and the potential risks involved. Patients being considered for these more aggressive local treatment options should undergo a thorough restaging evaluation.

Local treatment options in isolated breast cancer metastases most commonly refer to resection, although other less common options such as radiotherapy, radiofrequency ablation or cryotherapy have been used. Resection of isolated metastases can also aid in diagnosing a possible new second primary or re-assessing the ER or cerbB2 status.

Isolated lung metastases occur in 10% to 20% of MBCs (249). The International Registry of Lung Metastases which has the largest dataset reports that in 467 breast cancer patients, complete lung metastasectomy was possible in 84% and led to a median survival of 37 months (5-year OS 38%; 10-year OS 22%) (250). Good prognostic factors included a disease-free interval of more than 36 months, single metastases and completeness of resection.

Approximately 5% of patients have metastases confined to the liver with no extrahepatic disease (251). The resection of liver metastases in breast cancer is much less recognized, with median survival ranging from 14.5 months to 63 months and 5-year OS 14% to 61% (252). In a recent systematic review of 19 studies consisting of 553 patients who had undergone hepatectomy for liver metastases, the median survival was 40 months with a 5-year survival of 40% (253). Other alternative local therapies such as radiofrequency ablation or transarterial chemoembolization have only limited data (254,255).

There is a very limited role for resection of bony sites, and this distribution is usually associated with an indolent course and good response to systemic agents such as endocrine therapy if ER-positive. The first treatment choice for bone metastases which are not at risk of a fracture is systemic therapy.

Many patients in various studies have been treated with some form of systemic therapy either prior to or after local therapy, and there is some evidence albeit limited that this results in delayed relapse or improved survival (248,256,257). It is not clear if these highly selected patients had a better tumor biology and would have had a good outcome either way. The largest dataset for chemotherapy after local treatment consisting of either surgery or irradiation for single metastatic disease comes from the MD Anderson Cancer Center where a series of three doxorubicin-based chemotherapy trials (n = 259) and a docetaxel-based trial (n = 26) comprising of 285 stage IV NED patients altogether were evaluated retrospectively (248). For the doxorubicin-based trials, the median follow-up was 87 months and the 20-year DFS and OS reached 26% for both which demonstrated that long-term survival was achievable in selected cases. The first isolated recurrence was locoregional in 80% of cases, but of the 53 patients that had an initial distant site of recurrence 23% achieved long-term disease control. Median follow-up for the docetaxel trial was 44 months and the 5-year DFS and OS were 34% and 59% respectively. At recurrence, 54% had distant site involvement and this subgroup has less favorable results with the six deaths at the last follow-up all involving distant recurrences. The historical control group utilized in this study showed a 5-year DFS and OS rate of 7% and 36% respectively, although it had its shortcomings such as a higher number of ER-unknown status patients and a lack of c-erbB2 testing.

The overall data suggest that after local treatment of limited locally recurrent or metastatic disease, followed by "adjuvant" systemic treatment, survival time can surpass the normally expected median survival of 2 to 3 years for MBC. However, available data are mostly retrospective with relatively small patient numbers, the reported data often refer to a highly select group of patients with favorable prognostic factors and no randomized trials have been done comparing them to surgically untreated patients. Patients who are suitable for this therapeutic strategy may only represent 1% to 3% of the total MBC population. Hence clinical trials with adequate statistical power are difficult to achieve but much needed supporting the rationale of a more aggressive multidisciplinary approach for these patients. The necessity of chemotherapy after isolated locoregional recurrence has been treated by surgery or radiotherapy is currently being investigated in a joint study by the International Breast Cancer Study Group (IBCSG), the National Surgical Adjuvant Breast and Bowel Project (NSABP), and the Breast International Group (BIG) (258).

Bevacizumab

Bevacizumab is a recombinant humanized monoclonal antibody derived by incorporating ~7% murine VEGF-binding sequences into a human IgG framework (259). It inhibits VEGF-induced endothelial cell proliferation and migration resulting in slower tumor growth. It also decreases interstitial fluid pressure in tumors, improving drug delivery and penetration. Its accelerated FDA approval for breast cancer in 2008 was supported by the observed PFS benefit demonstrated in the interim analysis of the E2100 trial comparing first-line bevacizumab/paclitaxel versus paclitaxel (260). However, there was a requirement for verification of bevacizumab effect on PFS and OS from other trials like Avastin and Docetaxel (AVADO) and Regimens in Bevacizumab for Breast Oncology (RIBBOn)-1.

The pivotal phase III E2100 trial (n = 722) enrolled locally recurrent or MBC patients, majority of which had HER2-negative disease (96%), to receive paclitaxel 90 mg/m^2 weekly on days 1, 8, and 15 +/– bevacizumab 10 mg/kg on days 1 and 15 in 4-week cycles until PD (260). Those who had HER2-positive disease were required to have received trastuzumab. Patients who had received taxane-based adjuvant therapy (about 17% and 15% in the combination and taxane-only arms respectively) were required to have had a disease-free interval of at least 12 months after completion of taxane therapy. There was a significantly longer PFS in the combination arm (11.8 months vs. 5.9 months, HR 0.60; $p < .001$), and an increased ORR (36.9% vs. 21.2%; $p < .001$). The OS rate, however, was similar in the two arms (median 26.7 vs. 25.2 months, HR 0.88; $p = .16$). Stratification factors included disease-free interval (≤24 months vs. >24 months), number of metastatic sites (<3 vs. ≥3), previous adjuvant chemotherapy (yes vs. no), and ER status (positive vs. negative vs. unknown). A benefit in PFS was seen irrespective of the predefined subgroups. The HR for PFS in the TN subgroup was 0.53 which was comparable to that of the overall study population which was 0.6. Notably, those negative for ER and PR (majority of whom were HER2-negative, <2% in each arm were HER2-positive) had a PFS of only 4.6 months on paclitaxel alone as compared to 8 months for those who were ER/PR-positive which reflects the intrinsic poor prognosis of ER-negative disease. The addition of bevacizumab had little effect on the frequency or severity of expected paclitaxel-related toxic effects. Grade 3 or 4 neuropathy (23.5% vs. 17.7%; $p = .05$), hypertension (14.8% vs. 0; $p < .001$), proteinuria (3.5% vs. 0; $p < .001$), headache (2.2% vs. 0%; $p < .001$), cerebrovascular ischemia (1.9% vs. 0%; $p = .02$), infection (9.3% vs. 2.9%; $p < .001$), and fatigue (9.1% vs. 4.9%; $p = .04$) were more frequent in the combination group. The increased incidence of peripheral sensory neuropathy in the combination arm was reflective of the longer duration and increased cumulative dose of paclitaxel. A criticism was the lack of an independent radiological review and hence 649 (89.9%) of the patients had at least one image submitted for review after the study was completed upon the request of the FDA (261). The results were confirmed with a 52% lower risk of progression or death, and an improvement in PFS (11.3 months vs. 5.8 months) which was similar to that in the study. There were no significant differences in QOL between the groups.

The results of the AVADO and RIBBOn-1 trials confirmed those of E2100, albeit at a lower magnitude. The AVADO trial (n = 736) was a three-armed placebo-controlled study testing docetaxel 100 mg/m^2 for nine 3-weekly cycles with or without bevacizumab at two doses of 7.5 mg/kg or 15 mg/kg every 3 weeks (262). Those exposed to adjuvant taxanes (bevacizumab 15 mg/kg 17%, bevacizumab 7.5 mg/kg 15%, placebo 15%) had to have a lapse of at least 12 months before. At a median follow-up of 25 months, the median PFS (primary end point) for bevacizumab 7.5 mg/kg versus placebo was 9 months versus 8.1 months respectively (HR 0.8; $p = .045$), and for bevacizumab 15 mg/mg versus placebo arms, a significant difference of 10 months versus 8.1 months

(HR 0.67; $p < .001$) in stratified analysis. Response rates were also higher in the bevacizumb-containing arms compared to placebo (placebo 46%, bevacizumab 7.5 mg/kg 55% [$p = .07$]; bevacizumab 15 mg/kg 64% [$p < .001$]). The trial was not powered to detect a survival difference and because crossover to bevacizumab upon progression was allowed, it is unlikely that a survival benefit will be seen. The trial was also not designed to detect a statistically significant difference between the two bevacizumab-containing arms. The combination of bevacizumab with docetaxel had no major impact on the toxicity profile of docetaxel. Most AEs occurred at similar incidence in both bevacizumab arms, although epistaxis, hypertension, and proteinuria were more frequent in the bevacizumab 15 mg/kg arm. The double-blinded placebo-controlled nature of the AVADO study was likely to have reduced reporting bias compared to the E2100 study which had higher incidences of hypertension and proteinuria. Patients treated in the combination arm reported better QOL scores. A subanalysis of those ≥65 years old revealed a similar magnitude of benefit to the overall study population and bevacizumab was found to be well-tolerated (263). Notably, the ORR in the docetaxel arm (46%) was almost double that in the paclitaxel arm (21%) of E2100 and bevacizumab benefit may have been lessened in the presence of a more active agent. Prolonged weekly paclitaxel is tolerated for longer periods compared to 3-weekly docetaxel, leading to discontinuation at 4.9 months for the docetaxel control arm and 5.1 months for the paclitaxel control arm in the E2100 study. For the combination arm, weekly paclitaxel was discontinued at 7.1 months for the E2100 trial and docetaxel was discontinued at 5.1 months and 5.5 months in the lower and higher dose bevacizumab arms of the AVADO study. Hence, in general weekly paclitaxel is easier to administer.

In the RIBBOn-1 trial, chemotherapy agents by physician choice (capecitabine 2,000 mg/m^2 for 14 days, nab-paclitxel 260 mg/m^2, docetaxel 75 mg/m^2 or 100 mg/m^2, or doxorubicin or epirubicin combinations) in combination with bevacizumab or placebo as first-line MBC treatment were evaluated in 1,237 patients randomized in a 2:1 ratio (264). The primary objective median PFS was longer for each bevacizumab combination (capecitabine cohort: increased from 5.7 months to 8.6 months, HR 0.69; $p < .001$, and taxane/anthracycline cohort: increased from 8.0 months to 9.2 months, HR 0.64; $p < .001$), with a superior ORR for the group treated with bevacizumab. There was no significant difference in OS. Approximately 70% of patients received another study treatment after discontinuation of study treatment, with about 50% of patients treated with placebo plus chemotherapy crossing over to the bevacizumab combination therapy at time of first progression.

A meta-analysis of the above three trials in the first-line setting showed a PFS hazard ratio of 0.64 (95%CI 0.57–0.71) and an OS hazard ratio of 0.97 (95%CI 0.86–1.08), with similar outcomes for the TN population (265). Of note, the crossover to bevacizumab-containing regimens on tumor progression may have masked the effect on OS.

An analysis of the known AEs in the E2100, AVADO, and RIBBOn-1 studies found that hypertension ranged from 2.8% to 16% for the bevacizumab-containing arms and 0% to 2% for the placebo arms (266). With the exception of hypertension, bevacizumab-related grade 3–5 adverse effects occurred in <5% of patients (266).

The Phase IV Avastin THErapy for advaNced breAst cancer (ATHENA) trial (n = 2,251) in HER2-negative locally recurrent or MBC or HER2-positive disease progressing after trastuzumab therapy assessed the efficacy and safety of bevacizumab with taxane (68%) or other nonanthracycline chemotherapy according to the physicians' standard of care (267). The most frequent grade ≥3 AE was neutropenia (5.4%). Grade ≥3 AEs previously associated with bevacizumab included hypertension (4.4%), arterial/venous thromboembolism (3.2%), proteinuria (1.7%), and bleeding (1.4%). Median TTP was 9.5 months (95% CI 9.1–9.9). The TTP was more favorable when bevacizumab was combined with taxanes (11 months) compared with nontaxane drugs like capecitabine or vinorelbine (7 months for both). An analysis of those ≥70 years old (median OS 20.3 months, 1-year OS 68%) and in the TN cohort (median OS 18.3 months, 1-year OS 60%) showed that the combination of bevacizumab with first-line chemotherapy was active and feasible (268). An updated analysis (median follow-up 20.1 months; n = 2,264) showed that the median TTP was 9.7 months (95% CI, 9.4–10.1 months), median OS was 25.2 months (95% CI, 24.0–26.3 months), and 1-year survival 72.7% in the overall population in the ATHENA trial (269).

Bevacizumab has also been studied as second-line therapy and beyond. The RIBBOn-2 phase III trial (n = 684) assessed the efficacy and safety of second-line bevacizumab 10 mg/kg every 2 weeks or 15 mg/kg every 3 weeks, in combination with nonanthracycline-based chemotherapy in HER2-negative MBC (270). Patients were randomly assigned 2:1 to chemotherapy (i.e., capecitabine, docetaxel, paclitaxel, nab-paclitaxel, vinorelbine, or gemcitabine) plus bevacizumab or chemotherapy plus placebo; the primary end point being PFS. The PFS was superior with bevacizumab (7.2 months vs. 5.1 months, HR 0.78; $p = .0072$), with an increased ORR (39.5% vs. 29.6%; $p = .0193$), with no statistically significant difference in OS. The safety profile was comparable with other studies. The most common grade 3 AEs related to bevacizumab treatment were hypertension (9.0%) and proteinuria (3.1%), resulting in higher rates of discontinuation in the bevacizumab arm compared with placebo (13.3% vs. 7.2%).

The AVF2119 study examined its role in women with heavily pretreated MBC (271). The subjects were refractory to both an anthracycline and a taxane in either the metastatic or adjuvant settings, and had received at least one, but no more than two, prior chemotherapy regimens for metastatic disease. Some 462 patients received bevacizumab 15 mg/kg every 3 weeks plus capecitabine 2,500 mg/m^2 in two divided doses for 2 of every 3 weeks or capecitabine monotherapy. About 80% in each arm received one to two prior chemotherapy regimens for MBC, and about 26% and 20% were HER2-positive in the bevacizumab-containing and capecitabine only arms respectively. The PFS (primary end point; 4.86 months vs. 4.17 months, HR 0.98; $p = .857$) and OS (15.1 months vs. 14.5 months) were statistically similar, although ORR was significantly higher in the combination arm (19.8% vs. 9.1%; $p = .001$). There were no differences between side effects like diarrhea, hand-foot syndrome, thromboembolic events, or serious bleeds, although hypertension was more common with bevacizumab. The widely accepted explanation for this lack of observed benefit was the more heterogenous patient population and the late disease stage when there would be more numerous and redundant dysregulated angiogenic pathways. It is also possible that capecitabine may have been continued for a longer period on the RIBBOn trials due to the lower dose of capecitabine utilized although we do not have comparative data from the AVF2119g and RIBBOn-2 studies.

Nonetheless in November 2011, the FDA revoked the licensed indication of bevacizumab to treat MBC as the magnitude of PFS from the E2100 was not reproduced in confirmatory studies (AVADO, RIBBOn-1), no study demonstrated an improved OS advantage, and the benefit-to-risk ratio did not favor bevacizumab taking into account its toxicity

profile such as hypertension, hemorrhage, and GI perforation. The addition of bevacizumab to paclitaxel in MBC patients is also expensive given the clinical benefit in terms of quality-adjusted life years (QALYs) gained (272).

Currently several randomized phase III trials in the first-line HER2-negative MBC setting are ongoing in Europe including the TURANDOT (NCT00600340) study which has completed recruitment looking at capecitabine plus bevacizumab versus paclitaxel plus bevacizumab, an issue unanswered by the RIBBOn-1 study.

Preclinical studies have shown that long-term suppression of a single proangiogenic pathway like VEGF can lead to a "tumor escape" phenomenon whereby there is increased expression of alternative proangiogenic proteins such as bFGF or PIGF (273). However, a provocative theory of accelerated disease progression on cessation of bevacizumab causing the observed lack of OS advantage has not been borne out in a pooled analysis of five placebo-controlled clinical trials consisting of 4,205 patients with breast (AVADO trial), pancreatic, colorectal, and pancreatic cancers (274). The impact of first-line treatment on OS may also have been diluted by crossover to bevacizumab and other subsequent efficacious lines of therapy making it a less useful objective in an era of increasingly effective systemic treatment options. Indeed, the greatest benefit appears to be when bevacizumab is administered early on in the treatment of MBC such as the first-line setting.

So far, trials have been performed in otherwise unselected HER2-negative patients, perhaps obscuring a relatively responsive patient subset. We need a more rational patient selection including discovery and validation of tumor and patient-related biomarkers of response or resistance, so as to improve therapeutic responses and cost effectiveness.

CHEMOTHERAPY IN OLDER PATIENTS

Cancer care in older patients is further discussed in Chapter 84. Older patients are more likely to have a reduced life expectancy, less tolerance to physiologic stress, comorbidities, impaired organ function, reduced cognition and functional status, and sometimes inadequate social support which make chemotherapy administration in this patient group more challenging. While the population of older breast cancer patients is projected to increase substantially within the next two decades, data on chemotherapy for this group of patients with MBC remains scarce. Based on data collected from 2003 through 2007, 40% of patients with newly diagnosed breast cancer were ≥65 years, 20% were ≥75 years and 5% were ≥85 years; the median age of death from breast cancer being 68 years (275). There is no exact age cut-off that defines patients as "older" but physicians have arbitrarily often selected an age cut-off of 65. However, chronological age does not give always give an accurate reflection of the functional reserve and performance status of a patient. Knowledge of age appropriate treatments in this subgroup of patients is important because they may experience complications due to alterations in drug pharmacokinetics, polypharmacy and potential drug interactions, poor compliance with medications and need for dose reductions which may compromise efficacy. The important physiological alterations which affect drug delivery in this age group are altered body composition, decreased gastrointestinal tract absorption, altered liver metabolism of drugs, decreased renal function, lower bone marrow regeneration capacity, cardiac and other comorbidities, and a decline in neurological function (276). Based on current data, there is no specific regimen recommended as optimal for older patients but sequential single agents are still the best approach to preserve QOL and minimize toxicity.

Older age does not modify the survival benefit of chemotherapy in MBC (277), although toxicities such as myelosuppression, cardiotoxicity, mucositis, and diarrhea may be more pronounced. Doxorubicin monotherapy has been used in older patients with MBC although a decreased clearance has been found (278). Doxorubicin-induced cardiotoxicity is a definite concern in this population. The risk of anthracycline-induced cardiomyopathy is increased in those >70 years (279), although some retrospective data have shown that cardiopulmonary deaths were not more common in those >65 compared to those 50 to 64 (50). PLD at 60 m/m^2 6-weekly or 50 mg/m^2 4-weekly has been shown to have a reduced cardiotoxic effect and equivalent antitumor efficacy in this age group as in younger patients, although there was a reportedly higher incidence of hematological toxicity, anorexia, asthenia, and stomatitis with the 6-weekly schedule (280). No difference in toxicity was observed between the age groups with the 4-weekly schedule. The clearance of epirubicin in multi-agent regimens is decreased in elderly women, although weekly epirubicin 25 mg/m^2 has been studied in older patients and those with a poorer performance status and found to be active and well tolerated (281).

Weekly taxanes have been studied in older breast cancer population and have shown good activity and tolerability with reduced myelosuppression. Weekly paclitaxel 80 mg/m^2 had reportedly comparable efficacy and toxicity in older (≥65 years) and younger patients (<65 years), although the younger group were more heavily pretreated (282). The clearance of paclitaxel is diminished in elderly patients (283), but this does not seem to be the case for docetaxel, although neutropenia is more pronounced (284,285). Weekly docetaxel has been used as first or second-line therapy with RRs of about 30% to 35% (286,287). Fatigue appears to be the main limiting factor for both taxanes (285,288). Care must be taken as there is a potential for excess glucocorticoid toxicity. Nab-paclitaxel does not require glucocorticoid premedication but is much more costly and has potential neurologic toxicity.

The relative unpredictability and sometimes severe toxicity of the fluoropyrimidines remains a concern in this age group. Continuous IV 5-FU has decreased clearance in older patients but is seldom used in MBC. Oral formulations are ideal for these patients as these may minimize discomfort, shorten hospital visits, and have a smaller impact on activities of daily living. As such, the prodrug capecitabine remains an attractive option for older patients owing to its ease of administration, although compliance has to be emphasized. The standard capecitabine 2,500 mg/m^2 dose was observed to result in toxic deaths due to grade 4 diarrhea, but its lower dose at 2,000 mg/m^2 is a feasible alternative with equivalent efficacy (289). Care must be taken to monitor renal function when using this drug in this population. In a randomized phase II trial comparing capecitabine 1,225 mg/m^2 twice a day to IV CMF in women ≥55 years, capecitabine was better than CMF for RR (30% vs. 16%) and median TTP (4.1 months vs. 3 months), although survival was similar (19.6 months vs. 17.2 months) (27). The study was prematurely closed because of the superior clinical benefit with capecitabine. The median age of patients receiving capecitabine was 69 years and that for CMF was 70 years. Capecitabine side effects were mainly hand-foot syndrome and diarrhea, with 16% of patients necessitating stopping treatment because of toxicities, while CMF side effects were mainly gastrointestinal.

Vinorelbine is a viable well-tolerated option in older patients and has shown objective responses in 30% to 38% of patients (290–292). with a stable disease rate of 33% to 38% (291,292). Neutropenia and constipation appear to be

the most significant toxicities. Apart from its IV formulation, it also comes in oral tablets which eases administration in this population.

Gemcitabine monotherapy remains a viable and well-tolerated option for treatment of MBC in this population. However, a randomized phase III study studying the efficacy of first-line gemcitabine 1,200 mg/m^2 to epirubicin 35 mg/m^2 both given weekly in women aged ≥60 years (median 68 years) with MBC revealed that epirubicin was significantly better than gemcitabine with respect to RR (40.3% and 16.4%; $p < .001$), TTP (6.1 months and 3.4 months; $p = .0001$), and OS (19.1 and 11.8 months; $p = .0004$) (126). Neutropenia and thrombocytopenia were more common in the gemcitabine group. In the epirubicin group, about 17% of patients had

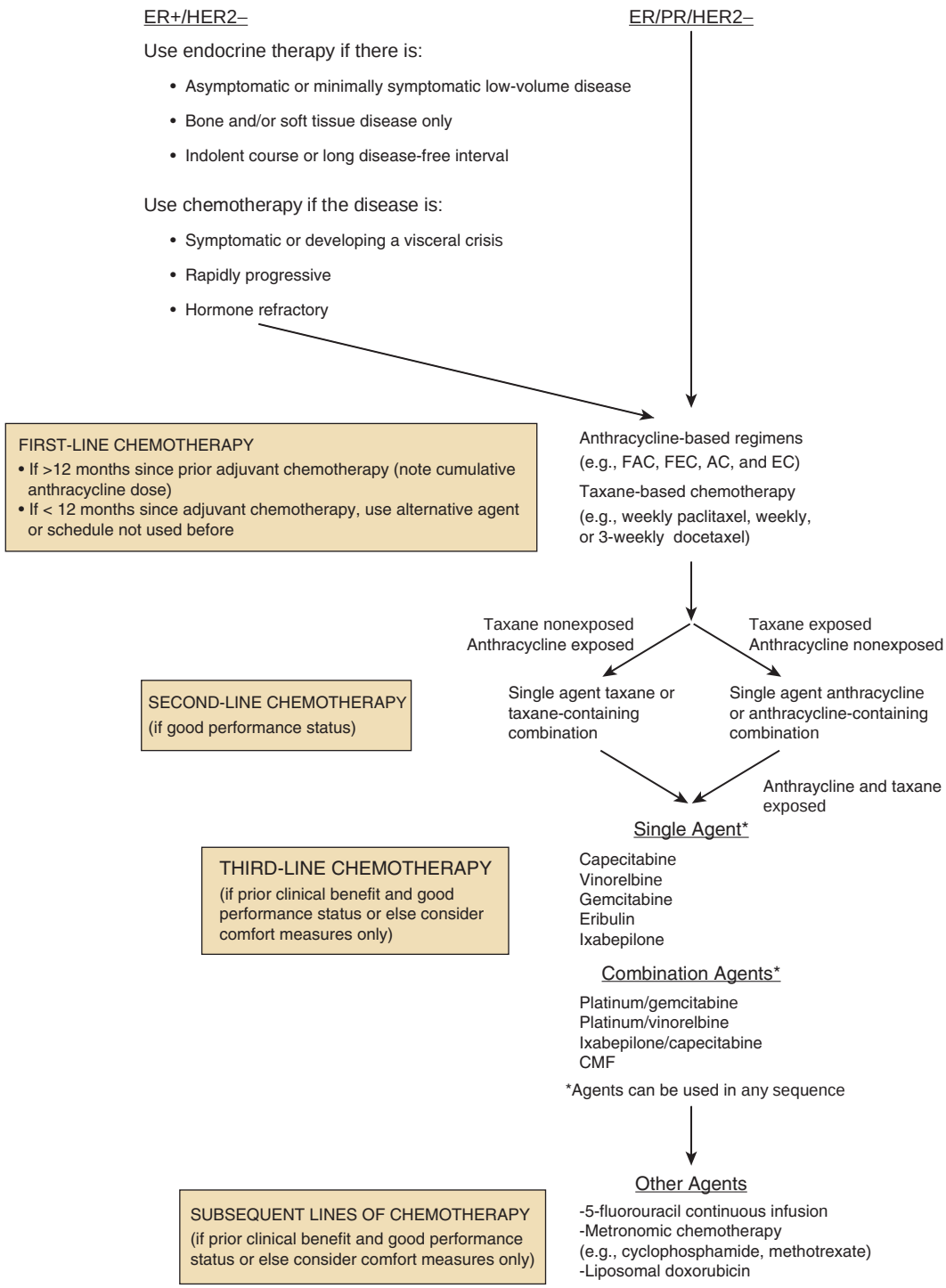

FIGURE 71-1 Decision algorithm for patients with ER/PR-positive, ERBB2-negative and triple-negative phenotypes. AC, doxorubicin, cyclophosphamide; EC, epirubicin, cyclophosphamide; ER, estrogen receptor; FAC, 5-fluorouracil, doxorubicin, cyclophosphamide; FEC, 5-fluurouracil, epirubicin, cyclophosphamide; CMF, cyclophosphamide, methotrexate, 5-fluorouracil; PR, progesterone receptor.

at least 10% decline in LVEF values from baseline. For those ≥70 years, mucositis and pulmonary toxicity occurred more frequently in the epirubicin and gemcitabine arms respectively. Of the 28 deaths, three were considered possibly or probably related to gemcitabine treatment.

For combination regimens, most studies have limitations such as small sample sizes, retrospective analyses and poor study design. A case-comparison study of patients with MBC in five clinical trials of the Piedmont Oncology Association comparing patients ≥70 years (n = 70), those aged 50 to 69 years (n = 60), and those younger than 40 years (n = 40) concluded that women aged ≥70 years or older were similar to their younger counterparts with respect to RRs, TTP, OS and toxicities (293). However, a 25% dose reduction for those ≥65 years was carried out for the first cycle in three of the five protocols.

The CMF dose has been reduced for those ≥65 years whereby the cyclophosphamide and methotrexate doses were modified based on creatinine clearance, and age was not found to affect the response rates in elderly patients using this modified CMF dose as compared to younger patients using standard dose CMF, although OS was worse in those >80 years (294).

In an older retrospective study of 1,011 patients treated between 1973 and 1984, doxorubicin-based combinations were found to yield a lower response rate, although TTP and OS were similar between those ≥65 years and 50 to 64 years (279). Notably, the hematologic toxicities were comparable between the two groups, but the dose intensity was lower for the older age compared to the younger patients. The toxicity and efficacy of the fluorouracil/epirubicin/cyclophosphamide combination was comparable in patients with MBC older or younger than 70 years (n = 20 each) in a retrospective study which studied chemotherapy-induced toxicity and therapeutic response of several different types advanced cancers (295). The oral vinorelbine/capecitabine combination as described above is an attractive option for elderly patients. The vinorelbine/gemcitabine combination has been shown to have serious toxicities (296).

Consensus opinion from the ASCO guidelines on the use of GCSF recommend using primary prophylaxis with CSF for patients aged >65 years even with regimens with febrile neutropenia rates of <20% (297). The use of primary prophylactic GCSF in those ≥65 years has been studied in the subanalysis of the NeuCup (Neulasta versus current practice neutropenia management) breast cancer trial and was found to reduce febrile neutropenia rates, febrile neutropenia-related hospitalizations, and dose reductions (298). However, chemotherapy dose-reduction in the palliative setting is potentially a simpler option that might circumvent the need for colony-stimulating support. The use of erythropoiesis-stimulating agents (ESAs) has been shown to result in increased mortality in a study of women receiving first-line chemotherapy for MBC (299). The increased mortality was due to breast cancer-related deaths as well as thrombotic/vascular events.

For elderly patients without life threatening or rapidly progressive disease, endocrine therapy is preferable. Chemotherapy can be considered once the tumor becomes endocrine refractory or as first line if the disease is very symptomatic or rapidly progressive.

IMMUNOTHERAPY TRIALS

Breast carcinomas are often infiltrated by inflammatory cells like macrophages and T lymphocytes. These inflammatory cells mediators represent an immune response against antigens expressed in cancer cells, and various studies have evaluated the expression of immune metagenes that may offer prognostic information in advanced disease (300). Vaccine-based studies have been explored for many years. In 2012, trials of monoclonal antibodies targeting antiprogrammed death receptors and ligands (PD-1 and PD-L1) were reported, and showed substantial antitumor activity in various solid tumors by modulating immune checkpoints via interference with inhibitory receptors on immune effector cells or their ligands (301,302). Trials are now exploring the clinical activity of these various antibody drugs against tumors that preferentially express the PD-1 ligand (PD-L1), including breast cancer.

CONCLUSION

A number of therapeutic advances have been made in the chemotherapy treatment of MBC in recent years. The advent of newer agents such as the epothilones and eribulin has enhanced our armamentarium of therapeutic options. However several unanswered questions still remain such as the optimal duration of chemotherapy, especially when combined with targeted therapy, the use of genetic profiling in personalising chemotherapy choices, and the identification of more effective treatment strategies for triple negative tumors. The choice of therapy for any particular patient is a complex individualized decision taking into account disease and patient-related characteristics. However with advancements in drug development, the natural history of MBC resembles more often that of a chronic disease process for which survival prolongation while preserving a reasonable QOL are goals of treatment. With a growing body of evidence for new agents and regimens, it is hoped that these may be expected to translate into improved patient outcomes in MBC.

MANAGEMENT SUMMARY (SEE FIG. 71-1)

- Upon clinical suspicion of metastatic disease, a full staging should be done with a CT scan of the thorax, abdomen, and pelvis; plus a bone scan; and imaging of the brain should there be any symptoms suggestive of brain metastases.
- Biopsy of a metastatic site should be considered whenever possible especially if it is easily accessible, to re-evaluate the ER, PR, and HER2-status.
- Consideration of the type of systemic therapy (endocrine therapy versus chemotherapy) should take into account tumor and patient-related factors such as ER-status, disease pace, extent and distribution, severity of symptoms, disease-free interval since previous adjuvant therapy, comorbidities, performance status, costs, and patient preferences. If the disease is HER2-positive, then anti-HER2 therapy should be used either in combination with chemotherapy (preferentially not with an anthracycline) or with endocrine therapy.
- Chemotherapy is the only option at present for those who have ER-negative disease, those who have progressed on hormonal therapy, and if there is extensive visceral disease, especially if it is symptomatic necessitating rapid therapeutic response. Anthracyclines and taxanes are the two most effective agents as first-line therapy although due consideration should be taken

regarding previous adjuvant therapy exposure as these drugs are almost invariably used as chemotherapy in the adjuvant setting.

- Combination therapy will yield higher response rates but is more toxic. Hence, sequential single agents may be as efficacious and certainly less toxic.
- The choice of second and subsequent lines of therapies should be made after careful consideration of disease and patient-related factors in association with the benefits and risks, although there is no standard approach to drug sequence. However, if disease recurrence occurs within less than 12 months of using a particular drug, a different class of agents is generally preferred.
- Disease response is monitored via a thorough history and physical examination, tumor markers if necessary, and imaging studies.
- Chemotherapy is generally given for at least six to eight cycles if there is disease response. There is no established total duration for chemotherapy although it can be maintained if there is continued clinical response with minimal drug toxicities. Due consideration should be given for chemotherapy drug holidays, especially if there are therapy-related toxicities. If the disease is ER-positive, endocrine therapy can be utilized as a form of maintenance systemic therapy after a course of chemotherapy upon disease stabilization.

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CHAPTER 72

Treatment of HER2-overexpressing Metastatic Breast Cancer

Shruti Sheth, Sumanta Kumar Pal, and Mark D. Pegram

CHAPTER CONTENTS

INTRODUCTION

In 2013, it is estimated that 232,340 new cases of breast cancer will be diagnosed in females, and 2,240 in males, with a combined mortality of 40,030 (1). Of the new cases, approximately 6% will have *de novo* metastatic disease at the time of initial presentation (2). Additionally, a substantial proportion of those patients diagnosed with early-stage disease will go on to develop metastatic breast cancer (MBC) despite advances in locoregional and systemic adjuvant and neoadjuvant therapies (3). Whereas traditional cytotoxic chemotherapy (and endocrine manipulation for ER-positive disease) has been the mainstay of treatment for these patients, targeted therapeutics directed against human epidermal growth factor receptor 2 (HER2/ERBB2) emerging over the past 15 years have significantly improved outcomes for this subset of patients with MBC (4).

The receptor tyrosine kinase HER2 is a member of the ERBB family of transmembrane receptors, including HER1 (ERBB1, or EGFR), HER3 (ERBB3), and HER4 (ERBB4) (5). The ERBB family of receptors possesses a wide range of biological activities relating to malignant phenotypes, including cell proliferation, invasion, migration, angiogenesis, and cell survival. With the exception of HER2, ERBB family receptors undergo a conformational change in the ectodomain as a consequence of binding to as many as a dozen soluble ERBB ligands. This conformational change exposes a β-hairpin loop dimerization domain that facilitates EGFR, HER3, and HER4 to undergo homo- or heterodimerization (6). Dimerization leads to structural (allosteric) activation of intracellular kinase domains, with subsequent activation of a number of signal transduction cascades, including Ras-mitogen-activated protein kinase (Ras-MAPK), phosphatidyl 3' kinase-protein kinase B (PI3K-PKB/Akt), and phospholipase C-protein kinase C (PLC-PKC) pathways (7). By contrast, HER2 does not bind to any of the soluble ERBB-family ligands, and analysis of the crystal structure of the HER2 ectodomain demonstrates that the dimerization domain is natively exposed in an open conformation, suggesting that this transmembrane receptor species remains constitutively poised for dimerization (8). This unique structural property has been offered as a rationale for enhanced mitogenesis seen with increased HER2 expression levels, such as those observed in HER2-amplified tumors and in preclinical models of enforced HER2 overexpression in breast and ovarian cell line and xenograft models (9). Indeed, clinical data defining the role of HER2 in association with an aggressive tumor phenotype has served as the impetus for the development of HER2-targeted therapies. Given that as many as 20% of breast cancer patients harbor tumors with HER2 gene amplification, the clinical impact of such therapies will remain relevant for the foreseeable future (10).

HUMANIZED ANTI-HER2 MONOCLONAL ANTIBODIES AS THERAPY FOR HER2-POSITIVE MBC

Development of Trastuzumab

Initially, several murine monoclonal antibodies with anti-proliferative activity specifically against HER2-overexpressing human cancer cell lines were identified and characterized (11,12). The complementarity-determining regions from one

of the most potent of these murine monoclonal antibodies were subsequently fused into a human IgG_1 framework, resulting in a humanized HER2-directed monoclonal antibody, trastuzumab (13). Preclinical studies of trastuzumab demonstrated that following the humanization procedure, the activity of the antibody against HER2-overexpressing cancer cell lines and xenografts was retained, particularly when used in combination with other cytotoxic therapeutics (14). Numerous studies have been conducted that focused on the mechanisms of trastuzumab-related anti-tumor activity. Several plausible hypotheses have been suggested to account for the clinical activity of trastuzumab. Resolution of the crystal structure of trastuzumab complexed with HER2 has led to identification of a trastuzumab-binding epitope in the juxtamembrane region (subdomain IV) of the HER2 ectodomain. It is possible that this juxtamembrane binding generates steric alteration of HER2 dimers to the extent that intracellular tyrosine kinase domains cannot efficiently interact and activate (8). Moreover, modification of key cell cycle regulators (i.e., increased levels of p27, a Cdk2 inhibitor) subsequent to trastuzumab binding have been observed (15). Studies additionally suggest that inhibition of HER2 ectodomain cleavage by metalloproteinases may serve as a mechanism of trastuzumab activity, because the truncated p95 fragment generated from cleavage retains intracellular kinase activity (16,17). Alternatively, preclinical data support stimulation of antibody-dependent cellular cytotoxicity (ADCC) as an important mediator of trastuzumab's mechanism(s) of action (18,19).

Single-Agent Trastuzumab for Metastatic Breast Cancer

Pilot clinical trials suggested only modest activity of single-agent trastuzumab in the setting of heavily pretreated MBC with HER2-overexpression (20). Subsequently, a much larger study in a pretreated MBC population explored a dosing regimen including a loading dose of 4 mg/kg followed by 2 mg/kg weekly maintenance therapy. In a total of 213 treated patients, 8 CRs and 22 PRs were observed (ORR 15%). The median duration of response was 9.1 months, and median overall survival (OS) was 13 months (21). Clinically significant cardiac dysfunction was noted in 4.7% of patients, comprised of congestive heart failure (CHF), cardiomyopathy, or a decrease in ejection fraction (>10%). These observed cardiac adverse events, along with events reported in a concurrent trial of trastuzumab in combination with chemotherapy, prompted further examination of potential risk factors for trastuzumab-associated cardiac toxicity (22). In a preliminary review of trastuzumab-related cardiac adverse events, 9 of 10 patients with cardiac events had prior anthracycline therapy, and additionally had at least one risk factor for anthracycline-induced cardiomyopathy (including cumulative doxorubicin dose greater than 400 mg/m^2, radiotherapy to the left chest, age greater than 70 years, and history of hypertension) (22). Consequently, there is a "boxed warning" concerning trastuzumab-associated cardiotoxicity in the trastuzumab prescribing information, and periodic serial assessment of left ventricular ejection fraction (LVEF) by echocardiography, or by technetium (Tc-99m) stannous pyrophosphate multi-gated acquisition (MUGA) scan, is recommended as clinically indicated.

Whereas the previous two studies assessed a heavily pretreated population of metastatic HER2-positive patients, a separate trial assessed the use of trastuzumab as first-line monotherapy for HER2-overexpressing MBC. A total of 114 women were randomized to receive one of two trastuzumab dosing regimens: (i) a loading dose of 4 mg/kg followed by 2 mg/kg weekly, or (ii) a loading dose of 8 mg/kg followed by 4 mg/kg weekly. Among 111 assessable patients, 7 CRs and 23 PRs were observed (ORR 26%). Reports of cardiac dysfunction in the previously noted trials (21,22) led to an evaluation of cardiac events in this trial. Only two patients (2%) were noted to have clinically significant cardiac dysfunction, requiring no intervention other than discontinuation of trastuzumab. Of note, variations in trastuzumab dosing did not lead to significant differences in clinical endpoints. Median OS was 25.8 months and 22.9 in those who received 4 mg/kg and 2 mg/kg, respectively (23). In summary, although trastuzumab is most commonly integrated in combination with chemotherapeutics in the clinic, and although the above data sets were generated prior to the adjuvant trastuzumab era, it is important to remember that the antibody has significant clinical activity as a single agent and may offer an important treatment consideration for patients who may not be suitable candidates for chemotherapy-based regimens.

Preclinical Rationale for Trastuzumab in Combination with Cytotoxic Therapy

As previously noted, initial studies of trastuzumab in cell lines suggested optimum efficacy of the antibody when combined with cytotoxic therapy (11). Initially, these experiments specifically assessed the combination of trastuzumab and the DNA-damaging agent cisplatin. Further preclinical studies have assessed several distinct classes of chemotherapeutics in combination with trastuzumab against a panel of four HER2-overexpressing breast cancer cell lines (SKBR3, BT-474, MDA-MB 361, and MDA-MB 453) and confirmed *in vivo* in HER2 overexpressing xenograft models.

Based on work done in cell lines, the efficacy of trastuzumab-based combinations using *in vivo* xenograft models were explored (24). Synergy has been observed using the combinations of trastuzumab with alkylating agents, platinum analogues, topoisomerase II inhibitors, and ionizing radiation. Additive interactions were observed with the combination of trastuzumab with taxanes and anthracyclines (25). Results of these experiments helped to inform and prioritize the design and conduct of subsequent clinical trials of trastuzumab in combination with cytotoxic chemotherapy (see Table 72-1).

Pivotal Trial of Trastuzumab with Chemotherapy

A pivotal phase III registration trial of trastuzumab and cytotoxic chemotherapy randomized patients to receive either standard chemotherapy alone or standard chemotherapy plus trastuzumab as first-line therapy for HER2-positive metastatic disease. HER2-overexpressors were defined as those possessing IHC scores of 2+ or 3+, using the same murine monoclonal antibody upon which trastuzumab was based, as the primary detection antibody. In this trial, patients were stratified according to their prior adjuvant treatment. Patients who had not previously received adjuvant therapy with an anthracycline received doxorubicin or epirubicin and cyclophosphamide with or without trastuzumab, whereas in those patients who had previously received adjuvant anthracycline, a regimen of paclitaxel alone or paclitaxel in combination with trastuzumab was utilized. Trastuzumab was administered at a loading dose of 4 mg/kg, followed by a maintenance dose of 2 mg/kg weekly, until the observation of disease progression. Compared to nonrecipients of trastuzumab (n = 234), patients who received trastuzumab (n = 235) had a significantly longer time to disease progression (7.4 months vs. 4.6 months, $p < .001$), a higher rate of objective response (50% vs. 32%, $p < .001$),

TABLE 72-1

Key Trials of Trastuzumab Therapy and Associated Response Rates

Author	*Year*	*Study Type*	*N*	*1st Line?*	*Regimen*	*RR*
Phase II Studies						
Single Agent Therapy						
Baselga et al.	1999	Phase II	43	No	Trastzumab 250 mg loading followed by 100 mg/wk × 10 wks	12%
Cobleigh et al.	1999	Phase II	213	No	Trastuzumab 4 mg/kg loading followed by 2 mg/kg/wk	15%
Vogel et al.	2002	Randomized phase II	111	Yes	Trastzumab 4 mg/kg loading followed by 2 mg/kg/wk, or Trastzumab 8 mg/kg loading followed by 4 mg/kg/wk, or	26%
Paclitaxel and Trastuzumab						
Leyland-Jones et al.	2003	Phase II	32	No	Paclitaxel 175 mg/m^2 q3wks with trastzumab 8 mg/kg loading followed by 6 mg/kg q3wks	59%
Gasparini et al.	2007	Randomized phase II	118	Yes	Paclitaxel 80 mg/m^2/wk alone or with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	75%*
Gori et al.	2004	Phase II	25	No	Paclitaxel 60–90 mg/m^2/wk with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	56%
Seidman et al.	2001	Phase II	88	No	Paclitaxel 90 mg/m^2/wk with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	61%
Docetaxel and Trastuzumab						
Esteva et al.	2002	Phase II	30	Yes**	Docetaxel 35 mg/m^2/wk with trastzumab 2 mg/kg/wk for 3 out of 4 wks/cycle	63%
Tedesco et al.	2004	Phase II	26	Yes**	Docetaxel 35 mg/m^2/wk for 6 wks followed by 2 wks rest with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	50%
Raff et al.	2004	Randomized phase II	17	No	Docetaxel 35 or 40 mg/m^2/wk for 3 wk, then 1 wk off, with trastzumab 4 mg/kg loading (day 1) followed by 2 mg/kg qwk (days 8 and 15) of a 28-d cycle	59%
Montemurro et al.	2004	Phase II	42	No	Docetaxel 75 mg/m^2 q3wks × 6 with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	67%
Marty et al.	2005	Randomized phase II	186	Yes	Docetaxel 75 mg/m^2 q3wks alone or with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	61%*
Vinorelbine/trastuzumab						
Burstein et al.	2001	Phase II	40	No	Vinorelbine 25 mg/m^2/wk with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	75%
Jahanzeb et al.	2002	Phase II	40	Yes	Vinorelbine 30 mg/m^2/wk with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	78%
Burstein et al.	2003	Phase II	54	Yes	Vinorelbine 25 mg/m^2/wk with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	68%
Chan et al.	2006	Phase II	62	Yes	Vinorelbine 30 mg/m^2/wk with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	63%
De Maio et al.	2007	Phase II	40	No	Vinorelbine 30 mg/m^2/wk on days 1 and 8 of a 3-wk cycle with trastzumab 8 mg/kg loading followed by 6 mg/kg qwk	50%
Papaldo et al.	2006	Phase II (two-arm)	68	Yes	Vinorelbine 25 mg/m^2/wk alone or with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	51%
Capecitabine and Trastuzumab						
Schaller et al.	2007	Phase II	27	No	Capecitabine 1,250 mg/m^2 bid for 14 d in a 21-d cycle given with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	45%
Bartsch et al.	2007	Phase II	40	No	Capecitabine 1,250 mg/m^2 bid for 14 d in a 21-d cycle given trastzumab 8 mg/kg loading followed by 6 mg/kg q3wks	20%
Yamamoto et al.	2008	Phase II	56	No	Capecitabine 1,657 mg/m^2 bid for 14 d in a 21-d cycle given with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	50%

TABLE 72-1 *(Continued)*

Key Trials of Trastuzumab Therapy and Associated Response Rates

Author	*Year*	*Study Type*	*N*	*1st Line?*	*Regimen*	*RR*
Cisplatin and Trastuzumab						
Pegram et al.	1998	Phase II	39	No	Cisplatin 75 mg/m^2 on days 1, 29, and 57 with trastuzumab 250 mg loading followed by 100 mg/wk for 9 wks	24%
Gemcitabine and Trastuzumab						
Bartsch et al.	2008	Phase II	26	No	Gemcitabine 1250 mg/m^2 on days 1 and 8 of a 3-wk cycle with trastzumab 8 mg/kg loading followed by 6 mg/kg q3wks	19%
Three Drug Regimens						
Perez et al.	2005	Phase II	43	Yes	Paclitaxel 200 mg/m^2 q3wks and carboplatin (AUC 6 mg/mL) q3wks with trastzumab 8 mg/kg loading followed by 6 mg/kg q3wks	65%
			48	Yes	Paclitaxel 80 mg/m^2/wk given with carboplatin (AUC 2 mg/mL) every 3 out of 4 wks with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	81%
Pegram et al.	2004	Phase II	59	Yes**	Docetaxel 75 mg/m^2 q3wks with carboplatin (AUC 6 mg/mL) q3wks with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	58%
			62	Yes	Paclitaxel 75 mg/m^2 q3wks with carboplatin (AUC 6 mg/mL) q3wks with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	79%
Miller et al.	2001	Phase II	42	Yes	Gemcitabine 1,250 mg/m^2 on days 1 and 8 and paclitaxel 175 mg/m^2 on day 1 of a 3-wk cycle with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	67%
Stemmler et al.	2005	Phase II	20	No	Gemcitabine 750 mg/m^2 with cisplatin 30 mg/m^2 on days 1 and 8 of a 3-wk cycle with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	40%
Phase III Studies						
Slamon et al.	2001	Phase III	469	No	Trastuzumab 4 mg/kg loading followed by 2 mg/ kg/wk	32%
					Taxane or anthracycline with cyclophosphamide given with trastuzumab 4 mg/kg loading followed by 2 mg/kg/wk	50%
Robert et al.	2006	Phase III	196	Yes	Paclitaxel 200 mg/m^2 q3wks alone with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	36%
					Paclitaxel 200 mg/m^2 q3wks with carboplatin (AUC 6 mg/mL) q3wks with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	57%
Burstein et al.	2007	Phase III	81	Yes	Vinorelbine 25 mg/m^2/wk with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk, or	51%
					Docetaxel/Paclitaxel, investigator preference, with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	40%
Pegram et al.	2007	Phase III	263	Yes	Docetaxel 100 mg/m^2 q3wks with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	73%
					Docetaxel 75 mg/m^2 q3wks with carboplatin (AUC 6 mg/mL) q3wks with trastzumab 4 mg/kg loading followed by 2 mg/kg qwk	73%

*Indicates RR for trastuzumab containing arm.
**indicates first- and second-line treatment included.

a longer mean duration of response (9.1 months vs. 6.1 months, $p < .001$) and prolonged median OS (25.1 months vs. 20.3 months, $p = .046$) (4). Along with the trastuzumab monotherapy noted above, these data supported regulatory approval of trastuzumab for the treatment of HER2-positive MBC by the U.S. Food and Drug Administration in 1998.

In addition to providing strong support for the combination of trastuzumab with cytotoxic chemotherapy, the study also provided important insights related to cardiac toxicity. Of 63 patients who experienced symptomatic or asymptomatic cardiac dysfunction in this study, 39 patients had received the combination of anthracycline, cyclophosphamide, and

trastuzumab. A much lower rate of cardiac dysfunction was observed in the remaining groups, with an incidence of 8%, 13%, and 1% in groups that had received anthracycline and cyclophosphamide alone, paclitaxel and trastuzumab, and paclitaxel alone, respectively. Grade III or IV New York Heart Association (NYHA) cardiac dysfunction was similarly observed at a much higher frequency in the group that received combined anthracycline and trastuzumab therapy. Increasing age was noted to be a risk factor associated with cardiac dysfunction within this subgroup. Notably, cumulative anthracycline dose did not correlate with cardiac toxicity; however, the vast majority of patients in this treatment arm received the prescribed six doses of anthracycline treatment (4). Results from this trial led to caution in formulating further trials of trastuzumab therapy with concomitant anthracycline.

The optimal schedule for regular cardiac follow-up has yet to determined in the metastatic setting of the treatment of HER2-positive breast cancer. Additional methods of assessing cardiac function both in terms of modality and introduction of newer methods such as biomarkers may play a role in the future of cardiac testing.

Combinations of HER2-Targeting Agents with Endocrine Therapy

Approximately half of HER2-positive MBC is also hormone receptor positive (26). Women with disease co-expressing both HER2 and one or both of the hormone receptors (ER or PR) may have less benefit from antihormonal therapies than with HER2-negative, ER positive disease (27). Preclinical studies suggest that there is cross talk between pathways related to HER2 and ER. Overexpression of HER2 was demonstrated to cause ligand independent down regulation of estrogen receptor and further suppression of ER transcripts (28). Given this association, it was thought plausible that inhibition of HER2 activity may augment endocrine therapy by enhancing ER expression. As validation of this hypothesis, the phase III TAnDEM trial randomized HER2-overexpressing, HR-positive postmenopausal patients to anastrozole alone, or the combination of anastrozole and trastuzumab. At the time of progression, patients were given the option to begin trastuzumab therapy if they were previously randomized to the monotherapy arm. Despite the crossover allowance, a modest (statistically insignificant) trend in OS was noted from combination therapy (28.5 vs. 23.9 months; p = .325) (29). Interestingly, in a *post hoc* exploratory analysis assessing the effects of crossover, median OS was significantly less in the group that received no trastuzumab therapy (i.e., anastrozole alone with no crossover; median OS, 17.2 months) versus survival in groups receiving anastrozole and trastuzumab initially (median OS 28.5 months) or at the time of crossover (median OS 25.1 months).

Direct HER2-tyrosine kinase inhibition with the small molecule HER2 kinase inhibitor lapatinib in combination with endocrine therapy has also been investigated. A phase I trial using the combination of lapatinib and letrozole suggested that the combination was safe and tolerable (30). Subsequently, a phase III trial was undertaken that compared the combination of letrozole plus lapatinib with letrozole plus placebo as first-line treatment of patients with HR-positive MBC, some with HER2-positive disease. Seventeen percent of the total study population (n = 1,286) had centrally confirmed HER2-positive disease with roughly equal distribution in the lapatinib and placebo groups (n = 111 and n = 108, respectively). In a pre-planned analysis of the HER2 positive population, the median PFS increased from 3 months for letrozole-placebo to 8.2 months for letrozole-lapatinib (HR = 0.71; 95% CI, 0.53–0.96; p = .019) (31). Clinical benefit, defined as objective response or stable disease for ≥6 months, was also significantly improved (29% to 48%; OR = 0.4; 95% CI, 0.2–0.8; p = .003) for the combined receptor blockade arm. There was also a (non-significant) trend toward improvement in OS. This regimen won regulatory approval by the U.S. FDA in 2010. In summary, since ER signaling has been suggested as an escape mechanism causing resistance to HER2 targeting agents, it is important to remember that ER+ tumors in the setting of HER2+ disease should also be treated with ER-directed therapies. This paradigm is also suggested by recent results from the TBCRC 006 trial, in which letrozole was used in addition to trastuzumab *and* lapatinib in 64 evaluable patients with HER2+/ER+ stage II/III tumors (32). Overall, in-breast pathologic complete response (pCR; ${}_{yp}T_{0\text{-}is}$) was 27% (ER+, 21%; ER–, 36%). The rate of low-volume residual disease (${}_{yp}T_{1a\text{-}b}$) was 22% (ER+, 33%; ER–, 4%). Thus, in these patients with locally advanced HER2-positive breast cancer, this approach resulted in a high pCR rate even in the absence of chemotherapy. These data support the hypothesis that selected patients with HER2-positive tumors may not need chemotherapy, and more-complete blockade of HER receptors and ER is an effective strategy worthy of further study (32).

Trastuzumab and EGFR Tyrosine Kinase Inhibitors

Whereas trastuzumab binds the extracellular domain of the HER2 moiety (8), a unique class of agents interacts with the intracellular domain of ERBB family proteins. Lapatinib, a dual inhibitor of EGFR and HER2 tyrosine kinase domains, is discussed elsewhere in this chapter (33). Gefitinib and erlotinib, two inhibitors with affinity for the EGFR tyrosine kinase domain, have demonstrable efficacy in non-small cell lung cancer (34,35). Response data for these agents in MBC, however, has been poor. In a pilot study of 22 patients with refractory MBC treated with erlotinib, no clinical responses were observed (36). Limited single agent data exists for gefinitib in the setting of MBC; two trials report activity of the drug in combination with docetaxel, but it is challenging to determine response attributable to the EGFR antagonist (35,37). In the setting of HER2-overexpressing MBC, Eastern Cooperative Oncology Group (ECOG) study 1100 assessed a regimen of daily oral gefinitib combined with weekly trastuzumab, utilizing a phase I/II design. During a planned interim analysis, TTP parameters did not meet pre-specified statistical endpoints for study continuation (38). More encouraging data was yielded from a phase I trial of erlotinib in combination with trastuzumab, spurned by preclinical data suggesting synergy between the agents in breast cancer cell lines (39). Among 14 evaluable patients with heavily pretreated HER2-overexpressing MBC, two partial responses were elicited. There is strong preclinical rationale for combined ERBB receptor blockade to include EGFR-HER2 heterodimeric interactions, HER2-HER2 interactions, as well as HER2-HER3 heterodimeric complexes that can be achieved with various combinations of ERB-targeting reagents, including antibodies and small molecules (40). However, clinical data to interrogate this important hypothesis are currently lacking.

Continuation of Trastuzumab beyond Initial Progression

A majority of the aforementioned trials utilizing trastuzumab-based regimens prescribed the continuation of trastuzumab therapy until the time of disease progression. Beyond the time of progression, the role of further trastuzumab-based regimens was unclear. Before the availability of salvage HER2-targeted therapy with lapatinib (discussed

later), a frequently employed strategy was the continuation of trastuzumab with an alternative chemotherapy beyond the initial time of disease progression. Use of this approach was addressed in an extension of the pivotal phase III trial of trastuzumab in combination with chemotherapy. A total of 247 patients with documented disease progression were enrolled in an extension study. Of these, 154 patients had originally received chemotherapy (group 1) and 93 had received chemotherapy and trastuzumab (group 2). The majority of patients enrolled in the extension trial received a combination of chemotherapy and trastuzumab, with the remainder receiving either trastuzumab alone or a combination of trastuzumab and palliative radiotherapy or hormonal therapy. The most commonly used chemotherapeutic agents used in the extension trial in combination with trastuzumab were paclitaxel, vinorelbine, docetaxel, and fluorouracil, although 8% of patients received concomitant doxorubicin. Although efficacy information from the trial was limited (safety was the primary objective), 14% of patients in group 1 and 11% of patients in group 2 experienced an objective response. These responses were observed both when trastuzumab was combined with chemotherapy and when single agent trastuzumab therapy was employed. The incidence of cardiac toxicity was relatively low, occurring in 9% of patients in group 1 and 2% of patients in group 2 (41). A relatively small retrospective review of the Hellenic Cooperative Oncology Group (HCOG) experience offers a similar suggestion of efficacy for trastuzumab in multiple lines of therapy for advanced disease, demonstrating a significant number of responses with second- and third-line therapy with trastuzumab, associated with improvements in median survival (42).

Despite these encouraging results, a separate retrospective review offers contrasting results. In a series of 184 HER2-overexpressing MBC patients who had received trastuzumab therapy over a 5-year period, relevant clinical endpoints such as time to second progression (TT-SP) and post-progression survival (PPS) were assessed. Among 132 patients who had progressed on trastuzumab-based therapy at the time of analysis, 21 patients experienced rapid progression and did not receive additional therapy, 40 patients received further trastuzumab-based regimens, and 71 patients received further non-trastuzumab-based regimens. In the latter two groups, there did not appear to be significant difference in TT-SP, PPS, RR, or OS (43). Because this data is complicated by issues related to retrospective methodology, further trials were necessary to clarify the role of trastuzumab therapy beyond the time of initial progression.

Further evidence in support of continuation of trastuzumab beyond the time of disease progression comes from a randomized trial conducted in a population of patients with advanced, HER2-overexpressing breast cancer that had progressed on treatment with trastuzumab. Patients (n = 78 in each arm) were then randomized to receive either capecitabine (at 2,500 mg/m^2 on days 1 to 14 every 3 weeks) alone, or in combination with trastuzumab (at 6 mg/kg every 3 weeks). With 15.6 months of follow-up, median times to progression were 5.6 months in the capecitabine group and 8.2 months in the capecitabine-plus-trastuzumab group with an unadjusted hazard ratio of 0.69 (95% CI, 0.48–0.97; two-sided log-rank p = .0338). OS rates were 20.4 months (95% CI, 17.8–24.7) in the capecitabine group and 25.5 months (95% CI, 19.0–30.7) in the capecitabine-plus-trastuzumab group (p = .257). Overall response rates were 27.0% with capecitabine and 48.1% with capecitabine plus trastuzumab (odds ratio, 2.50; p = .0115). Continuation of trastuzumab beyond progression was not associated with increased toxicity (44).

Although some questions and concerns continue regarding the efficacy of trastuzumab beyond progression, in light of the prospective, randomized data in support of treatment in multiple lines, and the potential for synergy by changing the chemotherapy base, continuation of trastuzumab beyond initial progression is widely practiced.

Mechanisms of Trastuzumab Resistance

In the pivotal phase III trial comparing the combination of cytotoxic chemotherapy to trastuzumab alone, an impressive overall response rate of 50% was achieved with combined therapy—substantially improved relative to previous trials of monotherapy with trastuzumab. However, the median duration of response on this therapeutic arm was just 9.1 months (4). In response to the observations that as many as half of chemotherapy + trastuzumab-treated subjects fail to achieve clinical response, and those that do have modest response duration, a significant body of evidence has been generated in the laboratory focused on mechanisms of trastuzumab resistance. Several studies have implicated a role for loss of PTEN in trastuzumab resistance. Reduction of PTEN, a dual phosphatase negatively regulating PI3K and Akt activities, through antisense oligonucleotides led to trastuzumab resistance in *in vitro* and *in vivo* models. Additionally, IHC analyses of clinical specimens demonstrated that PTEN-deficient breast tumors had poorer responses to trastuzumab-based therapy relative to tumors with normal PTEN expression (45). As a potential therapeutic approach in patients with PTEN-loss, it appears that inhibition of the PI3K-Akt pathway (e.g., through use of mTOR inhibitors) may lead to restoration of trastuzumab sensitivity in preclinical assays (46).

Alternatively, aberrant signaling through the insulin-like growth factor-I receptor (IGF-IR) pathway, leading to PI3K-Akt pathway activation, may mediate trastuzumab resistance. An assay of MCF-7 and SKBR-3 breast cancer cell lines revealed that treatment with IGF-I (and subsequent activation of IGF-IR) led to a diminution in trastuzumab-induced cell growth inhibition (47). This is supported a separate preclinical study of IGF-IR inhibition in combination with trastuzumab therapy in MCF-7 cells, showing a synergistic interaction using dual receptor inhibition (48). Similar to IGF-IR overexpression, overexpression of the Met receptor may serve to decrease trastuzumab sensitivity by offering a "bypass mechanism" for cell growth and proliferation. A recently published report suggested that Met knockdown in breast cancer cell lines using RNA interference significantly enhanced trastuzumab sensitivity. Conversely, co-activation of Met and HER2 through use of the ligands hepatocyte-growth factor (HGF) and neuregulin, respectively, led to substantial increases in cell growth (49).

Other purported mechanisms of trastuzumab resistance include limitations in drug distribution secondary to the size of the antibody. Fluorescently tagged trastuzumab injected in mice bearing MDA-MB 435 breast cancer xenografts displayed antibody accumulation in the periphery of tumors. Notably, this was not correlated with increased HER2 expression in peripheral regions. Additionally, vascular distribution of trastuzumab was highly irregular, and distribution of trastuzumab did not correlate with vascular density, as one would expect with unhindered trastuzumab transport (50). Approaches to HER2-overexpressing patients using small molecule inhibitors may help to circumvent such issues with drug delivery. Interestingly, preclinical studies indicate lapatinib has significant activity even in trastuzumab refractory cell lines (51), leading to clinical investigations of lapatinib-based regimens following trastuzumab in subsequent randomized trials (52).

LAPATINIB

Lapatinib Monotherapy

In contrast to trastuzumab, which binds an epitope located in the extracellular domain of the HER2 moiety (8), the orally active dual tyrosine kinase inhibitor lapatinib binds reversibly to the intracellular kinase domain of both HER2 and EGFR (53). Growth inhibition was observed with lapatinib therapy in HER2-overexpressing BT-474 breast cancer cell lines. Xenografts derived from BT-474 cell lines were similarly inhibited by lapatinib treatment (54). A separate analysis of HER2-overexpressing cell lines suggested marked reductions in tyrosine phosphorylation of EGFR and HER2 following exposure to lapatinib. Additionally, lapatinib led to inhibition of Erk1/2 and AKT, downstream effectors of cell proliferation and survival, respectively (55). In a phase I study, 67 patients with EGFR- or HER2-overexpressing tumors were randomly assigned to one of five dose cohorts of daily lapatinib therapy. A total of 4 PRs occurred among 57 evaluable patients; all were in patients with trastuzumab-refractory MBC. Stable disease occurred in a total of 24 patients, 10 of whom were patients with MBC. The most commonly observed adverse events were diarrhea and cutaneous rash, the former in a dose-dependent fashion (33).

A correlative study accompanying the aforementioned phase I clinical trial of lapatinib monotherapy in solid tumor malignancies focused attention on the four patients attaining PR in the clinical trial. Analysis of serial biopsies performed in each of these patients suggested that each of the four patients had elevated baseline levels of active, phosphorylated HER2 (determined by IHC). With lapatinib therapy, a decrease in the extent of HER2 phosphorylation was observed. In three of the four responders, inhibition of activated phospho-Akt and phosphor-Erk1/2 was noted, concordant with preclinical studies suggesting these moieties were inhibited by lapatinib. In contrast to assessment of phosphorylated HER2, level of EGFR phosphorylation at baseline did not seem to distinguish responders from non-responders. Notably however, decrements in EGFR phosphorylation were seen in responding patients (33).

Encouraging data from this phase I trial within the subset of patients with MBC led to the implementation of a phase II clinical trial including both HER2-overexpressing and non-HER2-overexpressing MBC. In 140 patients with HER2-overexpressing disease, an overall RR of 4.3% was determined by investigator assessment. All responders were noted to have overexpression of HER2 characterized as 3+ by IHC; 5 of 6 responders additionally had FISH amplification. No tumor responses occurred among 89 non-HER2-overexpressing MBC patients. As in the phase I monotherapy study, diarrhea and rash were the most commonly observed toxicities (56).

Lapatinib and Capecitabine

Given the limited data to support the clinical utility of lapatinib monotherapy, further efforts have focused on combinations of lapatinib with standard chemotherapeutics. In a series of preclinical experiments, four cancer cell lines with a range of HER2 and EGFR expression (MCF7/wt, BT-474, SKBR-3, and A-431) were exposed to varying concentrations and combinations of lapatinib, trastuzumab, epirubicin, gemcitabine, and 5-fluorouracil. Independent of HER2 and EGFR expression, lapatinib was noted to have synergy with 5-fluorouracil (57). This observation served as the rationale for a phase I trial of lapatinib and capecitabine in advanced solid tumors. Although only 7 of 45 patients enrolled (16%) carried a diagnosis of MBC, one CR and three confirmed PRs occurred; the CR occurred in a patient with MBC treated with lapatinib at 1,250 mg/d and capecitabine at 2,000 mg/m^2/d, representing the optimally tolerated dose regimen. The most common toxicities incurred with this regimen were diarrhea, rash, nausea, palmar-plantar erythrodysesthesia, mucositis, vomiting, and stomatitis (58).

The observed activity of the combination of lapatinib and capecitabine in MBC led to the initiation of a randomized phase III trial. In this study, HER2-overexpressing patients with MBC who had progressed after regimens including an anthracycline, a taxane, and trastuzumab received either capecitabine alone (2,500 mg/m^2/d on days 1 through 14 of a 21-day cycle) or in combination with lapatinib (with the optimal treatment regimen defined from the previous phase I trial). An interim analysis met pre-specified criteria for early reporting given superiority of the group receiving combination therapy. At the time of this analysis, 49 events had occurred in the combination group as opposed to 72 events in the monotherapy group (HR = 0.49; $p < .001$). Median TTP was prolonged from 4.4 months with monotherapy to 8.4 months with combination therapy. Overall RR was higher with combination therapy (22%) as compared to monotherapy (14%), although this was marginally significant ($p = .09$). In contrast to trastuzumab-containing regimens, no symptomatic cardiac events were observed with lapatinib therapy (52). In a more recent published update of the trial, including attempts at correlating response with various biomarkers, lapatinib response failed to correlate with baseline levels of HER2 ECD or EGFR expression (59). In 2007, the U. S. FDA granted approval to lapatinib ditosylate tablets for use in combination with capecitabine for the treatment of patients with advanced or metastatic breast cancer whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab.

Lapatinib and Taxanes

Lapatinib exhibits a chemosensitizing effect when used in combination with paclitaxel in a model of resistant EGFR-overexpressing ovarian cancer cell lines (60). Similar preclinical observations led to the initiation of multiple clinical trials investigating the combination of lapatinib and taxanes. In 192 patients receiving either docetaxel or paclitaxel in combination with lapatinib, the rates of neutropenia and rash were similar to each agent alone, although the frequency of diarrhea was more pronounced. Although the analysis was centered on safety, a preliminary report from one trial assessed suggested a response rate of greater than 70% with the combination of lapatinib and paclitaxel (61).

Data from placebo-controlled randomized trials combining lapatinib and paclitaxel have been reported. Interestingly, one trial evaluated a population of patients with stage IIIb/IIIc/IV at first diagnosis or relapse with either negative HER2 testing (0/1+ by IHC analysis, or no FISH amplification) or no prior testing. Central analysis of HER2 expression was performed in all available cases (representing 78% of test population). A total of 579 patients were randomized 1:1 to receive either lapatinib at a dose of 1500 mg daily with paclitaxel at 175 mg/m^2 every 3 weeks, or placebo and paclitaxel on the same schedule. From the study population, HER2-overexpression was elicited in 15% of patients enrolled in the study. Within this small subset of patients, treatment with paclitaxel-lapatinib resulted in statistically significant improvements in TTP, EFS, ORR, and CBR compared with paclitaxel-placebo. As anticipated, no such difference was observed in the larger subset of patients with normal HER2 expression (62). Although only a relatively small cohort of patients with HER2-overexpression was considered, these data informed the implementation of a prospective clinical

trial in a pre-selected HER-positive population. This phase III, randomized, double-blind study assessed the efficacy and safety of lapatinib plus paclitaxel compared with placebo plus paclitaxel in patients with newly diagnosed HER2-positive MBC. The primary end point was OS. Secondary end points included PFS, ORR, clinical benefit rate, and safety. The addition of lapatinib to paclitaxel significantly improved OS versus paclitaxel (treatment hazard ratio [HR] = 0.74; 95% CI, 0.58–0.94; $p = .0124$); median OS was 27.8 versus 20.5 months, respectively. Median PFS was prolonged by 3.2 months, from 6.5 months with placebo plus paclitaxel to 9.7 months with lapatinib plus paclitaxel (HR, 0.52; 95% CI, 0.42–0.64; stratified log-rank $p < .001$). ORR was significantly higher with lapatinib plus paclitaxel compared with placebo plus paclitaxel (69% vs. 50%, respectively; $p < .001$). The incidence of grades 3 and 4 diarrhea and neutropenia was higher in the lapatinib plus paclitaxel arm; however, just 4% of patients in this group reported febrile neutropenia. Cardiac events were low grade, asymptomatic, and mostly reversible. The incidence of hepatic adverse events was similar in both arms, and there were no fatal adverse events in the lapatinib plus paclitaxel arm (63).

Dual Targeting of the HER2 Receptor: Lapatinib and Trastuzumab

The rationale for dual inhibition of the HER2 receptor with monoclonal antibody and tyrosine kinase inhibitor treatment emerges from preclinical experiments assessing this combination in HER2-overexpressing BT-474 breast cancer cell lines. Treatment of BT-474 cell lines with lapatinib led to only a minimal increase in tumor cell apoptosis with an associated minimal decrease in phosphorylated HER2, Akt, Erk1/2, and most notably, survivin (a member of the inhibitor of apoptosis family of proteins). Similarly, treatment with trastuzumab had little effect on apoptosis or survivin concentration. However, the combination of lapatinib and trastuzumab led to markedly enhanced tumor cell apoptosis and downregulation of survivin (64). In a separate series of experiments examining a broad panel of breast cancer cell lines (including cells maintained in trastuzumab-conditioned media), synergy with concomitant trastuzumab and lapatinib treatment was observed in four cell lines (65).

Data from a phase I trial showed promise for dual inhibition. This open label trial used a two-stage design, with the initial stage comprised of lapatinib dose escalation to establish the optimally tolerated dose. The second stage included patients in an expansion cohort in which pharmacokinetic parameters were assessed. A total of 48 patients with HER2-overexpressing MBC were treated; among 27 evaluable patients, one CR and seven PRs were observed—all in trastuzumab-pretreated subjects. A lapatinib dose of 1000 mg daily was identified as the optimally tolerated regimen for further trials in combination with trastuzumab (66). A subsequent report focused on cardiac safety suggested that the combination of trastuzumab and lapatinib results in no symptomatic cardiac events in a total of 238 patients registered in four separate trials (67).

Recently, overall survival benefit with lapatinib in combination with trastuzumab for patients with human epidermal growth factor receptor 2-positive metastatic breast cancer was reported in the final results from the randomized, phase III EGF104900 study (68). In this campaign, patients with HER2-positive MBC whose disease progressed during prior trastuzumab-based therapies were randomly assigned to receive lapatinib monotherapy or lapatinib in combination with trastuzumab. Lapatinib plus trastuzumab showed superiority to lapatinib monotherapy in PFS (HR = 0.74; 95% CI, 0.58–0.94; $p = .011$) and offered significant OS benefit (HR = 0.74; 95% CI, 0.57–0.97; $p = .026$). Multiple clinical factors, including ECOG performance status 0, nonvisceral disease, <3 metastatic sites, and less time from initial diagnosis until randomization, were associated with improved OS. These data support dual HER2 blockade with a non-cytotoxic salvage regimen in patients with heavily pretreated HER2-positive MBC (68).

NEWER AGENTS TARGETING THE HER2 RECEPTOR

Pertuzumab

Pertuzumab is a second-generation humanized, monoclonal antibody employing the same IgG1 backbone as trastuzumab, but with a different target epitope on the HER2 ectodomain. This first-in-class agent targeted therapeutic is termed a HER dimerization inhibitor (HDI) (69). Whereas trastuzumab binds to the extracellular domain IV of HER2, pertuzumab binds to the extracellular domain II of HER2 and has a complementary mechanism of action (Fig. 72-1). It inhibits ligand dependent HER2-HER3 dimerization and reduces signaling via intracellular pathways such as phosphatidylinositol 3 kinase (PI3K/Akt).

Preclinical data focused on the comparisons between trastuzumab and pertuzumab and the synergy between the two agents. Pertuzumab is thought to act mechanistically by disrupting the HER2-HER3 interaction in the presence of heregulin. Heregulin is thought to promote tumorigenesis and cell proliferation. Agus and colleagues showed in cell lines that pertuzumab more readily disrupted this HRG mediated tumorigenesis than did trastuzumab (70).

Scheuer and colleagues showed that as compared to trastuzumab or pertuzumab monotherapy, there was a synergistic effect of the two agents (71). Interestingly, in both KPL-4 xenograft models and in BT474MI models, not only was there the initial tumor response but also the prevention of additional spread to other systemic sites. The same studies have also shown that the combination therapy was effective in KPL-4 and Calu-3 xenografts even after progression on trastuzumab (71).

Several phase I clinical trials testing pertuzumab as monotherapy or in combination with chemotherapy or trastuzumab in patients with metastatic breast cancer were undertaken in patients who were refractory to standard therapies. These phase I trials showed that pertuzumab was well tolerated (72).

Two phase II studies, both single arm studies, were conducted evaluating pertuzumab in combination with trastuzumab without chemotherapy in patients with HER2-positive metastatic disease who had progressed despite prior trastuzumab. The first study was designed with a target recruitment of 37 patients. However, as 54% of the 11 recruited patients developed LVEF decline, the study was stopped early (73). The response rate was 18%. CBR could not be calculated due to small numbers. A second trial conducted by Baselga and colleagues included 66 patients who had prior trastuzumab therapy and had progressed. These patients were then treated with combination of both pertuzumab and trastuzumab with the primary end point of ORR and/or CBR. The ORR was found to be 24.5% on this study with a CBR of 50%. No clinically significant cardiac events were seen in this trial, in contrast to the Portera study, most likely because the eligibility criteria were more stringent with regards to cardiac dysfunction and study entrance (74).

Another important study was an extension of that initial phase II completed by Baselga (74,75). This extension study

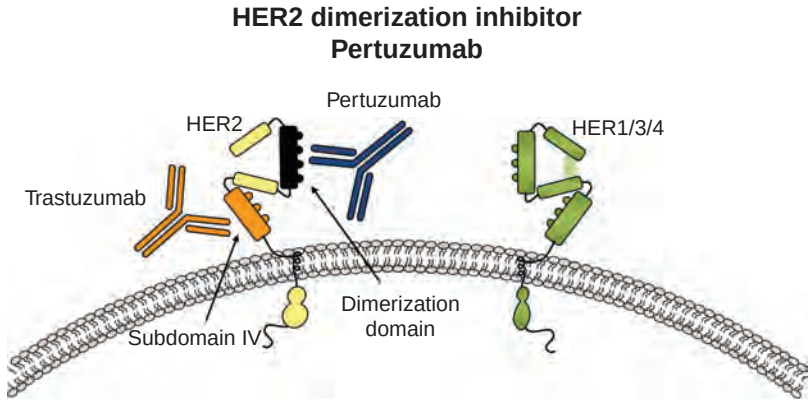

FIGURE 72-1 In contrast to trastuzumab, which binds to a juxtamembrane epitope in subdomain IV of the HER2 extracellular domain (ECD), pertuzumab binds to the dimerization interface contained in subdomain II of the HER2 ECD. Pertuzumab disrupts the ability of HER2 to dimerize with any other HER family member, thus attenuating signaling events triggered by HER family ligands. (Adapted from Cho et al. Structure of the extracellular region of HER2 alone and in complex with the Herceptin Fab. *Nature* 2003(421):756–759; Franklin et al. Insights into ErbB signaling from the structure of the ErbB2-pertuzumab complex. *Cancer Cell* 2004(4):317-328; Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. *Nat Rev Cancer* 2009(9):463–475.)

done by Cortes et al. (75) recruited an additional cohort of patients to assess the efficacy of pertuzumab monotherapy and the reintroduction of trastuzumab in combination with pertuzumab in patients who had already progressed on both drugs. In the pertuzumab monontherapy arm the ORR and CBR were 3.4% and 10.3%. However, in the patients who received dual blockade after progression on pertuzumab, the ORR and CBR were 17.6% and 41.2%. These results are similar to what was seen in the original cohort of patients. Again, there was no additional cardiac toxicity noted (75).

Based on these promising results, the CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab) trial was undertaken. This was a phase III, double-blind, randomized placebo-controlled trial that evaluated the role of dual anti-HER2 blockade with both pertuzumab and trastuzumab as first-line therapy in metastatic disease. Eight hundred and eight previously untreated metastatic HER2 patients were randomly assigned to receive either docetaxel with trastuzumab either with pertuzumab or placebo. The primary endpoint was independently assessed progression-free survival. The secondary endpoints were overall survival, ORR, and safety. This trial showed that the combination of pertuzumab, trastuzumab, and docetaxel when given in the first line as a treatment for metastatic HER2-overexpressing breast cancer significantly prolonged PFS with an increase of 6.1 months (12.4 months to 18.5 months) (HR 0.62; 95% CI, 0.51–0.75). Recently, a confirmatory OS analysis was performed that demonstrated a significant OS benefit for those subjects randomized to the pertuzumab-containing arm (HR = 0.66; 95% CI, 0.52–0.84, p = .0008) (76). Again, no increase in cardiac side effects was seen (76).

Based on these data, in 2012 the FDA approved the combination of pertuzumab, trastuzumab, and docetaxel as first-line therapy for previously untreated metastatic breast cancer patients.

Other ongoing trials are evaluating this dual blockade with other therapies. The PHEREXA (Pertuzumab Herceptin Evaluation with Xeloda) trial (NCT01026142) is a double-blind phase II trial studying the combination of pertuzumab, trastuzumab, and capecitebine versus trastuzumab and capecitabine in patients who have progressed on prior trastuzumab treatment. The VELVET study is exploring pertuzumab plus trastuzumab combination with vinorelbine. Additionally, MARIANNE (NCT01120184) is a phase III study that is evaluating the combination of pertuzumab with T-DM1. Results from these trials are eagerly awaited.

Antibody-drug Conjugate Ado-trastuzumab Emtansine (T-DM1)

Development of T-DM1

A variation on the antibody targeting model of trastuzumab is to use antibodies to deliver cytotoxic agents directly to the tumors. Trastuzumab-DM1 represents a novel agent in the class of anticancer therapeutics termed antibody-drug conjugates (ADCs). Trastustuzumab-DM1 is comprised of the monoclonal antibody trastuzumab chemically linked to the highly potent antimicrotubule DM1, derived from maytansine (Fig. 72-2) (77). Observations that anti-HER2 ADCs had both *in vitro* and *in vivo* potency and were active in trastuzumab refractory models of HER2-amplified breast cancer led to the testing and development of a trastuzumab-maytansine conjugate with a stable linker. This complex was designed to allow for endosomal reduction and intracellular release of the cytotoxic agent. In this construct, however, maytansine is held to the trastuzumab through a MCC linker that theoretically provides a stable bond between the two moieties, allowing for prolonged exposure and reduced toxicity.

Single Agent T-DM1 for Metastatic Breast Cancer

A phase I study in patients with HER2-overexpressed metastatic disease who had progressed on earlier trastuzumab-based therapy assessed the safety and tolerability of T-DM1 (n = 24) (78). Dose limiting toxicity of grade IV thrombocytopenia was observed, although rapidly reversible, and more importantly, there were no cardiac events requiring

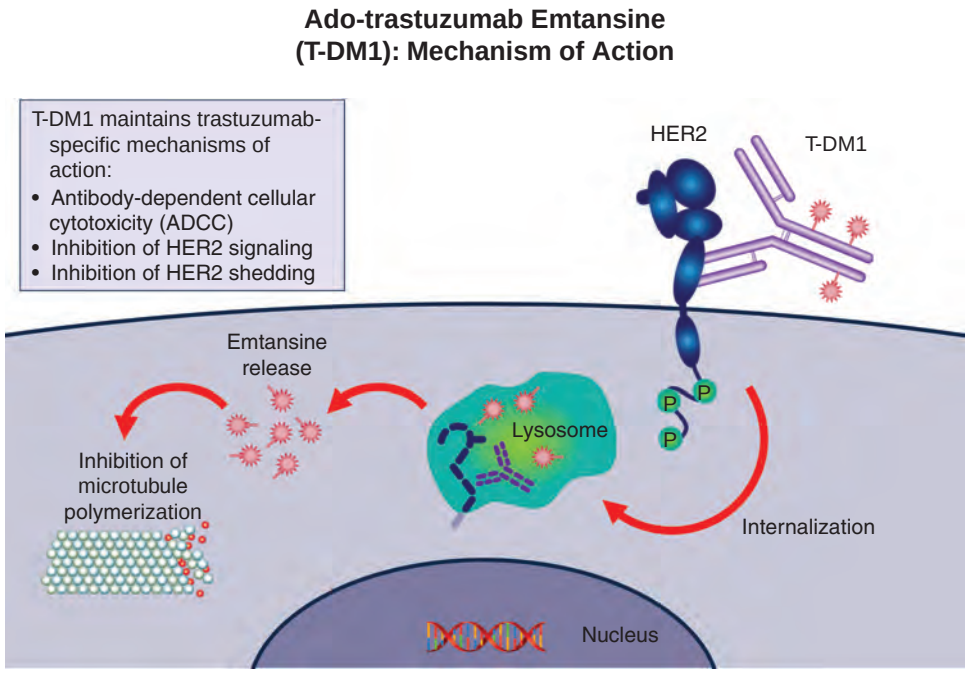

FIGURE 72-2 Following binding of the ADC T-DM1 to the HER2 ECD, the ADC/receptor complex is internalized by receptor-mediated endocytosis. Following endocytosis, the complex enters the lysosomal compartment, whereupon the complex undergoes extensive proteolysis that "frees" the potent emtansine moiety that then targets microtubule assembly, resulting in cytotoxicity. (Adapted from LoRusso PM, et al. Trastuzumab emtansine: A unique antibody-drug conjugate in development for human epidermal growth factor receptor 2-positive cancer. *Clin Cancer Res* 2011;17:6437–6447.)

discontinuation or dose modification. Five of the 24 patients had a confirmed partial response. For the 15 patients treated with MTD of 3.6 mg/kg every 3 weeks, the median progression free survival was 10.4 months.

These promising findings laid the groundwork for two phase II single arm studies of T-DM1 as monotherapy. In a study of 112 patients who had received previous chemotherapy and had progression on trastuzumab, T-DM1 was associated with an objective response rate of 25.9% based on independent review (79). Median duration of response was not reached as a result of insufficient events (lower limit of 95% CI, 6.2 months), and median progression-free survival time was 4.6 months (95% CI, 3.9 to 8.6 months). The response rates were higher among patients with confirmed HER2-positive tumors (immunohistochemistry 3+ or fluorescent in situ hybridization positive) by retrospective central testing (n = 74). T-DM1 was well tolerated with no dose-limiting cardiotoxicity. Most adverse events (AEs) were grade 1 or 2; the most frequent grade ≥ 3 AEs were hypokalemia (8.9%), thrombocytopenia (8.0%), and fatigue (4.5%). In a second study of 110 patients with HER2-positive metastatic breast cancer previously treated with multiple agents, the objective was to treat with T-DM1 as monotherapy to assess both ORR and progression-free survival. In this study, patients had previously been treated with anthracycline, taxane, capecitabine, trastuzumab, and lapatinib. The ORR was 34.5% (95% CI, 26.1%-43.9%) with a clinical benefit rate of 48.2% (95% CI, 38.8%-57.9%). Median PFS was 6.9 months while the median DOR was 7.2 months (95% CI, 4.6 months to not estimatible). By investigator assessment, the ORR was 32.7% (95% CI, 7.1 months to NE) and median PFS was 5.5 months (95% CI, 4.2 to 7.9 months). The most common AEs of any grade were fatigue, nausea, and thrombocytopenia. There was no evidence of LVEF decline to less than 45% and no patient was discontinued due to cardiotoxicity (80).

Pivotal Trial of T-DM1

The phase II studies provided the proof of concept and showed the clinical activity of T-DM1 in heavily pretreated metastatic HER2-positive patients. The phase III EMILIA study sought to assess the safety and efficacy of T-DM1 monotherapy as compared to lapatinib plus capecitabine in patients previously treated with trastuzumab and a taxane (81). A total of 991 patients were enrolled with 496 in the lapatinib plus capecitabine group and 495 in the T-DM1 group. Primary endpoints were progression-free survival and overall survival. Progression free survival in the group treated with T-DM1 was 9.6 versus 6.4 months (95% CI, 0.55–0.77, $p < .001$). Overall survival was also a primary end point and at the second interim analysis, T-DM1 significantly increased median overall survival (30.9 months vs. 25.1 months, 95% CI, 0.55–0.85; $p < .001$). The most commonly reported adverse events were grade 3 or 4 thrombocytopenia (12.9%). Based on this data, in 2013 T-DM1 was approved by the FDA for use in patients with metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane.

T-DM1 has also been tested in the first-line setting in HER2-positive MBC (82). In a randomized phase II study, patients (n = 137) with HER2-positive MBC or recurrent locally advanced breast cancer were randomly assigned to trastuzumab plus docetaxel (HT; n = 70) or T-DM1 (n = 67) as first-line treatment. ORR was 58.0% (95% CI, 45.5%-69.2%) with HT and 64.2% (95% CI, 51.8%–74.8%) with T-DM1. With a median follow-up duration of 14 months, median PFS was 9.2 months with HT and 14.2 months with T-DM1 (HR = 0.59; 95% CI, 0.36–0.97). T-DM1 had a favorable safety profile versus HT, with fewer grade ≥ 3 adverse events (AEs; 46.4% vs. 90.9%), AEs leading to treatment discontinuations (7.2% vs. 40.9%), and serious AEs (20.3% vs. 25.8%). Remarkably, in this study, first-line treatment with T-DM1 provided a significant improvement in PFS compared to a standard taxane/trastuzumab regimen. Moreover, the safety profile strongly favored T-DM1 over chemotherapy plus trastuzumab.

Future Directions-Combinations of T-DM1 with Other Agents

The MARIANNE trial is a three-arm phase III study that is evaluating combination of T-DM1 and pertuzumab versus T-DM1 and placebo versus trastuzumab plus taxane, all in the first-line setting for advanced breast cancer. This is

the first study to evaluate whether T-DM1 would be effective in earlier settings. Another study, the TH3RESA study is a multicenter phase III randomized trial that is evaluating T-DM1 or chemotherapy of physician's choice in patients with advanced breast cancers who have progressed on both trastuzumab and lapatinib (www.clinicaltrials.gov).

CNS METASTASES: THE ROLE OF HER2 AND TARGETED THERAPY

In data obtained from a large institutional review, it appears that the incidence of central nervous system metastases in breast cancer varies with stage at diagnoses. Only 2.5% of patients with localized disease at initial presentation ultimately developed CNS metastases, in contrast to 13.4% of patients who had metastatic disease at the time of presentation (2). A separate review of autopsy series including 144 patients carrying a diagnosis of breast cancer suggested an incidence of CNS metastases of 26% contrasting with the previous estimate and suggesting a high frequency of clinically occult disease (83). Subsequent to the introduction of trastuzumab therapy, several retrospective reviews of patients receiving trastuzumab suggested an incidence of CNS disease in the range of 25% to 48% substantially higher than the historically reported incidence (84–86). This increase in CNS metastases in the HER2-overexpressing population is supported by preclinical rationale. A subclone of the MDA-MB231 breast cancer cell line, 231 BR was generated with a property of selective metastases to the brain. When this subclone was transfected with varying levels of HER2, correlation was noted with the size and extent of brain metastases after implantation in a mouse model (87).

Risk of CNS metastases in early-stage HER2-positive breast cancer patients was assessed in NSABP B-31, a large randomized trial in which HER2-overexpressing patients received adjuvant chemotherapy alone or chemotherapy followed by 1 year of trastuzumab. In reviewing data among patients with distant recurrence, 28 CNS recurrences occurred in the arm receiving trastuzumab, whereas 35 occurred in the control arm (p = .35) (88). These findings suggest that adjuvant trastuzumab may be associated with a higher risk of CNS metastases as the site of *first* recurrence (since other sites of systemic metastasis are controlled for longer time periods). Thus, while trastuzumab serves to improve the overall clinical outcome in patients, the CNS may serve as a sanctuary site for trastuzumab therapy. Supporting this hypothesis, a study assessed six patients with HER2-overexpressing MBC with CNS metastases who had received WBRT after trastuzumab therapy. The ratio of trastuzumab concentration in serum as compared to CSF was 420:1 prior to WBRT. The ratio declined dramatically after WBRT (76:1) suggesting that disruption of the blood-brain barrier with radiation may serve as a mechanism to more effectively deliver trastuzumab (89).

Newer data come from a recent meta-analysis shows that receipt of adjuvant trastuzumab for 1 year increases the risk of CNS metastases as the *first* site of relapse (90). In this meta-analysis, 9,020 patients from four major trials were included. While the absolute incidence was small (2.6% vs. 1.94% in the control arm), the ratio of CNS events to total number of recurrence events was 16.94% (95% CI, 10.85%-24.07%) and 8.33 for the control arm, suggesting adjuvant trastuzumab is associated with a significant increased risk of CNS metastases as the site of *first* recurrence in HER2-positive breast cancer patients.

Lapatinib has been investigated as a potential treatment approach to the patient with HER2-overexpressing MBC with CNS involvement. In an updated analysis from the randomized phase III trial of capecitabine alone or in combination with lapatinib, it was noted that 13 patients in the monotherapy group had CNS progression, as compared to only 4 patients with combination therapy (p = .045) These data have encouraged further exploration of lapatinib and capecitabine for treatment CNS metastatic disease (52). The National Cancer Institute Cancer Therapy Evaluation Program (NCI/CTEP) 6969 trial included patients with HER2-overexpressing MBC with new or progressive brain metastases and at least one measureable lesion greater than 1.0 cm. Patients received lapatinib at a dose of 750 mg oral twice daily, with tumor measurements by magnetic resonance imaging (MRI) on 8-week intervals (91). Of the 39 patients enrolled, one PR in CNS disease by Response Evaluation Criteria in Solid Tumors (RECIST) criteria was recorded (ORR 2.6%). An additional 30% of patients were noted to have a decrease in the size of their initially noted CNS lesions that did not meet RECIST criteria. A radiographic volumetric analysis of CNS metastases suggested a greater than 30% decrement in tumor volume in three patients, and an additional seven patients had a decrease between 15% and 30%.

Additional data for the use of lapatinib were supported by trial EGF105084 in which eligible patients had HER2-overexpressing MBC, prior treatment with trastuzumab and cranial irradiation, and radiographic evidence of progressive brain metastases with at least one measurable lesion greater than 1.0 cm. Serial imaging was obtained with MRI, and patients were treated with the same dose in NCI/CTEP 6969 (92). Of the 242 patients enrolled, there was a greater than 50% volumetric reduction in CNS tumor load in 15 patients (6%) and a greater than 20% reduction in 41 patients (17%). In the 51 patients in the extension arm, 10 PRs were recorded (20%), and stable disease was observed in 20 patients (39%). These data require more validation. Data from the CEREBRAL trial will be forthcoming and is aimed at answering whether lapatinib or trastuzumab is superior in preventing brain metastases in advanced breast cancer.

With the recent development of T-DM1 and pertuzumab in HER2-positive MBC, newer treatment options may be becoming available for treating metastatic breast cancer with brain metastases. At this point, however, there do not appear to be any clinical trials evaluating use of these newer agents specifically for the treatment of brain metastases. However, other molecules such as Neratinib, which is an irreversible inhibitor of HER1, HER2, and HER4, is being investigated in a phase II trial of patients with metastatic breast cancer with brain metastases (clinicaltrials.gov NCT01494662). Afatinib is also an inhibitor of HER1 and HER2 and is currently being tested for use against brain metastases in the LUX-breast 3 study. Patients with progression after either trastuzumab or lapatinib therapy are randomized to treatment with either afatinib alone, afatinib plus vinorelbine, or investigators' choice of treatments (93).

CONCLUSION

A number of therapeutic advances have been made in the treatment of HER2-overexpressing MBC in recent years. The era of combination therapy with trastuzumab and conventional cytotoxic therapy has been supplanted largely by dual blockade and more targeted therapies aimed at several signaling pathways thought to promote tumorigenesis in HER2-overexpressed breast cancer. The therapy of HER2-overexpressing breast cancer thus represents an exciting frontier in which numerous paradigms for anticancer therapy continue to be established.

MANAGEMENT SUMMARY

- There is level I evidence, based on results of phase III CLEOPATRA trial, that pertuzumab in combination with trastuzumab and a taxane (docetaxel) yields superior progression-free and overall survival in the first-line metastatic setting compared to docetaxel plus trastuzumab. This regimen has secured regulatory approval in the United States and beyond and is a preferred first-line regimen recommended by National Comprehensive Cancer Network (NCCN) guidelines.
- For HER2-positive patients in the first line with ER-positive disease, particularly those with low volume disease burden that is asymptomatic and non-visceral predominant, or for those who are not ideal candidates for chemotherapy-based regimens, combined receptor blockade with an anti-estrogen plus a HER2-targeting agent yields significantly superior progression-free survival compared to anti-estrogen alone, based on data from randomized trials (the TANDEM trial explored anastrozole plus trastuzumab, and the EGF 30008 trial tested the combination of letrozole with lapatinib, the latter garnering regulatory approval by the U.S. FDA).
- For patients with metastatic HER2-positive disease who have progressed following prior treatment with a taxane and trastuzumab, or relapsed within 6 months of completion of an adjuvant trastuzumab regimen, ado-trastuzumab emtansine (T-DM1) has been shown to be significantly superior (both for progression-free and overall survival) to lapatinib plus capecitabine and is arguably better tolerated. Ado-trastuzumab emtansine also has regulatory approval in the United States.
- Upon disease progression following a prior pertuzumab-containing regimen and T-DM1, lapatinib-based regimens (either lapatinib plus capecitabine or lapatinib plus trastuzumab) are a logical next choice. However, neither of these regimens have efficacy datasets yet available in the setting of prior progression after multiple HER2-targeting antibody strategies.
- In later lines of treatment, clinicians regularly default to sequential salvage chemotherapeutics given in combination with trastuzumab in multiple lines, although this practice is not evidence-based.
- It is important to remember that in the era of non-anthracycline-based trastuzumab-containing adjuvant therapy (e.g., TCH), that anthracylines—even as single agents—have activity against HER2-positive disease, particularly in those tumors (~35%) with co-amplification of the topo-isomerase IIα gene (94). Therefore, anthracylines should be given some consideration in the salvage setting in anthracycline-naïve subjects. A wash-out period from prior trastuzumab administration is advised to avoid cardiotoxicity, or anthracyclines could be employed following progression on lapatinib-based regimens or T-DM1, both of which have shorter half lives compared to trastuzumab.
- HER2-overexpressing MBC patients with CNS metastases may benefit uniquely from lapatinib alone or in combination with capecitabine, whereas HER2-antibody-based therapeutics remain to be rigorously tested in the setting of CNS progression.
- For patients being treated with HER2-targeting agents, baseline and then periodic serial assessment of left ventricular ejection fraction (by MUGA or ECHO) remains a recommendation, although not a requirement, since at some point in the natural history of HER2-positive metastatic breast cancer, the risk of further disease progression without HER2-directed treatment may well exceed the risk of congestive heart failure. Therefore, sound clinical judgment is necessary to determine the optimal timing and frequency of LVEF assessment.

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CHAPTER 73

Palliative Care in Breast Cancer

M. Jennifer Cheng and Thomas J. Smith

CHAPTER CONTENTS

INTRODUCTION

Breast cancer is still the most common cancer in women and nearly half of those diagnosed will die from it. The American Cancer Society estimates that in 2013 there will be 234,580 new cases of breast cancer and 40,340 deaths in the United States. (1). All oncologists do palliative care, but we can improve the end of life care of our patients by adapting some of the techniques of hospice and palliative medicine (2). In this chapter we will review the following: evolving models of care; predicting end of life; communication issues; incorporation of hospice and advance care planning into standard care; symptom and pain management; managing the time right before death; helping with caregivers; and end with a management summary.

EVOLVING MODELS OF CARE

The models of care for breast cancer patients have changed in the past decades, both during active treatment and near the end of life. The current suggested model of care (3) is shown in Figure 73-1, and illustrates that disease-directed treatment is given concurrently with palliative care along the time course of treatment, with palliative care and hospice care assuming a greater role if the patient is dying.

The American Society of Clinical Oncology (4) and the National Comprehensive Cancer Center Network (NCCN) guidelines (5) now call for concurrent palliative care for all people with serious illness. The recommendations for concurrent care are based on the evidence from multiple randomized clinical trials and show benefits including better quality of life for patients and families; less aggressive end of life care including less death in the hospital; more deaths at the place of one's choice; increased use of hospice; improved communication; improved symptom control; and possibly better survival with no trials showing worse survival.

PREDICTING END OF LIFE: WHY IT IS IMPORTANT, AND HOW TO PREDICT ACCURATELY

Nearly all modern-day breast and other cancer patients want to know their prognosis, treatment options, curability, and estimated length of survival. A consistent theme in a review of 46 studies is that most patients will want this information at the onset, but with some negotiation about the content and extent of the information as the disease progresses (6).

The reason to give people information about their prognosis is to help them with decision making. We have known for decades (7) that people who understood that they had less than 6 months to live, compared to those who do not, lived just as long and are far more likely to die a "good" death. Those who overestimated their survival and wanted life-extending treatments rather than symptom management are 1.6 times more likely to die on a ventilator or with resuscitation, and be readmitted to the hospital. All of these, including chemotherapy in the last weeks of life for breast cancer patients, are considered a sign of poor quality of care (8).

The American Society of Clinical Oncology has made recommendations that oncologists have frank, personalized discussions with patients about prognosis, treatment outcomes, and end of life care transitions, and that such discussions are particularly important near the end of life (9). As stated by ASCO, "Central to all of these goals is the need for realistic conversations about options and alternatives that should occur throughout the course of the patient's illness. Such conversations may currently occur in less than 40% of patients with advanced cancer. *All patients are owed comprehensive information about their prognosis and treatment options, with the amount of detail tailored to the individual patient. All patients must have a regular opportunity to make their preferences about how to live their final weeks and months clear to their oncologist*. Given that the default care plan in

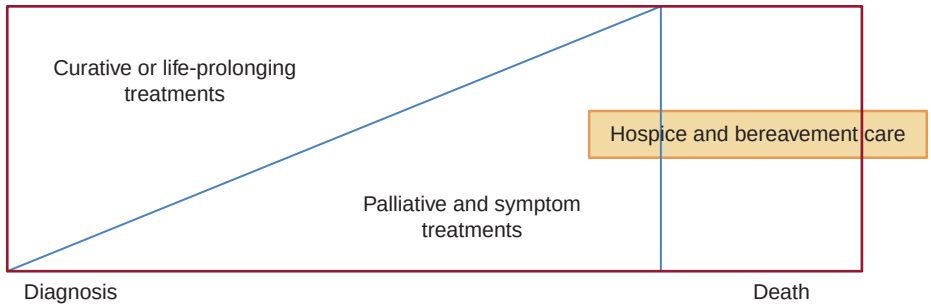

FIGURE 73-1 The changing patterns of care that incorporate palliative and end of life care.

the absence of these conversations is often further systemic therapy, *there is a need to regularly and specifically address the question of whether further anticancer-directed therapy is consistent with the patient's wishes and the current clinical picture*. Only through these discussions do we have the opportunity to match patients' goals with the actual care delivered."

The ability to predict when a person with breast cancer is potentially facing the end of life is straightforward, based on the available evidence. Any person with metastatic breast cancer is facing a terminal illness, and for most patients with HER-2 negative cancer the average survival is still less than 2 years. There is no known harm to addressing end of life issues earlier rather than later, other than the discomfort of raising the issues for patients, families, and healthcare professionals.

Performance status remains one of the best predictors of survival of less than 6 months, regardless of whether Karnofsky (score <60) or ECOG (score >2) is used, and the predictive value has not changed much in the past 30 years. Salpeter and colleagues (10) also note uniform average survival of less than 6 months with any of the following: poor performance status, multiple brain metastases, leptomeningeal disease, spinal cord compression, peritoneal disease and ascites, and progressive disease on chemotherapy, as shown in Table 73-1. All of these are common occurrences in breast cancer and should trigger the recognition that the disease course has changed from stability to predictable end of life.

There are other prognostic aids in common use by palliative care specialists and increasingly by oncologists. The Palliative Performance Scale gives 100 to 0 (PPS, 100 is normal function, 0 is death) scores based on routine clinical observations and is reliable, valid, and accurate. In Ontario, 25% of cancer patients died within 6 months of their first clinical encounter, and the PPS was highly predictive of death (11). For each 10-point decline in the PPS, the hazard of death increased by a factor of 1.7. The PPS is being tested as a referral trigger for palliative care and hospice consultation.

COMMUNICATION ISSUES AND THE SUBSEQUENT PATTERNS OF CARE

Despite our ability to predict with reasonable certainty, and a decades-long emphasis on honest prognostic information, ASCO notes that fewer than 40% of patients receive such information. Only 37% of dying patients remembered a conversation with their oncologist about dying (12). In a more recent study, only 22% of oncologists documented any "end of life" conversations, most such conversations were held by doctors other than the oncologist, and only 33 days before death (13). Half of all oncologists prefer to wait till "no more treatment options are left" before having these conversations (14). Nearly three-quarters of lung and colorectal cancer patients with incurable disease thought a person like themselves could be cured (15). The available data suggests that breast cancer patients have just as many unmet communication needs.

We have listed, in Table 73-2, some of the barriers that oncologists perceive. The skills to conduct these difficult discussions, such as how to be empathic listeners and to break bad news effectively, are readily learnable from programs such as Oncotalk (16). Other options include the free Education in Palliative and End-of-life Care (EPEC®)-Oncology course (http://www.cancer.gov/aboutnci/epeco) available from the National Cancer Institute.

Negotiating the palliative care conversation can be difficult, and introducing hospice services can be particularly stress-producing. We have created a guide for carrying out such discussions as shown in Table 73-3. The discussion goes easier if we have a script, just like with adjuvant treatment or lumpectomy versus mastectomy.

Goals of care and hospice discussions can be challenging for both patients and providers. Here are some tips for enhancing the quality of these conversations: First, *listen for clues*. Knowing they have a serious illness, most patients have thought about death and dying and are looking for permission to openly speak about it. Listen closely to the responses patients give you as their comments about mortality are not always straightforward. When given a vague statement ("I've been thinking about life and what this all means."), rather than overlooking the comment ask, "Tell me more about what you mean." Second, *restate the patient's goals*. Restating, or summarizing, patient's comments minimizes misconceptions, emphasizes the goals as important to the provider, and demonstrates attentive listening. This also provides patients with the opportunity to clarify and elaborate on their goals. Finally, *Ask, Tell, Ask*. (Always ask people how much they want to know, and what they do know. Then tell them, in understandable words. Ask "Now that we have discussed this, what is your understanding of your situation?")

In reality, this is not one talk but a series of discussions at predictable transition points (17). We have outlined these in Figure 73-2.

To date, every study shows that most breast cancer patients want to have all the available information, and will tell us if they do not. Most of us use Adjuvant!, the decision-making tool that has been shown to be useable, well accepted, and lead to better decision making. Most of us print the decision aids to share with the patient. The same types of decision aids have been tested in metastatic breast cancer with good acceptance, no distress, and no harm. They want to know the details, and the survival, so that they can plan just like with adjuvant treatment.

TABLE 73-1

Predicting Survival of Breast Cancer Patients with Metastatic Disease

Setting	*Prediction Models*	*Comment*
HER-2 not amplified		
	1st line modern treatments gave median survival of 19–22 months 2nd line modern chemotherapy gave median survival 16–18 months. (RIBBON-2 Trial) 3rd line chemotherapy with best option eribulin gave median survival of 13 months, versus 10 months with other regimens	Since treatment is not curative, discussing advance directives at the start of metastatic cancer is appropriate. Remember that these figures are from clinical trial patients with ECOG 0-1 and no comorbidities.
Triple negative	11–12 months overall survival in contemporary US patients treated at the best centers	
Specific situations with less than 6 months		
Any metastatic cancer with	KPS <60 ECOG performance status ≥2 Peritoneal or leptomeningeal metastases Hypercalcemia >11.2 mg/dL Spinal cord compression with decreased ability to walk Serum C-reactive protein >10 mg/L and serum albumin <3.5 g/dL	See review by Salpeter et al., 2012 and the supplemental data file available at http://online.liebertpub.com/doi/suppl/10.1089/jpm.2011.0192/suppl_file/Supp_Data.pdf
Any metastatic cancer with brain metastases and 1 or more of the following presentations	KPS <80 (ECOG performance status ≥2) ≥2 brain metastases plus extracranial metastases Triple negative cancer	
Any metastatic breast carcinoma with 3 or more of these presentations	KPS <80 (ECOG performance Status ≥2) Serum lactate dehydrogenase >500 IU/L Any liver metastasis At least 2 sites of metastases Disease-free interval from initial presentation to metastatic disease of <24 months. Recurrent or refractory disease after initial chemotherapy Triple negative cancer	

Data from Phase III trial of doxorubicin, paclitaxel, and the combination of doxorubicin and paclitaxel as front-line chemotherapy for metastatic breast cancer: an intergroup trial (E1193). Sledge GW, Neuberg D, Bernardo P, et al. *J Clin Oncol* 2003;21(4):588; Hayes DF. Systemic treatment for metastatic breast cancer: combination chemotherapy. Up to Date, 2012; Brufsky AM, Hurvitz S, Perez E, et al. RIBBON-2: a randomized, double-blind, placebo-controlled, phase III trial evaluating the efficacy and safety of bevacizumab in combination with chemotherapy for second-line treatment of human epidermal growth factor receptor 2-negative metastatic breast cancer. *J Clin Oncol* 2011;29(32):4286–4293. Epub 2011; Cortes J, O'Shaughnessy J, Loesch D, et al. Eribulin monotherapy versus treatment of physician's choice in patients with metastatic breast cancer (EMBRACE): a phase 3 open-label randomised study. *Lancet* 2011;377(9769):914–23; O'Shaughnessy J, Schwartzberg LS, Danso MA, et al. A randomized phase III study of iniparib (BSI-201) in combination with gemcitabine/carboplatin (G/C) in metastatic triple-negative breast cancer (TNBC). *J Clin Oncol* 2011;29:(suppl; abstr 1007).

INCORPORATION OF HOSPICE AND ADVANCE CARE PLANNING INTO STANDARD CARE

Best use of hospice requires a basic understanding of the Medicare (and most insurer) hospice benefits. The hospice provider is paid about $150 a day that must include all the services provided. Inpatient hospice is reimbursed at about $500 a day and must cover all the services provided. Currently, inpatient hospice is tightly regulated and patients must have a very high likelihood of dying within 7 to 14 days. There are a few communities with "expanded access hospice" that allow chemotherapy and radiation therapy, but these must still be covered within that $150 per diem, plus charity.

The easiest way to ensure timely hospice referral is to get palliative care involved by consultation. Hospitals with an active palliative care program referred 33% of hospice-appropriate patients to hospice, while hospitals without a program referred only 1%. More use of palliative care would save New York $84 to 234 million dollars (18), allow the end of life care to mirror what people choose—if given the choice, (19) and possibly increase survival (20).

TABLE 73-2

Why We May Not Have Realistic Discussions with People, Why It Matters, and How to Make Discussions a Reality

Barriers	*Reality*	*How to Move to Actuality*
People don't want this information.	People DO want this information. A small percentage will not, but we will not know who they are without asking.	Always "Ask, Tell, Ask" What do you want to know about your situation? What DO you know about your situation? Tell in understandable terms. Ask "Now that we have reviewed this, what is your understanding of your situation?"
It will make people depressed.	It won't make people depressed. Depression is 3-fold more common in those who had no discussion and could not plan.	Ask, Tell, Ask. And screen for depression with "Are you depressed?" or a similar tool.[a]
It will take away hope.	It won't take away their hope.	Ask people "What are you hoping for?"
They will die sooner, or hospice will kill them.	It won't make them die sooner.	Tell patients that the data show hospice and palliative care patients live longer and better.
We cannot really predict.	We CAN give realistic forecasts for survival.	Use a prognostic aid such as the Palliative Prognosis Scale. Remember that the better we know patients the more we overestimate their survival.
It is not culturally appropriate.	It is always culturally appropriate to ask "How much do you want to know about your illness?"	Recognize that cultures will vary within themselves, and change over time, too. "Ask, Tell, Ask."

[a]Skoogh J, Ylitalo N, Larsson Omeróv P, et al. Swedish-Norwegian Testicular Cancer Group. 'A no means no'—measuring depression using a single-item question versus Hospital Anxiety and Depression Scale (HADS-D). *Ann Oncol* 2010;21(9):1905–1909. doi: 10.1093/annonc/mdq058. Epub 2010 Mar 15.

Modified from Mack JW, Smith TJ. Reasons why physicians do not have discussions about poor prognosis, why it matters, and what can be improved. *J Clin Oncol* 2012;30(22):2715–2717. doi: 10.1200/JCO.2012.42.4564. Epub 2012 Jul 2.

The data show we do not use palliative and hospice care early enough, with one third of our patients entering hospice with less than a week to live and the average less than 20 days (21). This influences where people spend their last weeks of life. Over 60% of Medicare cancer patients are hospitalized in their last month of life, 30% die there, 25% are in the Intensive Care Unit, and the average person spends just 8 days in hospice once discharged (22). When one insurer offered concurrent palliative care along with oncology care, which allowed transition to hospice earlier because the patient and family know who would be taking care of them and had been introduced, hospitalizations were reduced nearly 10-fold and costs were 22% less in the last 40 days of life (23).

One large provider is already incorporating "best practices" in their pathways. As soon as incurable disease is identified, someone in the office sets up advance directive and power of medical attorney discussions, and a hospice information visit in the first three visits—not the last three. With this program, hospice use has increased to over 80%, with most patients spending more than a month in hospice care. The survival is as good or better and the cost is one third less (24) so this is being used as one model for national care plans.

There are at least 3 good ways to reliably predict a needed transition to hospice: prior number of regimens, disease status, and performance status. The 2013 NCCN guidelines call for a switch to nonchemotherapy based palliative care with "Failure to achieve a tumor response to 3 sequential chemotherapy regimens or ECOG performance status of 3 or greater." (http://www.nccn.org/professionals/physician_gls/pdf/breast.pdf, page 49) Both ASCO and NCCN endorse that patients with ECOG PS 3 or 4 not routinely be treated with chemotherapy (25). Note ECOG 3 is not "in bed more than 50% of the time" but "*in bed or chair* more than 50% of the time." We use a simple prompt: "Did this patient walk unaided into the clinic?" If not, we do not rule out chemotherapy completely, but ECOG 3 should prompt a discussion about the low chance of response, more toxicity, and a hospice information visit. We do a "hospice information visit" when the person has about 6 months to live. This moves the anxiety about death and hospice further upstream when the patient and family will have more time and perhaps energy to manage it, establishes the care plan, and establishes a link for "who will take care of me when I am not getting chemotherapy?" This has not been formally studied but empirically works well for nearly all patients, except those who do not want to consider hospice ever.

This switch is best accepted if the oncologist has said at the beginning "At some point chemotherapy will not be able to control this cancer, because it will grow resistant, and at some point chemotherapy can do harm with no chance of real benefit." We have found that keeping a list of "Prior treatments and response" makes it easier to summarize the situation for the patient. We also have added "Code status" and Advance Care Planning/Advance Directives to our records. Recent data suggests that less than 15% of cancer patients expected to die within a year, have any Advance Directives in their chart, and that e-mail and other prompts can increase the use of appropriate care planning (Table 73-4) (26).

TABLE 73-3

Useful Language to Negotiate Decisions and Advance Care Planning

Steps	*Useful language and questions*	*Comments*
Establish the setting	"Different people like to receive different amounts of information. How much do you want to know about your current health situation? Are there certain things you would not want to know or talk about?" "Is there anyone else you want to be here?"	Ensure privacy and comfort. Sit down with the patient. While most patients want to know the details of their cancer, some prefer to defer decision making to a family member or friend. If they do, ask why.
Assess patient's understanding of prognosis	"Can you share with me what you think is happening with your cancer/cancer treatment?" "Tell me about your understanding of the most recent tests/studies."	Start with open-ended questions. This allows patients to tell their stories and for you to identify any knowledge gaps.
Assess patient's expectations and goals	"What do you expect in the future?" "What are your hopes for the coming weeks/months?" "What is most important to you right now?" "What are you worried about now? In the future?"	Identify: 1. Patient's expectations and whether there is a disconnect between the patient's expectations and yours. 2. The most important goals for the patient. This will help you formulate the most appropriate plan of care.
Information sharing	"I would like to share with you the test results/your prognosis." "Would it be helpful if I write down the key information on a piece of paper for you to take home?"[a]	Use straightforward language without medical jargon. Deliver information one concept at a time. Pause in between to ask for patient understanding (see *Ask, Tell, Ask*).
Reframe goals	"I wish we had chemotherapy that could cure your breast cancer. But even though there is no cure, I think we can meet some of your other goals such as attending your son's graduation next month."	If patients have unrealistic expectations, gently redirect with "wish" statements and explore "second-best" options.
Identify needs for care	"How are you and your family coping?" "Is there anything you or your family need more help with?" "Are you bothered by pain or other symptoms?"	Most cancer patients have multiple symptoms and supportive care needs—but patients may not volunteer the information.
Hospice information visit referral for patients with 3–6 months prognosis	"Hospice service includes a team of people specialized in taking care of seriously ill patients at home. We routinely set up hospice information sessions for our patients so you will be familiar with what they do, should you need their services in the future."	Standardizing referrals for hospice information visits introduces hospice upstream as part of your clinic's "best practice" and a routine part of care.
Hospice referral	"From our discussion, I hear that it is important to stay at home and have your symptoms controlled. Hospice is one of the best ways to meet these goals. What have you heard about hospice?" "I know there are many misconceptions about hospice. I would like to explain what hospice is and what it can provide."	Emphasize how hospice services can meet patient's needs. Explore patient's understanding and preconceptions of hospice. Most people are not familiar with hospice services.
Summarize and be concrete	Summarize the discussion and strategize next steps. Ask for patient's understanding of key topics, and offer to answer any remaining questions.	Set up follow-up plans.

[a]Smith TJ. The art of oncology: when the tumor is not the target. Tell it like it is. *J Clin Oncol* 2000;18(19):3441–3445.

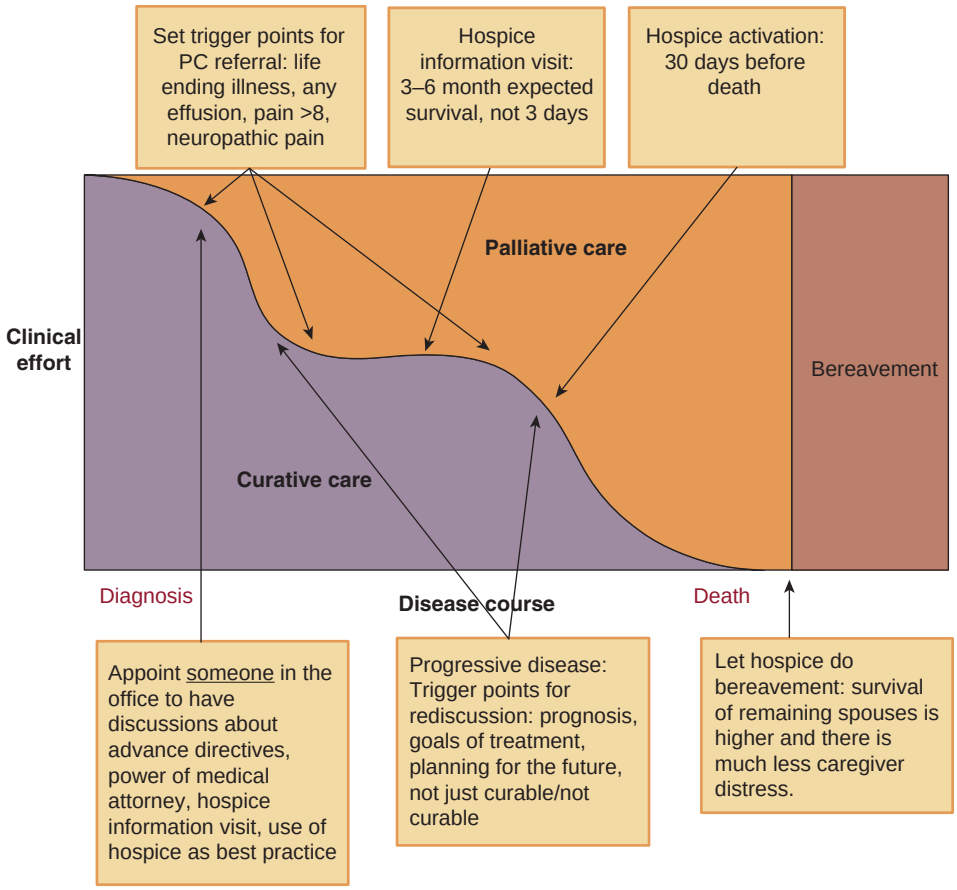

FIGURE 73-2 Triggers to have specific conversations with breast cancer patients.

ASCO is in the process of outlining what every oncologist and oncology office should be able to do as part of "primary palliative care." Most important is "the talk" triggered by progressive disease or a change in performance status. We use the same sort of script we use when talking about adjuvant chemotherapy: "If we are talking about 2nd or 3rd line chemotherapy, there are some other important issues to discuss. Do you have a will? Do you have a Living Will? What does it say about CPR? Who do you want to make medical decisions, if you can't? Have you discussed this with her/him? Are there spiritual issues? Are there family issues? Have you met with hospice yet? (3 to 6 months before death). Have you thought about where you would like to be for your death? Let's start with you doing a life review—what you want people to remember about you. What are you hoping for? What is important to you?" Patients and families almost universally thank us for having such a difficult conversation.

TABLE 73-4

Rearranging the Chart for Transition Prompts

Make headers called:
Prior treatments

1. Doxorubicin and cyclophosphamide, PR for 2 cycles, then PD
2. Cisplatin 75 mg/m^2, PD after 2 cycles
3. Paclitaxel Plus investigational drug, PD after 2 cycles
4. Capecitabine, PD after 2 cycles

Code status: _ _Full _x_DNR __Not discussed yet, discuss

Advance directive: _x_ Present __ Not Done __ Not discussed yet

Power of Medical Attorney: husband, Bill, phone xxx-xxx-xxxx

COMMON SYMPTOMS AT THE END OF LIFE, AND TREATMENTS

Breast cancer patients have multiple symptoms during their troubles with metastatic disease. In Table 73-5 we have tried to list all the common symptoms experienced by dying breast cancer patients, and some of the alternatives.

Pain is still the most common symptom experienced by patients. Most oncologists have become experienced in treating both chronic pain and breakthrough pain with opiates (the preferred term over "narcotics") and ensuring a bowel regimen. Methylnaltrexone subcutaneously has become part of usual care for refractory constipation but due to expense is not often used. For neuropathic pain, gabapentin and morphine work better (27) than either alone. For chemotherapy induced peripheral neuropathy, duloxetine (Cymbalta) is the only drug shown to work better than placebo for treatment, but it only worked for oxaliplatin neuropathy, not taxane neuropathy (28). Intraspinal and epidural treatments relieve pain significantly better than medical therapy, but are underused in practice.

TABLE 73-5

Common Symptoms at the End of Life

Symptom	*Alternatives*
Pain, Somatic	Opioid: Short acting breakthrough + Long acting; + Bowel regimen
Neuropathic pain	Antidepressants (TCA, SNRI) Anticonvulsants (Gabapentin, pregabalin)
Refractory pain	Infusion pumps Percutaneous Kyphoplasty Vertebroplasty/Radiofrequency ablation
Fatigue	Nonpharmacologic: no data. Pharmacologic: American ginseng 2,000 mg/day improved fatigue in a randomized trial compared to placebo; both methylphenidate and modafinil have effect only in those with high levels of fatigue. Dexamethasone 4 mg bid reduced fatigue and improved quality of care late in life.
Depression	Psychosocial interventions and antidepressants work in patients with advanced cancer; methylphenidate (Ritalin) may improve mood in patients with only weeks to live.
Hypercalcemia	Hydration (isotonic saline) + Bisphosphonate (Zoledronic acid superior to Pamidronate). Use a diuretic only if there is fluid overload. For severe symptomatic use Calcitonin to lower the calcium abruptly.
Delirium	Use Assessment Tools such as the CAM (Confusion Assessment Method); MDAS (Memorial Delirium Assessment Scale). Environmental—orientation (place, time, lighting, sounds), family education. Removal/replacement of potentiating medications (psychoactive drugs, corticosteroids; quinolone antibiotics; anticonvulsants; H2 blockers.) Opioid induced neurotoxicity—opioid rotation, dose reduction, hydration. Neuroleptics such as Haloperidol, atypical antipsychotics are the drug of choice.
Nausea/Vomiting	The Cleveland Clinic Protocol for Nausea and Vomiting in Advanced Cancer 1st line: Metoclopramide > Haldol; 2nd line: Olanzapine; 3rd line: Ondansetron Chemotherapy related: 5-HT3 antagonist substance/neurokinin receptor antagonists CNS metastasis related: Dexamethasone Noncomplete Bowel obstruction related: Metoclopramide Cancer related: Scheduled metoclopramide, prochlorperazine
Loss of appetite	Enteral tube feeding/parenteral nutrition do not improve comfort or survival. Megestrol acetate stimulates appetite in about a third of patients.
Bowel obstruction	Antiemetics (Metoclopramide IV > Haldol), Anticholinergics (Glycopyrrolate), Antisecretory (Octreotide), Dexamethasone Pain: Opioid (cautious, can aggravate colic); Opioid-sparing: Ketorolac, Prednisone
Dyspnea	Opioids (strong evidence), nebulized opioids (weak evidence) Benzodiazepine (panic-related) Corticosteroids (carcinomatous lymphangitic spread) Oxygen (mixed evidence: inferior to morphine for subjective dyspnea and hypoxemia; helpful for short term end of life dyspnea)

Fatigue is among the most common symptoms, and is less often noted by physicians. A simple "0–10" scale suffices for diagnosis, and both American ginseng (29) (2,000 mg a day) and dexamethasone (30) 4 mg bid have substantial benefits. The most commonly used drug methylphenidate (31) has little activity compared to placebo except in those with fatigue scores of at least 8/10. Depression is treated just as successfully in advanced cancer patients as the general public; for those with only weeks to live, methylphenidate may give some boost before typical antidepressants can act (32).

Delirium is prevalent at the end of life and often highly upsetting to families and staff. There are simple assessment methods such as the Confusion Assessment Method (CAM) and haloperidol and similar drugs clearly work at low doses (33) and are preferred over benzodiazepines.

Nausea and vomiting at the end of life is usually due to brain or bowel issues, not chemotherapy. The expensive serotonin-inhibitors have less use than simple inexpensive drugs such as metoclopramide, haloperidol, prochlorperazine, and olanzapine (34). Bowel obstruction can be treated with oral atropine but there are few data. Hospice providers have much expertise in this field but nearly all their treatments are empirically derived and not evidence-based.

Dyspnea is reliably assessed with a 0–10 scale just like pain but does not correlate with oxygen levels. Opiates are the mainstay of treatment, started in the same way as pain management with small as-needed doses and assessment one hour after treatment. There is no compelling evidence that any route of administration of opiates—oral, subcutaneous, intravenous, nebulized—is better. Oxygen is the most commonly used remedy but in the largest trial was no more effective than room air, (35) and is only effective if there is hypoxemia. If oxygen is automatically put on in the hospital, we do a twenty minute trial to see if the patient does just as well without it before insisting on a cannula tether and $25 to $150 a day charges at home.

There are other situations near the end of life that will arise in every oncology practice: requests for physician assisted suicide, and the need for palliative sedation. Most oncologists are asked several times a year "Isn't there some way to end this?" yet we get very little training in how to respond to such questions. Experts in the area suggest involvement of colleagues and palliative care specialists to ensure that all the palliative options are available (36). While one in ten US physicians reported "having sedated a dying patient with the specific intention of making the patient unconscious until death," most remain firmly opposed to the concept (37). Palliative sedation is the relief of refractory symptoms with the unintended consequence of sedation to unconsciousness, used only when other methods have failed (38).

CONCLUSIONS

Most breast oncologists provide end of life care but have had little training in the area. The skills of primary palliative care (open communication, symptom management, hospice referral) are readily learnable, with excellent sources available. For secondary and tertiary palliative care we must develop referral patterns to local and regional palliative care specialists just as we do for nephrologists.

The benefits of concurrent palliative care are now well established from multiple randomized trials. Palliative care alongside oncology, with transition to hospice care when appropriate, improves quality of life and symptoms, reduces aggressive and unhelpful end of life care, helps patients understand their illness, reduces caregiver distress, and may allow patients to live longer.

MANAGEMENT SUMMARY

- Nearly all patients want to know all the information about their illness including curability, prognosis, likely outcomes, and advance care planning.
- Concurrent oncology and palliative care for all seriously ill cancer patients is now recommended by ASCO and NCCN.
- Use the natural history of the disease to prompt us to discuss important issues: (i) Discuss curability at onset. (ii) At each recurrence do "Ask, Tell, Ask" about prognosis, advance care planning, and goals of care. At second or third progression ensure a hospice information visit when there are 3 to 6 months left to live.
- For fatigue, American Ginseng 2 g/day or dexamethasone 4 mg bid for 15 days has been proven effective in randomized clinical trials.
- For chemotherapy induced neuropathic pain, duloxetine is the only drug with effectiveness proven in a randomized clinical trial.
- For dyspnea, oxygen is no better than room air in the documented absence of hypoxemia. Opioids are the mainstay of dyspnea treatment, starting at low doses and increasing slowly as with pain management.
- For delirium, low doses of haloperidol or other antipsychotics are more effective than benzodiazepines.

All oncologists do palliative care. We can learn to do this part more effectively by doing assessments of symptoms including depression, spirituality, coping, and goals of care.

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CHAPTER 74

Management Summary for the Care of Patients with Metastatic Breast Cancer

Marc E. Lippman

Very unfortunately, metastatic breast cancer remains largely incurable. Therefore, the primary goals of therapy are the alleviation of symptoms, the avoidance of complications of disease progression, and the prolongation of survival so long as a reasonable quality of life can be maintained. Exceptional circumstances may occasionally offer a more optimistic appraisal. Survival curves for metastatic breast cancer are not normally distributed and some patients can survive well over a decade or longer with a proven diagnosis of metastatic disease. These circumstances are most commonly ER-positive patients with remarkable responses to endocrine therapy. Additionally, so-called Stage IV NED patients may have long secondary disease free intervals and recent data reviewed in Chapter 69 suggest that addition of adjuvant systemic chemotherapy in this setting is likely of benefit.

The consequences of a diagnosis of metastatic disease are so life altering for a patient and her family that we believe, under almost all circumstances, that formal histologic confirmation is required. Furthermore, the determination of specific tumor characteristics such as estrogen, progesterone, and HER2 expression (which clearly can change with or without intervening therapy from determinations on primary tumors) provide an additional indication for biopsy. This is likely to become even more important in coming years as the availability of specific targeted therapies become even more widespread. As reviewed in Chapter, these determinations may soon be reliably obtained on circulating tumor cells or even circulating DNA derived from tumor cells.

Local symptoms are often best treated by specific local therapies that are commonly associated with less toxicity than systemic therapy, and, with respect to pain control, generally more effective. Many aspects of localized treatment, including stereotactic body radiation therapy, intracranial stereotactic radiosurgery, and radiofrequency ablation, have greatly improved control of localized sites of metastases particularly in the liver and the CNS. Because at least 90% of all patients with metastatic breast cancer will have bone metastases at some point, lifetime management with bisphosphonates or rank ligand inhibitors is commonly indicated. Whenever possible, multidisciplinary discussion and review with appropriate team members, including surgeons, radiation oncologists, medical oncologists, and experts in palliative care, should be sought. While the data remain controversial, the preponderance of analyses have suggested that mastectomy or other means of definitive local control of breast cancer improves survival for patients presenting at the outset with stage IV disease. If for no other reason than optimal local control, we endorse this for patients felt to have a reasonable survival expectancy (see Chapter 68).

The exact choice of an optimal systemic therapy is almost never limited to a single option or two and the number of active agents has increased in recent years and will almost certainly continue to do so. We strongly urge the participation in clinical trials whenever possible. Choices clearly need to balance patient expectations, urgency of the need for a response, the need for interdigitation of systemic therapy with local treatment, and prior treatments in either the neoadjuvant, adjuvant or advanced disease setting. Unfortunately, costs of therapy may need to be a consideration and the treating physician needs to be aware that often highly marketed (and often exceedingly costly options) are often not proven to offer superiority to generic choices. It is also the case, particularly in the United States, that many patients are treated with anticancer agents beyond the point where reasonable expectations of gain are supportable. It is very important to have frank and honest discussions with patients and their family that fairly assess the likelihood of gain as compared to harms from multiple regimens. We cannot overemphasize the need and value of including palliative care expertise in the equation and appropriately discussing hospice care at the right time. Many oncologists understandably find these discussions difficult and often think it less stressful to initiate multiple lines of therapy even after such treatments hold little hope for serious palliation. Some discussion of hospice care ought, reasonably, to be formally considered after a second line of therapy for metastatic disease for most women. This is particularly true in that adroit management of symptoms with antiemetics, neuroleptics, antidepressants, pain medications, and nutritional support are often either overlooked or incompletely attended to by oncologists. In many cases, patients are not forthcoming about these issues and information about symptomatology needs to be carefully elicited.

SECTION XI

New Breast Cancer Therapeutic Approaches

CHAPTER 75

Newer Targeted Therapy

Ingrid A. Mayer and Carlos L. Arteaga

CHAPTER CONTENTS

Advances in tumor genetics and drug development over the last decade have led to the generation of a wealth of anti-cancer targeted therapies. These drugs aim at targeting a particular vulnerability in the tumor generated in most cases as a result of dependence on an oncogene and/or loss of a tumor suppressor. Several recent examples indicate that these drugs are mainly, if not exclusively, active against tumors of a particular genotype that can be identified by a diagnostic test, usually detecting a somatic alteration in tumor DNA. However, for the majority of targeted therapies in development, there are still no clinical tools to determine which patients are most likely to benefit or, alternatively, be resistant *de novo* to these novel agents or drug combinations. In this chapter, we will review some of the newer (molecule) targeted therapies, the molecular targets and/or pathways they engage, the rationale for their use in breast cancer, pharmacodynamics and predictive biomarkers indicative of drug target modulation and clinical response, respectively, and the latest completed and planned clinical trials with them.

PHOSPHATIDYLINOSITOL-3 KINASE (PI3K)/AKT INHIBITORS

Multiple PI3K families exist in higher eukaryotes. To date only class I_A PI3K has been implicated in cancer. Class I_A PI3Ks are heterodimers consisting of a p85 regulatory subunit and a p110 catalytic subunit. Growth factor receptor tyrosine kinases (RTKs) such as EGFR, HER2, insulin receptor, IGF-IR, MET, etc. also signal via class I_A PI3K (1). These transmembrane receptors do not bind PI3K directly but activate this enzyme by phosphorylating adaptor proteins such as GAB1/2, IRS-1/2, and HER3 (ErbB3), which via YXXM motifs bind the amino terminal domain of p85. This binding relieves the inhibition of p110 by p85 and recruits the p85-p110 heterodimer to its substrate, the lipid phosphatidylinositol-4,5-bisphosphate (PIP2), at the plasma membrane. PI3K (p110) then phosphorylates PIP2 to produce the second messenger phosphatidylinositol-4,5-trisphosphate (PIP3). A Ras-binding domain (RBD) in p110α also mediates activation by Ras. PTEN (phosphatase and tensin homologue) dephosphorylates PIP3, thus, negatively regulating the product of PI3K (2). Several pleckstrin homology (PH) domain-containing proteins, including Akt, SGK, and PDK1, bind to PIP3 at the plasma membrane. The phosphorylation of Akt at Thr^{308} by PDK1 and at Ser^{473} by a complex involving mTOR/Rictor (TORC2) results in full activation of this enzyme. Akt phosphorylates a host of cellular proteins, including GSK3α, GSK3β, FoxO transcription factors, MDM2, BAD, and $p27^{KIP1}$ to facilitate survival and cell cycle entry (3). In addition, Akt phosphorylates and inactivates Tuberin, a GTPase-activating protein (GAP) for the Ras homologue Rheb. Inactivation of Tuberin allows GTP bound-Rheb to accumulate and activate the mTOR/Raptor (TORC1) complex, which ultimately regulates protein synthesis and cell growth and inhibits autophagy (4) (Fig. 75-1).

The PI3K/AKT pathway is the most frequently mutated pathway in breast cancer, with mutation and/or amplification of the genes encoding the PI3K catalytic subunits p110α (*PIK3CA*) and p110β (*PIK3CB*), the PI3K regulatory subunit p85α (*PIK3R1*), receptor tyrosine kinases (RTKs) such as HER2 (*ERBB2*) and FGFR1, the PI3K activator K-Ras, the PI3K effectors AKT1, AKT2, and PDK1, and loss of the lipid phosphatases PTEN and INPP4B (5). The three genes *PIK3CA, PIK3CB*, and *PIK3CD* encode the homologous p110α, p110β, and p110δ isozymes, respectively. Expression of p110δ is largely restricted to immune and hematopoietic cells, whereas p110α and p110β are ubiquitously expressed. The p110α isozyme is essential for signaling and growth of

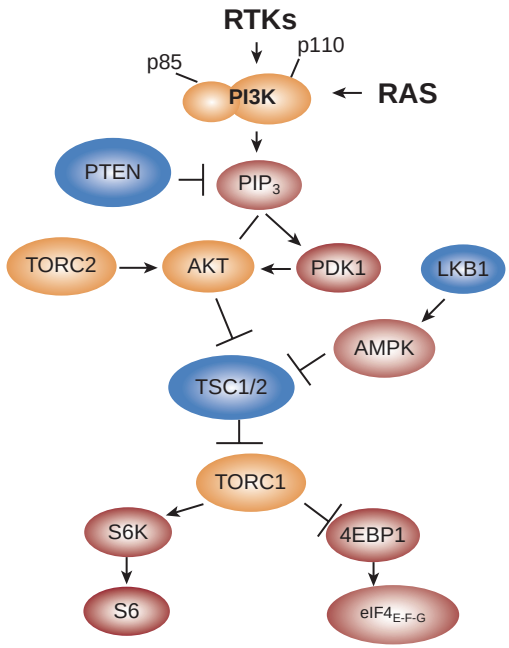

FIGURE 75-1 RTKs activate the p85/p110 PI3K dimer via phosphorylation of adaptor proteins (i.e., GAB1, GAB2, IRS-1, IRS-2, HER3), which have YXXM motifs that engage the N-SH2 domain of p85. This binding relieves the inhibition of p110 by p85 and recruits the p85-p110 heterodimer to its substrate, the lipid phosphatidylinositol-4,5-bisphosphate (PIP2), at the plasma membrane. PI3K phosphorylates PIP2 to produce the second messenger phosphatidylinositol-3,4,5-trisphosphate (PIP3). A Ras-binding domain (RBD) in p110α mediates activation by the small GTPase Ras. PTEN dephosphorylates PIP3, thus negatively regulating the product of PI3K. A subset of pleckstrin homology (PH) domain-containing proteins, including Akt and PDK1, bind to PIP3 and are thereby recruited to the membrane. The phosphorylation of Akt at Thr^{308} by PDK1 and at Ser^{473} by a complex involving mTOR/Rictor (TORC2) results in full activation of this enzyme. Akt phosphorylates a host of cellular proteins, including GSK3α, GSK3β, FoxO transcription factors, MDM2, BAD, and $p27^{KIP1}$ to facilitate survival and cell cycle entry. In addition, Akt phosphorylates and inactivates Tuberin (TSC1/2), a GTPase-activating protein (GAP) for the Ras homologue Rheb. The tumor suppressor LKB1 activates AMPK, which, in turn, can also inactivate Tuberin. Inactivation of Tuberin allows GTP bound-Rheb to accumulate and activate the mTOR/Raptor (TORC1) complex, which ultimately regulates protein synthesis and cell growth. Tumor suppressors are noted in blue and oncogenes in pink.

tumors driven by *PIK3CA* mutations, RTKs, and/or mutant Ras, whereas p110β lies downstream of GPCRs and has been shown to mediate tumorigenesis in PTEN-deficient cells. *PIK3CA* mutations are the most common genetic alterations of this pathway, where ≥80% occur within the helical (E542K and E545K) and kinase (H1047R) domains of p110α. Such mutations confer increased catalytic activity through different mechanisms, but both induce characteristics of cellular transformation including growth factor- and anchorage-independent growth, and resistance to anoikis.

Drug Resistance and Rationale for Combinations

Activation of the PI3K/AKT pathway has been shown to confer resistance to antiestrogen in various experimental models, including PTEN- and INPP4B-deficient cells and in cells overexpressing HER2, IGF-IR, and mutant AKT1 (6). Tumor cells with acquired endocrine resistance have been shown to upregulate IGF-IR, InsR, HER2, and EGFR levels as well as PI3K/AKT/mTOR activity (7). Inhibitors of the PI3K pathway trump this adaptation of ER+ cells to estrogen +deprivation. A recent study showed that in ER+ breast cancer cells treated with the PI3K/TOR inhibitor BEZ235 or with p110 siRNAs, exogenous estradiol prevents BEZ235- and siRNA-induced apoptosis (8). Because most breast cancers that adapt to antiestrogen therapy retain ER, these data imply that unopposed estrogen will protect ER+ tumors from the action of PI3K inhibitors used as single agents.

Clinical evidence suggests that activation of PI3K as a result of overexpression of HER2 or FGFR1 or loss of INPP4B also confer resistance to antiestrogens. Of interest, the activating mutations in PIK3CA correlate with good patient prognosis in some retrospective series. However, PI3K has been shown to interact with ER directly and indirectly, resulting in ER phosphorylation and an increase in estrogen- and tamoxifen-induced as well as ligand-independent ER transcription. In turn, estrogen can rapidly activate PI3K via Ins/IGF-IR, EGFR, and Src. Further supporting cross-talk between these two pathways, Guo et al. reported that a constitutively active mutant of AKT reduces ERα expression, whereas AKT inhibition results in an increase in ERα. Upon inhibition of PI3K/AKT, the transcription factor FoxO3a translocates to the nucleus where it transactivates ERα mRNA; expression of dominant negative FoxO3a reduces ERα levels in MCF-7 cells (9,10). This co-regulation supports the need of combined inhibition of both pathways in ER+ breast cancers with aberrant activation of PI3K/AKT. Indeed, preclinical evidence with ER+/PI3K mutant breast cancer cells suggests that simultaneous inhibition of PI3K and ER is synergistic (8,11), providing a rationale for combinations of antiestrogens with PI3K pathway inhibitors. In breast cancers with *HER2* gene amplification, HER2/HER3 dimers potently activate PI3K which, in turn, is critical for tumor cell progression and survival. Indeed, sustained inhibition of PI3K is required for the antitumor action of the HER2 inhibitors trastuzumab and lapatinib. A significant fraction of HER2+ tumors also harbor somatic alterations in the PI3K pathway that further dysregulate PI3K/AKT signaling and, as a result, confer resistance to HER2 inhibitors (12). In a large-scale siRNA genetic screen, Berns et al. identified PTEN as the only gene whose knockdown conferred trastuzumab resistance (13). Further, induced overexpression "hot spot" *PIK3CA* mutants similarly conferred trastuzumab resistance. Patients with "hot spot" *PIK3CA* mutations and undetectable or low PTEN measured by IHC exhibited a poorer outcome after treatment with chemotherapy and trastuzumab compared to patients without those alterations. An earlier study had also shown that loss of PTEN correlates with a lower response to trastuzumab. More recently, Esteva et al. found that PI3K pathway activation, defined as PTEN loss and/or *PIK3CA* mutations, was associated with a poor response to trastuzumab as well as a poorer overall survival (14). In addition, human breast cancer cell lines containing endogenous mutations in *PIK3CA* are intrinsically resistant to trastuzumab. Human breast cancer cell lines in which *PIK3CA* mutations are ectopically expressed exhibit an attenuated response to lapatinib. On the other hand, loss of PTEN has not been consistently associated with resistance to lapatinib.

A causal role of aberrant activation of the PI3K pathway with *de novo* and acquired drug resistance is further supported by the effects of inhibitors of PI3K/AKT. For example, combinations of trastuzumab with the PI3K inhibitor XL147, or trastuzumab or lapatinib with the dual PI3K-mTOR inhibitor BEZ235, inhibit growth of *PIK3CA* mutant xenografts resistant to anti-HER2 therapies (15). In a model of trastuzumab resistance caused by PTEN loss, targeting mTOR or AKT was able to at least partially overcome resistance. Evidence is also emerging from the clinic that targeting the PI3K axis in addition to HER2 may be a strategy to overcome resistance. For example, in a phase II study, the combination of the TORC1 inhibitor everolimus with trastuzumab and chemotherapy showed a partial response rate of 19% and a clinical benefit rate of 81% in patients with HER2+ metastatic breast cancer that had previously shown progression on trastuzumab plus a taxane (16).

Therapeutic Inhibitors

Several drugs targeting multiple levels of the PI3K network (i.e., PI3K, AKT, mTOR) have been developed (Tables 75-1 and 75-2). A number of ATP-mimetics that bind competitively and reversibly to the ATP-binding pocket of p110 are in early clinical development. These include the pan-PI3K inhibitors BKM120, XL-147, PX-866, PKI-587, and GDC-0941, the p110α-specific inhibitors BYL719, GDC-0032, and INK-1117, the p110δ-specific inhibitor CAL-101, and the dual PI3K/mTOR inhibitors BEZ235, BGT226, PF-4691502, GDC-0980, and XL-765. The pan-PI3K and p110α-specific inhibitors are equally potent against oncogenic p110α mutants. The rationale for the development of isozyme-specific antagonists is to allow higher doses of anti-p110α and anti-p110β drugs to be delivered without incurring side effects caused by pan-PI3K inhibitors. Interim results from a phase I trial with the p110δ-specific inhibitor CAL-101 in patients with hematologic malignancies showed that treatment reduced P-AKT levels >90% in peripheral blood lymphocytes and induced objective clinical responses. Recently completed phase I trials with BKM120, BEZ235, and XL-147 showed that treatment partially inhibited PI3K as measured by levels of P-S6 and P-AKT in patients' skin or tumors, and 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) uptake measured by PET. Main toxicities were rash, hyperglycemia, diarrhea, fatigue, and mood alterations (17). Few clinical responses were observed in patients with and without detectable PI3K pathway mutations, although screening for genetic lesions in this pathway was not comprehensive.

Both allosteric and ATP-competitive pan-inhibitors of the three isoforms of AKT are also being developed. AZD5363, GDC-0068, GSK2141795, and GSK690693 are ATP-competitive compounds that have shown antitumor activity

TABLE 75-1

PI3K/AKT Pathway Inhibitors in Clinical Development

Drug target	*Drug*	*Source*	*Mechanism*	*Phase of Development*
Pan-PI3K	BKM120	Novartis	ATP-competitive	Phase III
	GDC0941	Genentech	ATP-competitive	Phase
	XL-147	Exelixis/Sanofi	ATP-competitive	Phase I
	PX-866	Oncothyreon	ATP-competitive	
	CH5132799	Chugai Pharma	ATP-competitive	
p110α	BYL719	Novartis	ATP-competitive	Phase II
	GDC0032	Genentech	ATP-competitive	Phase II
	MLN-1117	Millennium	ATP-competitive	Phase I
p110δ	CAL-101	Calistoga	ATP-competitive	Phase III
p110β	AZD6482	AstraZeneca	ATP-competitive	Discontinued
	GSK2636771	GSK	ATP-competitive	Phase I
PI3K/mTOR	BEZ235	Novartis	ATP-competitive	Phase II
	GDC0980	Genentech	ATP-competitive	Phase II
	PKI-587	Pfizer	ATP-competitive	
	PF-4691502	Pfizer	ATP-competitive	
	XL-765	Exelixis-Sanofi	ATP-competitive	Phase II
	GSK1059615	GSK	ATP-competitive	
	DS-7423	Daiichi Sankyo	ATP-competitive	Phase I
TORC1/2	MLN-128	Millennium	ATP-competitive	Phase II
	OSI-027	OSI-Astellas	ATP-competitive	Discontinued
	AZD2014	AstraZeneca	ATP-competitive	Phase I
	CC-223	Celgene	ATP-competitive	Phase II
TORC1 (rapalogs)	Everolimus	Novartis	Allosteric	FDA-approved
	Temsirolimus	Pfizer	Allosteric	FDA-approved
	Ridaforolimus	Merck	Allosteric	Phase II
AKT	MK-2206	Merck	Allosteric	Phase II
	AZD5363	AstraZeneca	ATP-competitive	Phase I
	GDC0068	Genentech	ATP-competitive	Phase II
	GSK690693	GSK	ATP-competitive	

TABLE 75-2

Current Clinical Trials with PI3K Inhibitors

Study Design	*Clinical Trial*	*Type of inhibitor*	*Patient Population*	*Clinicaltrials.gov*
Phase I	Safety and Efficacy of BKM120 and Lapatinib in HER2+/PI3K-activated, Trastuzumab-resistant Advanced Breast Cancer	pan-PI3K	Trastuzumab-resistant HER2+ metastatic breast cancer	NCT01589861
	A Study of PI3-Kinase Inhibitor GDC-0941 in Combination with Paclitaxel, with and without Bevacizumab or Trastuzumab, in Patients with Locally Recurrent or Metastatic Breast Cancer		Trastuzumab-resistant HER2+ metastatic breast cancer; HER2-negative metastatic breast cancer	NCT00960960
	Phase I of BKM120/ Olaparib for Triple Negative Breast Cancer or High Grade Serous Ovarian Cancer	pan-PI3K PARP	Patients with triple negative breast cancer or high grade serous ovarian cancer	NCT01623349
	Phase I Study of PI3 (Phosphoinositol 3)-Kinase Inhibitor BAY80-6946 with Paclitaxel in Patients with Advanced Cancer	PI3Kα and PI3Kβ	HER2-negative metastatic breast cancer	NCT01411410
Phase Ib/II	Phase Ib/II Trial of BEZ235 with Paclitaxel in Patients with HER2 Negative, Locally Advanced or Metastatic Breast Cancer	PI3K/ mTOR	HER2-negative, locally advanced or metastatic breast cancer	NCT01495247
Phase II	A Trial of BKM120 (a PI3K Inhibitor) in Patients with Triple Negative Metastatic Breast Cancer	pan-PI3K	Triple negative metastatic breast cancer	NCT01629615
	BKM120 and Fulvestrant for Treating Postmenopausal Patients with Estrogen Receptor-Positive Stage IV Breast Cancer		Postmenopausal patients with estrogen receptor–positive Stage IV breast cancer	NCT01339442
	FERGI: Study of GDC-0941 or GDC-0980 with Fulvestrant Versus Fulvestrant in Advanced or Metastatic Breast Cancer in Patients Resistant to Aromatase Inhibitor Therapy		Postmenopausal patients with ER+ metastatic breast cancer resistant to aromatase inhibitor therapy	NCT01437566
	Akt Inhibitor MK2206 in Treating Patients with Advanced Breast Cancer	Akt	Metastatic breast cancer	NCT01277757
	MK-2206 and Anastrozole with or without Goserelin Acetate in Treating Patients with Stage II-III Breast Cancer		Patients with Stage II-III ER+ breast cancer	NCT01776008
	MK2206 in Treating Patients with Stage I, Stage II, or Stage III Breast Cancer		Stage I, Stage II, or Stage III breast cancer	NCT01319539
Phase III	BELLE-3: A Phase III Study of BKM120 with Fulvestrant in Patients with HR+,HER2-, AI Treated, Locally Advanced or Metastatic Breast Cancer Who Progressed on or after mTOR inhibitors	pan-PI3K	Postmenopausal patients with HR+,HER2-, AI treated, locally advanced or metastatic breast cancer who progressed on or after mTOR inhibitors	NCT01633060
	BELLE-2: Phase III Study of BKM120/ Placebo with Fulvestrant in Postmenopausal Patients with Hormone Receptor Positive HER2-negative Locally Advanced or Metastatic Breast Cancer Refractory to Aromatase Inhibitor		Postmenopausal patients with hormone receptor–positive HER2-negative locally advanced or metastatic beast cancer refractory to aromatase inhibitor	NCT01610284

in preclinical models and recently entered phase I trials. Allosteric inhibitors such as MK-2206 bind to the AKT PH domain and/or hinge region to promote an inactive conformation of the AKT protein that is unable to bind to the plasma membrane. MK-2206 inhibits AKT signaling *in vivo*, and suppresses growth of breast cancer xenografts harboring *PIK3CA* mutations or *ERBB2* amplification (18). Phase I data showed that treatment with MK-2206 decreases levels of P-AKT, P-PRAS40, and P-GSK3β in tumor cells, peripheral blood mononuclear cells, and hair follicles.

Another approach to block this pathway has been the development of ATP-competitive inhibitors of the mTOR kinase, which block both mTORC1 and mTORC2. Several dual TORC1/2 inhibitors have been identified, including INK128 (Intellikine), CC223 (Celgene), OSI-027 (OSI Pharmaceuticals), AZD8055 (AstraZeneca), AZD2014 (AstraZeneca), and Palomid 529 (Paloma Pharmaceuticals).

Dual PI3K/mTOR inhibitors have also been developed in the hope of overcoming the loss of feedback inhibition or PI3K activation observed with rapalogs. The mTORC1 pathway is one of the prominent negative feedback regulators of the PI3K pathway; inhibition of mTORC1 can release this feedback inhibition and activate the PI3K pathway (19). BEZ235, a dual PI3K/mTOR inhibitor, showed higher antiproliferative activity than rapamycin in a preclinical study trastuzumab-resistant and -sensitive human breast cancer cell lines (15). In breast cancer, dual PI3K/mTOR inhibitors are being combined with everolimus, endocrine therapies (exemestane and letrozole), chemotherapy (paclitaxel), and anti-HER2 therapy (trastuzumab).

Overall, the profile of PI3K inhibitors regarding adverse events has been acceptable, with no unexpected toxic effects. Toxic effects have been primarily mild to moderate and manageable with supportive medication. Dose-limiting toxic effects reported with multiple agents include hyperglycemia, maculopapular rash, gastrointestinal intolerance (anorexia, nausea, vomiting, dyspepsia, diarrhea), and stomatitis. Although some of these toxic effects are "off-target" effects, others may be related to target engagement and directly related to mechanisms of action.

Clinical Trials

Several early-stage clinical trials as both single agents and in combination have already been reported or are underway with AKT inhibitors (allosteric such as MK-2206, and catalytic inhibitors such as GDC-0068 and GSK690693) and all three categories of PI3K inhibitors: (i) pan-PI3K inhibitors that target all p110 isoforms (GDC-0941, XL147, BKM120; the irreversible pan-PI3K inhibitor PX-866) (ii) isoform-specific PI3K inhibitors that target a specific p110 isoform (such as the p110δ-selective inhibitor CAL-101, and the p110α-selective INK1117 and BYL719); and (iii) PI3K/mTOR dual inhibitors that inhibit all p110 isoforms as well as mTOR (SF1126, BEZ235, XL765, and GSK1059615).

PI3K Inhibitors and Endocrine Therapy

A phase Ib trial of letrozole and BKM120 (pan-PI3K inhibitors that target all p110 isoforms) for postmenopausal patients with ER+/HER2– metastatic breast cancer (MBC) evaluated safety and preliminary anti-tumor activity of two different schedules of BKM120 administration in combination with letrozole: continuously or intermittently (5 on/2 off days) (20). Fifty-one patients were accrued in total; 40/51 (78%) had previously progressed on an aromatase inhibitor in the metastatic setting. The dose-limiting toxicity (DLT) in the continuous BKM120 schedule was transaminitis, and in the intermittent BKM120 schedule, mood disorders. Of note, the overall rate of grades 1–3 toxicities was higher in the continuous schedule arm. Six of 20 (30%) patients in the continuous BKM120 schedule arm and 10/31 (32%) of patients in the intermittent BKM120 schedule arm received therapy for >6 months. Interestingly, 45% of evaluable patients with a PI3K mutant cancer maintained stable disease for ≥6 months but duration of therapy. However, this clinical benefit has also been observed in a similar number of patients with PIK3CA wild-type tumors. A large phase II-III neoadjuvant trial with letrozole with or without BKM120 or BYL719 in patients with ER+ operable breast cancer is under way.

PI3K Inhibitors and HER2-targeted Therapy

Early clinical studies have also combined dual PI3K/mTOR inhibitors with trastuzumab. A phase I/Ib dose-escalation study of BEZ235, a dual PI3K/mTOR inhibitor, with trastuzumab aimed to enrich for patients with PI3K pathway alterations by limiting the study to patients with mutations in PIK3CA or PTEN or loss of PTEN by IHC in tumor samples. The maximum tolerated dose (MTD) for BEZ235 is estimated to be 600 mg per day in combination with trastuzumab, and this dose is being carried forward to the dose-expansion cohort. The combination also appears to be clinically active, with a clinical benefit rate (CBR) of 27%. In this study, there does not appear to be an association between PI3K pathway alteration and response (21). Given the short half-life of BEZ235, a twice-daily schedule was investigated in a phase Ib/II study in combination with trastuzumab, but found to be too toxic.

The safety and efficacy of a novel PI3K inhibitor (XL147) administered in combination with trastuzumab or with paclitaxel and trastuzumab are being evaluated in patients with HER2-positive metastatic breast cancer that progressed during previous trastuzumab treatment (NCT01042925).

Combinations of MEK and PI3K pathways inhibitors are being explored in attempts to block escape pathways, which may become prominent when the PI3K pathway is inhibited. Several new generation PI3Kα-selective inhibitors are currently being evaluated in phase I clinical trials, including BYL719 (NCT01219699), INK-1114 (NCT01449370), and GDC-0032 (NCT01296555), as a single agent or in combination with endocrine therapies (letrozole and fulvestrant) or HER2-targeted agents (trastuzumab).

INHIBITORS OF MTOR

mTOR kinase is a serine-threonine kinase and member of the PI3K-AKT pathway that integrates signals from growth factors and nutrients to regulate key metabolic and macromolecular processes, such as mRNA translation, ribosome biogenesis, protein synthesis and cell motility. mTOR nucleates two protein complexes, TORC1 and TORC2, that mediate different functions in part through mRNA translational control (4). TORC1 also contains the regulatory protein Raptor, which recruits substrates to TORC1 for phosphorylation, including the eIF4E binding/inhibiting protein (4E-BP, inhibited by phosphorylation) and ribosomal protein S6 kinases 1,2 (S6K1,2). S6K1,2 phosphorylate S6 and the initiation factor eIF4B, stimulating its RNA binding activity and cap-dependent translation. The second complex, TORC2 contains the rapamycin-insensitive component of mTOR (Rictor). It regulates cytoskeletal organization in response to growth factors and lead to phosphorylation of AKT (in Ser473) and its activation. AKT activates TORC1/Raptor via inactivation of TSC1 (22).

Support for the combination of mTOR inhibitors with either tamoxifen or an aromatase inhibitor (AI) has been demonstrated in preclinical models of antiestrogen-sensitive and -resistant ER+ breast cancer (23). MCF-7 cells expressing constitutively active Akt were able to proliferate under reduced estrogen conditions and were resistant to the growth inhibitory effects of tamoxifen, both *in vitro* and *in vivo* (23). However, co-treatment with temsirolimus inhibited mTOR and restored sensitivity to tamoxifen, primarily through induction of apoptosis, thus suggesting that Akt-induced tamoxifen resistance may in part be mediated by signaling through the mTOR pathway. Further, everolimus has also been shown in *in vitro* (24) and *in vivo* (25) models to restore sensitivity of cancer cells to letrozole.

Rapamycin and its analogs form complexes with FK506-binding protein (FKBP12). This complex then binds to mTOR and inhibits the kinase activity of TORC1 but not TORC2. Formulation problems of rapamycin prompted the development of analogs such as CCI-779 (temsirolimus), RAD001 (everolimus), AP-23573 (deferolimus), and MK-8669 (ridaferolimus). These rapalogs have shown cytostatic activity in preclinical models and clinical trials, particularly in patients with renal cell cancer and in patients with mutations in the TSC complex (upstream of TORC1) who harbor renal angiolipomas. Compounds that target the ATP-binding cleft of mTOR (i.e., OSI-027, AZD8055, INK-128), and are thus active against both TORC1 and TORC2, are also in phase I trials. Of note, treatment with rapalogs results in compensatory stimulation of AKT-TORC1 through activation of TORC2 (19). This has stimulated the interest on development of small molecule catalytic inhibitor of TORC1/2.

CLINICAL TRIALS

mTOR Inhibitors and Endocrine Therapy

Combinations with tamoxifen and aromatase inhibitors have already been evaluated in phase II and III clinical trials (Table 75-3). A phase II, 3-arm study evaluated daily letrozole alone or in combination with daily temsirolimus (10 mg/day or 30 mg/day for 5 days every 2 weeks) in postmenopausal women with locally advanced or MBC; median progression-free survival (PFS) was 11.5 months in the letrozole /temsirolimus 10 mg arm, 13.2 months in the letrozole/temsirolimus 30 mg arm, and 11.6 months in the letrozole alone arm (26). However, the subsequent HORIZON study, a large phase III randomized, double-blind, multicenter trial of temsirolimus plus letrozole versus placebo plus letrozole in postmenopausal women with newly diagnosed locally advanced or MBC, showed that both treatment arms had virtually identical median PFS and ORRs (27). Interestingly, although the combination arm had higher incidence of mTOR inhibitor–related toxicities than the single-agent arm, the occurrence of these toxicities was lower than that seen in several everolimus studies.

In a phase II randomized trial of 270 postmenopausal women (28), those who received 4 months of preoperative therapy with letrozole and everolimus had a clinical response rate of 68% compared with 59% in those receiving letrozole alone, suggesting that both ER blockade and mTOR inhibition augments the efficacy of ER-targeting. Of note, patients in this trial whose tumors had activating mutations in exon 9 of PIK3CA showed strong antiproliferative response (Ki-67) to mTOR/AI combination therapy but poor response to AI alone.

In patients with acquired aromatase inhibitor resistance, the value of blocking ER and the PI3K/AKT/mTOR pathway is shown in several key papers. Results from the phase II TAMRAD study conducted in postmenopausal patients with AI-resistant ER+ MBC found the addition of everolimus to tamoxifen almost doubled time to progression (4.5 months vs. 8.6 months for tamoxifen alone and tamoxifen-everolimus), corresponding to a 46% reduction in risk of progression with combination therapy (29). Interestingly, a subgroup analysis revealed that for the tamoxifen-everolimus arm, this risk reduction was greatest among patients with secondary resistance to endocrine treatment (54%). Higher clinical benefit rates (CBRs; defined as the absence of progression at 6 months) were also observed in patients with secondary hormone resistance who received the combination vs. tamoxifen alone (74% vs. 48%, respectively).

The benefit of everolimus in AI-resistant advanced breast cancer has been further supported by the phase III BOLERO-2 study, which compared the combination of exemestane and everolimus versus exemestane alone in patients with ER-positive MBC (30). Of 724 patients enrolled in this trial, 84% had demonstrated previous sensitivity to endocrine treatment with more than 50% having received ≥3 previous therapies. At interim analysis according to local assessment, the addition of everolimus to exemestane significantly prolonged median PFS by 4.1 months versus exemestane alone (6.9 months vs. 2.8 months, respectively; p <.001); the CBR was 33% among patients receiving the combination compared to 18% for exemestane only (30). These data led to the FDA approval of everolimus for the treatment of postmenopausal women with advanced ER+ breast cancer refractory to prior AIs in July 2012. The safety profile was consistent with AEs previously reported for everolimus. In both studies above, the combined everolimus/endocrine therapy had substantially higher stomatitis (56%), rash (36% to 44%), fatigue (33% to 72%), diarrhea (30% to 39%), and anorexia (29% to 43%) than single-agent endocrine therapy.

In summary, the cumulative clinical experience suggests that targeting mTOR with endocrine therapy should be limited to populations with acquired AI resistance. But considering how heterogeneous ER+ breast cancers are, the difference in patient selection, prior endocrine therapy exposure, and the specific drug combination being tested, potential predictive markers to understand the role of combining mTOR inhibition with antiestrogen therapy are still sorely needed.

mTOR Inhibitors and HER2-targeted Therapy

A phase I-II study of everolimus in combination with paclitaxel and trastuzumab in trastuzumab-refractory HER2-positive metastatic breast cancer (31) demonstrated clinical activity with an ORR of 44% and control of disease for 6 months or more in 74% of the patients. Based on this study, paclitaxel and trastuzumab with either everolimus at a dose of 10 mg/day or placebo is being tested in a phase III randomized study. An additional phase I study combined everolimus with weekly trastuzumab and vinorelbine in pretreated HER2-positive metastatic breast cancer (32). Antitumor activity was noted, with an ORR of 19.1%, disease control rate of 83%, and median PFS of 30.7 weeks. Grade 3 or 4 neutropenia were the dose-limiting toxicities, and everolimus 5 mg/day and 30 mg/week were deemed safe. Since everolimus crosses the blood-brain barrier, the combination of everolimus, vinorelbine, and trastuzumab is now being tested for the treatment of progressive (post-radiation) or new brain metastases (prior to radiation) in patients with HER2+ MBC). Everolimus is also currently in phase III clinical trials in combination with vinorelbine and trastuzumab in locally advanced or metastatic HER2-positive breast cancer

TABLE 75-3

Current Clinical Trials with mTOR Inhibitors

Study Design	*Clinical Trial*	*Type of inhibitor*	*Patient Population*	*Clinicaltrials.gov*
Phase I	Dose Finding Study of RAD001 (Everolimus, Afinitor®) in Combination with BEZ235 in Patients with Advanced Solid Tumors	PI3K/ mTOR inhibitors	HER2-negative MBC	NCT01482156
	A Study of Combination of Temsirolimus (Torisel®) and Pegylated Liposomal Doxorubicin (PLD, Doxil®/Caelyx®) in Advanced or Recurrent Breast, Endometrial and Ovarian Cancer	TORC1 inhibitor	Advanced or recurrent breast, endometrial and ovarian cancer	NCT00982631
	A Phase I Study of BKM120 and Everolimus in Advanced Solid Malignancies	PI3K + TORC1 inhibitors	HER2-negative MBC	NCT01470209
Phase Ib/II	Phase 1b/2 Trial Using Lapatinib, Everolimus and Capecitabine for Treatment of HER-2 Positive Breast Cancer with CNS Metastasis	TORC1 inhibitor	HER2+ MBC with brain mets	NCT01783756
	Phase I/II Study of Weekly Abraxane and RAD001 in Women with Locally Adv. or Metastatic Breast Ca	TORC1 inhibitor	HER2-negative MBC	NCT00934895
	Cixutumumab and Temsirolimus in Treating Patients with Locally Recurrent or Metastatic Breast Cancer	TORC1 inhibitor	HER2-negative MBC	NCT00699491
	Everolimus (RAD001) and Carboplatin in Pretreated Metastatic Breast Cancer	TORC1 inhibitor	HER2-negative MBC	NCT00930475
Phase II	Study to Compare Vinorelbine in Combination with the mTOR Inhibitor Everolimus vs. Vinorelbine Monotherapy for Second-line Treatment in Advanced Breast Cancer	TORC1 inhibitor	HER2-negative MBC	NCT01520103
	A Study of Everolimus, Trastuzumab and Vinorelbine in HER2-Positive Breast Cancer Brain Metastases	TORC1 inhibitor	HER2+ MBC with brain mets	NCT01305941
	A Phase II Study of Everolimus in Combination with Exemestane Versus Everolimus Alone Versus Capecitabine in Advanced Breast Cancer	TORC1 inhibitor	ER+ MBC	NCT01783444
	Study of How Well Letrozole Works in Combination with Lapatinib Followed by an Addition of Everolimus in Postmenopausal Women with Advanced Endocrine Resistant Breast Cancer	TORC1 inhibitor	ER+ MBC	NCT01499160
	Study of Fulvestrant +/- Everolimus in Post-Menopausal, Hormone-Receptor + Metastatic Breast Ca Resistant to AI	TORC1 inhibitor	ER+ MBC	NCT01797120
	Cisplatin and Paclitaxel with or without Everolimus in Treating Patients with Stage II or Stage III Breast Cancer	TORC1 inhibitor	Stage II/III TNBC	NCT00930930
	Lapatinib and RAD-001 for HER2 Positive Metastatic Breast Cancer	TORC1 inhibitor	HER2+ MBC	NCT01283789
	Everolimus in Breast Cancer Patients after Pre-operative Chemotherapy	TORC1 inhibitor	Postoperative Stage II/III HER2-negative BC	NCT01088893

(Continued)

TABLE 75-3 *(Continued)*

Current Clinical Trials with mTOR Inhibitors

Study Design	*Clinical Trial*	*Type of inhibitor*	*Patient Population*	*Clinicaltrials.gov*
	A Phase II Trial of Ridaforolimus and Exemestane, Compared to Ridaforolimus, Dalotuzumab and Exemestane in Participants with Breast Cancer	TORC1 inhibitor	ER+ MBC	NCT01605396
	Safety Study of Adding Everolimus to Adjuvant Hormone Therapy in Women with Poor Prognosis, ER+ and HER2- Primary Breast Cancer, Free of Disease after Receiving 3 Years of Adjuvant Hormone Therapy	TORC1 inhibitor	Stage III ER+ BC	NCT01805271
	S1207 Hormone Therapy with or without Everolimus in Treating Patients with Breast Cancer	TORC1 inhibitor	Stage II/III ER+ BC	NCT01674140
Phase III	Safety Study of Adding Everolimus to Adjuvant Hormone Therapy in Women with Poor Prognosis, ER+ and HER2- Primary Breast Cancer, Free of Disease after Receiving 3 Years of Adjuvant Hormone Therapy	TORC1 inhibitor	Stage III ER+ BC	NCT01805271
	S1207 Hormone Therapy with or without Everolimus in Treating Patients with Breast Cancer	TORC1 inhibitor	Stage II/III ER+ BC	NCT01674140

resistant to trastuzumab and previously treated with a taxane (BOLERO-3, NCT01007942).

Novel Strategies/Combinations

Pre-clinical studies indicate that the dual inhibition of IGFR and mTOR may be additive or synergistic and abrogates the feedback activation of AKT due to rapamycin analog mTOR inhibitors. A phase I study of the mTOR inhibitor ridaforolimus and the anti-IGFR antibody dalotuzumab (33) demonstrated that the combination was feasible and well tolerated at doses that were nearly those used for the two single agents and with dose-limiting toxicity of stomatitis, similar to ridaforolimus as monotherapy. A preliminary signal of anti-tumor activity, including partial responses and prolonged progression free survival, was observed in ER+ breast cancer, especially in high-proliferation tumors.

A randomized, phase II study in HER2-positive early-stage breast cancer is assessing whether adding everolimus to trastuzumab for 6 weeks in the neoadjuvant setting improves clinical tumor response rate. Studies with other combinations, including temsirolimus and neratinib (HKI272) (phase I/II) or everolimus and lapatinib (phase II) are also in progress.

CYCLIN DEPENDENT KINASE (CDK) INHIBITORS

A key element in cancer pathogenesis is dysregulation of the G1-to-S cell cycle transition and cell cycle progression (34). During this transition, mitogenic signals converge to activate the expression of D-type cyclins. These cyclins bind CDK4 or CDK6, which, in turn, phosphorylate and inactivate the Rb tumor suppressor and related proteins p107 and p130. The Rb proteins control the activity of the E2F family of transcription factors. Upon phosphorylation, Rb protein uncouple from E2F factors, which, in turn, modulate the expression of genes that coordinate subsequent cell cycle progression (cyclin A and cyclin E), DNA replication (MCM7 and PCNA), and mitosis (cyclin B1 and Cdk1) (35). In breast cancer, several mechanisms contribute to dysregulate CDK function, thus making them a potential target for therapeutic intervention. These include HER2 overexpression, cyclin D1 gene amplification, overexpression of cyclin E, loss of the CDK inhibitors p16 and $p27^{KIP1}$, and functional inactivation or genetic loss of Rb, among others (5,36). Cyclin D_1 is overexpressed in >50% of breast cancers (37).

Published studies support a role for cyclin D1 and activity of a CDK4/6 inhibitor against luminal ER+ breast cancer, its synergism with tamoxifen in antiestrogen-sensitive cell lines, as well as the reversal of acquired endocrine resistance. Cyclin D1 amplification and/or overexpression has been more commonly associated with ER+ tumors (38) and is associated with tamoxifen resistance (39). Further, cyclin D1 can directly activate ER in ligand-independent manner that is also independent of CDK and pRb function (40). Based on the widely accepted paradigm that the entire contribution of cyclin D1 to tumorigenesis is achieved through its activation of Cdk4/6, much effort has been directed toward finding small molecule CDK inhibitors or activators of endogenous Cdk inhibitors (41).

Dinaciclib is a potent, selective inhibitor of CDK1, 2, 5, and 9 with pre-clinical activity in breast cancer cell lines and tumor xenografts. A randomized, multicenter, open-label

TABLE 75-4

Current Clinical Trials with CDK Inhibitors

Study Design	*Clinical Trial*	*Type of inhibitor*	*Patient Population*	*Clinicaltrials.gov*
Phase I	Dinaciclib and Epirubicin Hydrochloride in Treating Patients with Metastatic Triple-Negative Breast Cancer	CDK inhibitor	Metastatic TNBC	NCT01624441
Phase II	PD 0332991 and Anastrozole for Stage 2 or 3 Estrogen Receptor Positive and HER2 Negative Breast Cancer		Stage II or III ER+ BC	NCT01723774
	PD 0332991 and Anastrozole for Stage 2 or 3 Estrogen Receptor Positive and HER2 Negative Breast Cancer		ER+ MBC	NCT01723774

phase II study was conducted to compare the efficacy of dinaciclib and capecitabine in patients with advanced, previously treated breast cancer (42). The study included 19 patients treated with dinaciclib, including 6 patients who crossed over. Partial responses were reported in 2/12 (17%) evaluable patients who received dinaciclib up front (both patients had ER+/HER2-negative cancers) and in 4/15 (27%) evaluable patients who received capecitabine. The median time to progression for dinaciclib (n = 9) and capecitabine-treated (n = 11) patients was 2.8 and 4.2 months, respectively (Table 75-4).

PD0332991 (palbociclib) is an oral, potent, and highly selective inhibitor of CDK4 and 6; at low nM concentrations, it blocks pRb phosphorylation, thus inducing G_1 arrest in sensitive cell lines (43), as well as primary bone marrow cells *ex vivo* (44). A screen for sensitivity using a large panel of human breast cancer cell lines revealed that luminal ER+ lines (including HER2 gene amplified) were most sensitive to growth inhibition by PD0332991, whereas cells with non-luminal and basal-like gene expression were most resistant (45). Analysis of variance identified 450 differentially expressed genes between sensitive and resistant cells. pRb and cyclin D_1 were elevated, and *CDKN2A* (p16) was decreased in the most sensitive lines. PD 0332991 was synergistic with tamoxifen and trastuzumab in ER+ and HER2 gene-amplified cell lines, respectively (45). These data provide a rationale for the clinical development of PD0332991 in ER+ luminal and HER2-overexpressing breast cancer in combination with antiestrogen or anti-HER2 therapy, respectively.

A randomized phase II combining PD0332991 with letrozole (46) enrolled 165 patients with ER+ MBC who had not been previously treated for metastatic disease. The addition of PD 0332991 to letrozole increased median PFS from 7.5 to 26.1 months (HR = 0.37, p <.001). Of note, the majority of patients enrolled had aggressive disease (*de novo* metastatic disease or a short disease-free interval following adjuvant therapy), which may explain the underperformance of the control arm. ORR was 34% in the PD0332991-containing arm and 26% in the letrozole arm. CBR was 70% in patients treated with PD0332991/letrozole versus 44% in the letrozole arm. Grade 3/4 neutropenia increased from 1% to 51% and leukopenia from 0% to 14% in the combination arm, with 71% of patients requiring dose interruptions and 35% requiring dose reductions. Ten percent of patients discontinued PD0332991. Cyclin D1 gene amplification and p16 protein were prospectively evaluated as potential biomarkers, but only ER status was predictive of activity. A phase III trial is expected to initiate accrual in 2013.

INSULIN/IGF-I RECEPTOR INHIBITORS

The insulin/IGF-I receptor network includes the ligand insulin, IGF-I and IGF-II; the insulin and IGF-I transmembrane receptor tyrosine kinases (RTKs); and IGF-binding proteins (IGF-BPs). The IGF-IR is closely related to the InsR, which is activated by both insulin and IGF-II. In normal physiology, ligand-induced activation of the IGF-IR plays a role in fetal growth and linear growth of the skeleton and other organs, whereas insulin-activated InsR regulates glucose homeostasis. A fetal form of the InsR (insulin receptor A), which has been detected in cancer cells, can also bind IGF-II with high affinity. These receptors can assemble and exist as hybrid heterotetramers, where a dimer of α and β chains of the IGF-IR is joined to a dimer of α and β chains of the InsR. The structure of these receptor chains is such that ligand binding to their extracellular domain is required for physical interaction of the tyrosine kinase domains and activation of signaling. Different to other amplified RTKs, constitutive (ligand-independent) activation of these receptors is not seen, even in experimental systems of artificial overexpression (47). There are six high-affinity IGF-BPs that complex with IGFs in extracellular fluids. Most circulating IGF-I is complexed with IGF-BP3; in this complex, IGF-I cannot bind its cognate receptor (48). Of note, most IGF-BPs have higher affinity for the ligands than for the receptors.

Activating mutations of IGF-IR have not been reported in human tumors. However, there are reports of IGF-I and IGF-BP3 gene polymorphisms associated with an increased risk of breast cancer (49). Overexpression of InsR and IGF-IR has been detected in primary breast cancers and overexpression of either receptor has been shown to induce tumors in mice. Phosphorylated InsR/IGF-IR is present in all subtypes of breast cancer, and high levels have been correlated with poor survival. The IGF-IR has been pursued as the main therapeutic target but increasing evidence implicates and InsR and hyperinsulinemic states such as type II diabetes in mammary transformation and breast cancer mitogenesis (50). Higher levels of IGF-IR, IRS-1, and IGF-II have been found in ER+ human breast cancer cells that adapt to estrogen deprivation or that became resistant to tamoxifen (51). Further, induced overexpression of IGF-IR in HER2 gene amplified breast cancer cells confers resistance to trastuzumab (52). Finally, cell lines and primary tumor with acquired resistance to trastuzumab overexpress IGF-IR.

Several therapeutic approaches that inhibit the InsR/IGF-IR axis are in clinical development (Table 75-5) (53).

TABLE 75-5

Current Clinical Trials with IGF-1R Inhibitors

Study Design	*Clinical Trial*	*Type of inhibitor*	*Patient Population*	*Clinicaltrials.gov*
Phase I	MEDI-573 plus standard endocrine therapy for ER+ metastatic breast cancer	IGF-IR I and II	ER+ MBC	NCT01446159
Phase I/II	BYL719 plus AMG479 in patients with solid tumors	IGF-IR	ER+ MBC	NCT01708161
	Cixutumumab and Temsirolimus in Treating Patients with Locally Recurrent or Metastatic Breast Cancer		HER2-neg MBC	NCT00699491
Phase II	Capecitabine and Lapatinib with or without Cixutumumab in Treating Patients with Previously Treated HER2-Positive Stage IIIB, Stage IIIC, or Stage IV Breast Cancer		HER2+ MBC	NCT00684983

Because of the role of the insulin- or IGF-II stimulated InsR, dual targeting of InsR and IGF-IR is increasingly advocated in order to achieve maximal inhibition of this receptor network in cancer cells. These include small molecule ATP mimetics against IGF-IR. Because of the homology of the kinase domains of InsR and IGF-IR, these small molecules (OSI-906 or linsitinib, BMS-754807, XL-228, etc.) inhibit both receptors. Other compounds include neutralizing IGF-IR monoclonal antibodies, recombinant IGF-BPs, soluble receptor fusion proteins, and antibodies against IGF-I and IGF-II (MEDI-573, MedImmune and BI836845, Boehringer). The clinical development of several IGF-IR antibodies has been discontinued recently. At this time, dalotuzumab (MK-0646, Merck) and ganitumumab (AMG-479, Amgen) have been or are being tested as part of novel combinations in patients with breast cancer. Although they have different Fc domains and are either humanized or fully human, they both bind to the ectodomain of the IGF-IR and cause receptor internalization, thus preventing ligand binding and removing the receptor from the cell surface. Interestingly, blockade of IGF-IR with therapeutic antibodies results in compensatory upregulation of circulating IGFs and insulin, which can be manifest clinically as hyperinsulinemia, type II diabetes, or metabolic syndrome. To ameliorate this compensation and potentially enhance their anti-cancer effect, the anti-diabetic drug metformin has been used in combination with IGF-IR antibodies to dampen gluconeogenesis and lower insulin levels.

AMG-479 (ganitumumab) is a fully human monoclonal antibody against IGF-IR. Because of preclinical data suggesting that dual inhibition of ER and IGF-IR results in greater suppression of ER+ breast cancer proliferation, a double-blind, randomized phase II study of AMG-479 added to either exemestane or fulvestrant in postmenopausal patients with ER+ MBC who had progressed on prior endocrine therapy was conducted (54). Patients were randomized to receive AMG-479 with exemestane or fulvestrant versus placebo plus exemestane or fulvestrant. Stratification factors included which hormonal therapy the patient received, as well as the extent of disease. In all, 106 women were included in the AMG 479 group and 50 in the placebo group. Median PFS was 4.8 months among women who received exemestane/AMG479 and 7.3 months for the exemestane/placebo arm (HR, 1.31). Among women who received fulvestrant, it was 3.7 months and 5.4, respectively (HR, 1.11). The objective response rate for patients in the AMG-479 group was 8% versus 13% for those in the control group. CBR was 35% for women on AMG-479 and 31% of women on placebo. Median overall survival at the final analysis was 23·3 months in the ganitumumab group and not reached in the placebo group (HR 1.78, 80% CI, 1.27–2.50; p = .025).

Despite the biological rationale for targeting the Ins/IGF-I receptor pathway, the studies of investigating inhibitors of these receptors in breast cancer have yielded disappointing results. In the absence of a predictive biomarker that can identify tumors that depend on this pathway, it seems unlikely at the time of this chapter that these agents will play a significant role in the treatment of breast cancer.

HISTONE DEACETYLASE (HDAC) INHIBITORS

Epigenetic changes, such as histone hypoacetylation and abnormal methylation of DNA in the promoter region of important genes, contribute to tumorigenesis and drug resistance in several cancers, including breast cancer. Importantly, epigenetic changes may be reversible and thus represent an active and attractive area of basic and clinical investigation (55).

In breast cancer cells, multiple genes are methylated, and thus silenced. Gene methylation is likely related to cancer progression. HDAC inhibitors may also alleviate gene repression that is mediated through promoter hypermethylation. It is presumed that HDAC inhibitors can increase expression of the genes that are not methylated but may not induce the expression of hypermethylated genes. Some of the genes that are often methylated in breast cancer include ERα and the retinoic acid receptor (RAR) β, also critical for cell differentiation. Other hypermethylated genes in breast cancer include cyclin D, Twist, RASSF1A, APC, and HIN-1. Investigators have evaluated hypermethylation of a panel of seven genes in a variety of breast tissues (56). In invasive breast cancers, up to 100% of specimens contained at least one hypermethylated gene, 80% contained two, and 60% contained three or more methylated genes (57). Among 44 DCIS specimens, 95% had

at least one methylated gene. In contrast, the percentage of women with benign breast disease having at least one methylated gene was only 15%. Only one of 8 reduction mammoplasty specimens contained hypermethylated genes.

Suberoylanilide hydroxamic acid (SAHA, Vorinostat) is a small molecule histone deacetylase (HDAC) inhibitor that binds directly at the enzyme's active site in the presence of Zn and is currently in clinical trials in breast cancer (58). Because aberrant HDAC activity has been implicated in a variety of cancers, development of HDAC inhibitors is a rational approach to the design of targeted anti-cancer therapeutics. Several HDAC inhibitors from multiple chemical classes have been developed and are currently in clinical trials (Table 75-6). Of these, vorinostat targets most human class 1

TABLE 75-6

Current Clinical Trials with HDAC Inhibitors

Study Design	*Clinical Trial*	*Type of inhibitor*	*Patient Population*	*Clinicaltrials.gov*
Phase I	Ixabepilone and Vorinostat in Treating Patients with Metastatic Breast Cancer	HDAC Inhibitor,	HER2 negative MBC	NCT01084057
	Study of the Combination of Vorinostat and Radiation Therapy for the Treatment of Patients with Brain Metastases		HER2 negative MBC with brain mets	NCT00838929
Phase I/II	HDAC Inhibitor Vorinostat (SAHA) With Capecitabine (Xeloda) Using a New Weekly Dose Regimen for Advanced Breast Cancer		HER2 negative MBC	NCT00719875
	Trial for Locally Advanced Her2 Positive Breast Cancer Using Paclitaxel, Trastuzumab, Doxorubicin and Cyclophasmide on a Weekly Basis		Stage II/III HER2+ BC	NCT00574587
	Entinostat and Lapatinib Ditosylate in Patients with Locally Recurrent or Distant Relapsed Metastatic Breast Cancer Previously Treated With Trastuzumab		HER2+ MBC	NCT01434303
	Re-expression of ER in Triple Negative Breast Cancers		Metastatic TNBC	NCT01194908
Phase II	Phase II Trial of SAHA & Tamoxifen for Patients with Breast Cancer		ER+ MBC	NCT00365599
	Entinostat and Anastrozole in Treating Postmenopausal Women with Triple-Negative Breast Cancer That Can Be Removed by Surgery		Stage I – III TNBC	NCT01234532
	Azacitidine and Entinostat in Treating Patients with Advanced Breast Cancer		Metastatic TNBC	NCT01349959
	Vorinostat in Treating Patients with Stage IV Breast Cancer Receiving Aromatase Inhibitor Therapy		ER+ MBC	NCT01153672
	Vorinostat and Lapatinib in Advanced Solid Tumors and Advanced Breast Cancer to Evaluate Response and Biomarkers		HER2+ MBC	NCT01118975
	Vorinostat in Treating Women Who Are Undergoing Surgery for Newly Diagnosed Stage I, Stage II, or Stage III Breast Cancer		Stage I - III HER2-negative BC	NCT00262834
	Carboplatin and Paclitaxel Albumin-Stabilized Nanoparticle Formulation with or without Vorinostat in Treating Women with Breast Cancer That Can Be Removed by Surgery		Stage II/ III TNBC	NCT00616967

and class 2 HDACs (59). Among those currently in trials, vorinostat is the most potent HDAC inhibitor that can be administered orally with excellent bioavailability. The most common drug-related adverse with this class of drugs are diarrhea (49%), fatigue (46%), nausea (43%), and anorexia (26%), mostly being <grade 2 (60).

PARP INHIBITORS

Poly-ADP-ribose polymerase (PARP) is an abundant, constitutively expressed nuclear enzyme that catalyzes the transfer of ADP-ribose from NAD+ to target proteins, through which it facilitates DNA repair, cellular proliferation, and signaling to other critical cell cycle proteins and oncogenes (61). At sites of DNA damage, PARP activates intracellular signaling pathways that modulate DNA repair and cell survival through poly (ADP-ribosyl)ation of several nuclear proteins involved in the chromatin architecture and DNA metabolism. Immediate catalytic activation of PARP in response to DNA single- and double-strand breaks has been reported at levels up to 500-fold (62,63).

There are at least three roles of PARP inhibitors in cancer treatment: sensitization to chemotherapy and radiotherapy, synthetic lethality in patients with hereditary mutations in BRCA1/2 genes (inherited defect in homologous recombination), and, finally, leveraging of putative "BRCA-like" defect tumors and defects in DNA repair such as triple negative breast cancer (TNBC).

BRCA1 and *BRCA2* genes encode for proteins critical for DNA integrity and genomic stability (64,65). BRCA1 and BRCA2 are tumor-suppressor proteins essential for cell division, DNA error control, DNA repair and apoptosis. In 2005 Bryant (66) and Farmer (67) showed that BRCA-deficient cells were extremely sensitive to PARP inhibition. Single-agent PARP inhibitors led to impaired SSB repair, causing double strand breaks (DSBs) in replicative cells. In cells with wild-type BRCA, DSBs are repaired via homologous recombination (HR). In BRCA-deficient cells, HR is impaired and alternative pathways lead to complex rearrangements, loss of repair mechanisms, and cell death (so called "synthetic lethality") (68). Significant single-agent activity was recently reported with the PARP inhibitor olaparib in patients with BRCA-deficient MBC. Overall responses ranged from 22% (100 mg bid) to 41% (400 mg bid) with minimal toxicity (69).

There are several molecular and pathologic similarities between TNBC and BRCA-deficient breast cancers, whose homologous recombination-dependent DNA repair is impaired. The association between basal-like breast cancer (BLBC), TNBC, and BRCA pathway dysfunction has therapeutic implications. Although the terms "triple negative" (TN) and "basal-like" are not synonymous, at least 80% of clinical TNBCs (ER/PR/HER2-negative) classify as basal-like (70). In addition, TNBC expresses a high proportion of basal-like cytokeratins (CK) 5, 14, and 17, and overexpress P-cadherin and EGFR (71). Because a clinically applicable test for the basal molecular classification has yet to be developed, the triple-negative phenotype is a reasonable surrogate for the basal-like molecular subtype, a gene expression profile common *BRCA1* mutation carriers (72). Indeed, two-thirds of cancers among 400 patient carriers of a BRCA1 mutation were triple-negative tumors (73). The tight association between *BRCA1* mutations, BLBC, and TNBC has raised the question as to whether *BRCA1* loss of function through other mechanisms participates in the pathogenesis of sporadic basal-like and TNBC—an association that could be exploited therapeutically.

BSI-201/iniparib binds to PARP1 in the NAD binding pocket and inhibits PARP enzyme activity at high μm concentrations. A phase II, open-label, 2-arm randomized, safety and efficacy trial (Study 20070102) investigated BSI-201 (5.6 mg/kg) in combination with gemcitabine/carboplatin in patients with metastatic TNBC (Table 75-7). This is the only randomized study with final safety and efficacy data. The final analysis of 123 randomized patients showed that addition of BSI-201 to gemcitabine/carboplatin improved the clinical benefit rate from 33.9% to 55.7% (p = .015) and ORR from 32.3% to 52.5% (p = .023). Addition of BSI-201 prolonged the median PFS) from 3.6 to 5 9 months (hazard ratio [HR], 0.59; p = .012) and the median OS from 7.7 to 12.3 months (HR, 0.57; p = .014) (74). The incidence of adverse events (AEs) was similar in both groups. The most frequent AEs were fatigue, nausea, neutropenia, anemia, and thrombocytopenia. There was a >5% increase in the incidence of grade 3/4 anemia and thrombocytopenia in patients receiving BSI-201/gemcitabine/carboplatin compared to gemcitabine/carboplatin, but the differences were not statistically significant (74). Following this trial, a phase III study evaluating gemcitabine/carboplatin ± BSI-201 in patients with metastatic TNBC with 0–2 prior treatment regimens in the metastatic setting was completed. The trial did not meet the pre-specified criteria for significance for the co-primary endpoints of OS and PFS. The results of a pre-specified analysis in patients treated in the second- and third-line setting showed an improvement in OS and PFS, consistent with what was seen in the smaller phase II study. Similarly, the addition of BSI-201 did not add to the toxicity profile of gemcitabine and carboplatin (75). It is unclear whether investigation of molecular biomarkers that would identify a responsive group of patients is planned or ongoing. Of note, however, more recent pre-clinical data have shown that BSI-201 does not possess characteristics typical of the PARP inhibitor class. Investigations into potential targets of BSI-201 and its metabolites are ongoing. The following observations regarding the cellular effects of BSI-201 have been made: BSI 201 (i) induces γ -H2AX (a marker of DNA damage) in tumor cell lines (76); (ii) induces cell cycle arrest in the G2/M phase in tumor cell lines (77); and (iii) potentiates the cell cycle effects of DNA damaging modalities in tumor cell lines (78). Additional targets are under investigation.

FIBROBLAST GROWTH FACTOR (FGF) RECEPTOR INHIBITORS

The FGFs and their receptors (FGFRs) play an important role in embryological development such as in brain patterning, morphogenesis, and limb development, as well as physiological functions in the adult such as angiogenesis, wound repair, and endocrine functions. The FGF family consists of 18 ligands that signal through four high-affinity FGFRs (FGFR1-4). FGF ligands bind to receptors in a trimeric complex with heparins, leading to a conformational change in FGFRs, receptor dimerization, kinase activation, and autophosphorylation of intracellular FGFR tyrosines and other transducers such as PLCγ, FRS2 (an adaptor that links to activation of ERK and PI3K), STATs, and Src. Under physiological conditions, this complex FGFR signaling network is tightly regulated. Dysregulation of the FGF signaling pathway results in its aberrant activation, leading to transformation and subsequent enhanced cancer cell proliferation, migration, and survival (79).

Several lines of evidence support a role for FGFRs in breast cancer (80). For example, the mouse mammary tumor virus (MMTV) induces tumors through integration

TABLE 75-7

Current Clinical Trials with PARP Inhibitors

Study Design	*Clinical Trial*	*Type of inhibitor*	*Patient Population*	*Clinicaltrials.gov*
Phase I	Olaparib in Combination with Carboplatin for Refractory or Recurrent Women's Cancers	PARP inhibitor	Women's cancers; males with BRCA mutations	NCT01237067
	AZD2281 Plus Carboplatin to Treat Breast and Ovarian Cancer		Breast and ovarian metastatic cancers	NCT01445418
	Study to Assess the Safety and Tolerability of a PARP Inhibitor in Combination with Carboplatin and/or Paclitaxel		TNBC and ovarian metastatic cancers	NCT00516724
	Phase I of BKM120/Olaparib for Triple Negative Breast Cancer or High Grade Serous Ovarian Cancer		TNBC and ovarian metastatic cancers	NCT01623349
	Veliparib with Radiation Therapy in Patients with Inflammatory or Loco-regionally Recurrent Breast Cancer		Inflammatory or loco-regionally recurrent breast cancer	NCT01477489
Phase I/II	A Study of Oral Rucaparib in Patients with gBRCA Mutation Breast or Ovarian Cancer, or Other Solid Tumor		gBRCA mutation breast or ovarian cancer	NCT01482715
Phase II	A Phase 2 Study of Standard Chemotherapy Plus BSI-201 (a PARP Inhibitor) in the Neoadjuvant Treatment of Triple Negative Breast Cancer		Stage II/III TNBC	NCT00813956
	A Study Evaluating INIPARIB in Combination with Chemotherapy to Treat Triple Negative Breast Cancer Brain Metastasis		TNBC with brain mets	NCT01173497
	Phase II Study of AZD2281 in Patients with Known BRCA Mutation Status or Recurrent High Grade Ovarian Cancer or Patients with Known BRCA Mutation Status/ Triple Neg Breast Cancer		TNBC and ovarian metastatic cancers; BRCA mt cancers	NCT00679783
	PARP Inhibition for Triple Negative Breast Cancer (ER-/PR-/HER2-)with BRCA1/2 Mutations		TNBC metastatic BRCA mt cancers	NCT01074970
	ABT-888 with Cyclophosphamide in Refractory BRCA-Positive Ovarian, Primary Peritoneal or Ovarian High-Grade Serous Carcinoma, Fallopian Tube Cancer, Triple-Negative Breast Cancer, and Low-Grade Non-Hodgkin's Lymphoma		Metastatic TNBC	NCT01306032
	Study of SAR240550 (BSI-201) in Combination with Gemcitabine/ Carboplatin, in Patients with Metastatic Triple Negative Breast Cancer		Metastatic TNBC	NCT01045304
	Two Regimens of SAR240550/Weekly Paclitaxel and Paclitaxel Alone as Neoadjuvant Therapy in Triple Negative Breast Cancer Patients		Stage II/III TNBC	NCT01204125
	ABT-888 and Temozolomide for Metastatic Breast Cancer and BRCA1/2 Breast Cancer		Metastatic breast cancer and BRCA1/2 breast cancer	NCT01009788
	Rucaparib (CO-338; Formally Called AG-014699 or PF-0136738) in Treating Patients with Locally Advanced or Metastatic Breast Cancer or Advanced Ovarian Cancer		Metastatic breast, ovarian, and BRCA mt cancers	NCT00664781

into the genome, thereby transcriptionally activating the expression of nearby genes. *FGF3* and *FGF8*, along with *WNT* genes, are the most common sites of integration of MMTV. Studies in transgenic mice have shown that overexpression of FGF3 and activated FGFR1 in the mouse mammary gland result in invasive mammary carcinomas. A single nucleotide polymorphism (SNP) within the second intron of the *FGFR2* gene has been associated with an increased risk of breast cancer. A SNP in the *FGFR4* gene has been shown to confer a more virulent cancer behavior and poor outcome in multiple tumor types, including breast cancer. *FGFR2* gene amplification occurs in a small cohort of breast cancers that includes all three major clinical subtypes (ER+, HER2+, and triple negative). On the other hand, *FGFR1* is one of the most commonly amplified genes in cancer with approximately 10% of breast cancers, mainly ER+ tumors, exhibiting *FGFR1* amplification. *FGFR1* amplification correlates with the luminal B subtype of ER+ breast cancer and has been shown to confer resistance to tamoxifen (81). FGFRs and FGFR3-activating mutations are found in other tumor types, but evidence of them has not been found in breast cancer. Although FGFRs are constitutively phosphorylated/activated in gene amplified breast cancer cell lines, there is no published evidence of ligand-independent signaling in primary tumors, where the data seem to support enhanced ligand-induced receptor activation.

Expression of the cytoplasmic FGF2 ligand was found to be specific to basal-like breast cancer. This ligand is abundantly expressed in tumor stroma. One study reported elevated levels of FGF2 in nipple aspirates of patients with breast cancer. FGF2 is highly angiogenic, and its overexpression has been associated with resistance to VEGFR inhibitors. Finally, *FGFR*-amplified cell lines exhibit high sensitivity to FGFR inhibitors, suggesting the FGFs and/or FGFRs are a therapeutic target. Based on these data, several pharmaceutical companies have developed drugs targeting FGF ligands and FGFRs, the most common being small molecule TKIs of FGFRs (82). Several of these inhibitors also inhibit receptors in the PDGFR and VEGFR families. More recently, selective FGFR inhibitors have been developed. The kinase domains of FGFR1-3 are highly homologous so more recently developed selective FGFR inhibitors block all three family members. FGFR4 has diverged from FGFR1-3 and consequently these inhibitors are less potent against FGFR4. Other inhibitors include receptor-specific FGFR1-3 neutralizing antibodies and an FGF multi-ligand trap (83).

TKI258 (i.e., dovitinib) is a potent TKI with an IC_{50} of <20 nmol/L for VEGFR1, 2 and 3, PDGFRβ, FGFR1 and 3, FLT-3, KIT, RET, TRKA, and colony-stimulating factor 1 (CSF-1). Dovitinib exerts antitumor activity through inhibition of FGFR and PDGFR and has shown antiangiogenic activity through the inhibition of FGFR, VEGFR, and PDGFR (84). A phase I dose-escalating trial of orally administered dovitinib studied 35 patients with advanced solid tumors. The most frequent drug-related adverse events were gastrointestinal disorders and fatigue. Cardiovascular events were seen in 5 patients (14%). One melanoma patient had a partial response (PR) and 2 patients exhibited stable disease (SD) for >6 months. Five of 14 evaluable patients showed modulation of phosphorylated ERK levels in peripheral blood mononuclear cells (85). A two-step phase II study evaluated dovitinib in patients with previously treated, metastatic, HER2-negative breast cancer. Patients were stratified into four groups according to FGFR1 and hormone receptor (HR) status. Antitumor activity was observed in the FGFR1 amplified/ER+ subset (25% had nonconfirmed PR and/or SD ≥4 weeks). Biomarker analysis suggested that co-amplification of FGFR1 and FGFR3 might identify a subgroup of dovitinib-sensitive tumors (86). These observations were used as the rationale behind the design of an ongoing multicenter, randomized phase II trial of fulvestrant with and without dovitinib for postmenopausal, HER2-negative/ER+ patients with MBC who were on endocrine therapy. Prospective molecular screening is expected to enrich for patients with tumors with FGFR1, FGFR2, or FGFR3 amplification (clinicaltrials.gov; NCT01528345).

AZD4547 is a highly active pan-FGFR small molecule TKI. Its activity against VEGFR2 is approximately 120-fold lower than that against FGFR1. AZD4547 suppresses FGFR signaling and growth in tumor cell lines with dysregulated FGFR expression. In a representative FGFR3-driven human tumor xenograft model, the oral administration of AZD4547 was well tolerated and resulted in potent antitumor activity (87). AZD4547 is currently being evaluated in a phase I clinical trial. A second expansion phase will include patients with FGFR1- and/or FGFR2-amplified cancers (clinicaltrials.gov; NCT00979134). A randomized, double-blind phase IIA study will assess the safety and efficacy of AZD4547 when taken in combination with exemestane versus exemestane alone in patients with ER+ breast cancer with FGFR1 polysomy or amplification (clinicaltrials.gov; NCT01202591).

HEAT SHOCK PROTEIN (HSP) 90 INHIBITORS

Hsp90 is a molecular chaperone that regulates the folding, function, and viability of key proteins within cells (called client proteins) under conditions of environmental stress (88–90). When Hsp90 is inhibited, its client proteins are rendered unstable, ultimately undergoing ubiquitination and proteasomal degradation (89). A number of Hsp90 client proteins, including nuclear steroid receptors, AKT, RAF1, CDK4, HER2, EGFR, BCR-ABL, PDGFRA, and KIT, are important Hsp90 client proteins involved in oncogenesis, cancer cell proliferation, and survival (91,92). Consequently, Hsp90 has become an attractive therapeutic target in cancer.

Several natural products, including geldanamycin, bind selectively to an amino-terminal pocket in HSP90 and inhibit its function (Table 75-8) (93). Geldanamycin is hepatotoxic, but its derivative, tanespimycin (17-AAG, 17-demethoxygeldanamycin; KOS-953) has reduced toxicity (94). HER2 is among the most sensitive client proteins of HSP90, demonstrating degradation within 2 h of inhibition of HSP90 in cultured cells (95). Geldanamycin analogues (17-allylamino-17-demethoxygeldanamycin [17-AAG] and 17-dimethylaminoethylamino-17-demethoxygeldanamycin [17-DMAG]) have demonstrated potent inhibition of HSP90 function and growth of HER2-overexpressing cells *in vitro* and *in vivo* (95,96). In the clinic, initial studies with the tanespimycin (KOS-953) (97) and the second-generation Hsp90 inhibitor, alvespimycin (KOS-1022) (98), have demonstrated safety and antitumor activity and tolerability in combination with trastuzumab in patients with trastuzumab-refractory HER2-overexpressing breast cancer.

As a proof of concept, the phase I of 17-AAG with trastuzumab showed evidence of objective tumor regressions and meaningful clinical benefit for the subset of patients with advanced HER2 positive breast cancer who had progressed on trastuzumab (99). This led to a single-arm phase 2 trial of tanespimycin (17-AAG) plus trastuzumab in patients with

TABLE 75-8

Current Clinical Trials with HSP90 Inhibitors

Study Design	*Clinical Trial*	*Type of inhibitor*	*Patient Population*	*Clinicaltrials.gov*
Phase I/II	Combination of AUY922 with Trastuzumab in HER2+ Advanced Breast Cancer Patients Previously Treated With Trastuzumab	HSP90 inhibitor	HER2+ MBC	NCT01271920
Phase II	Randomized Phase II Study of Fulvestrant with or without Ganetespib in Patients with ER+ MBC		ER+ MBC	NCT01560416
	Open Label Multicenter Phase 2 Window of Opportunity Study Evaluating Ganetespib (STA-9090) Monotherapy in Women with Previously Untreated Metastatic HER2 Positive or TNBC		Metastatic HER2+ or TNBC	NCT01677455

HER2+ metastatic breast cancer after progression on trastuzumab (100). Thirty-one patients were treated with the combination until disease progression. Overall, the combination was well tolerated, with mostly grade 1 diarrhea, nausea, fatigue, and headache as main side effects. The overall response rate was 22%, with a CBR of 59%, a median PFS of 6 months (95% CI, 4–9), and a median OS of 17 months (95% CI, 16–28).

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SECTION XII

Site-Specific Therapy of Metastatic Breast Cancer

CHAPTER 76

Brain Metastases

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CHAPTER CONTENTS

The management of patients with brain metastases from breast cancer remains a challenging clinical problem. The goals of treatment are to extend life and improve or stabilize patient symptoms while minimizing treatment-related toxicities. Of note, because of their unique location, even relatively small tumors in the central nervous system (CNS) may result in neurological symptoms that negatively impact quality-of-life (QOL). Intracranial involvement with breast cancer can also occur as leptomeningeal involvement, and this is covered in Chapter 78. Because most systemic therapies do not effectively treat brain metastases, progression in the brain can represent a significant mortality risk. Indeed, for a subset of women with advanced breast cancer, control of CNS disease has become a vital component of overall disease control as well as QOL.

INCIDENCE AND RISK FACTORS

Because of incomplete reporting, the true incidence of brain metastases is difficult to determine with certainty. Registry data from the Netherlands and the United States indicate that among patients with primary lung, breast, melanoma, renal, and colorectal cancers presenting at any stage, the combined incidence of brain metastases is between 8.5% and 9.6% (1,2). Of patients diagnosed with brain metastases, between 13% and 20% will carry a primary diagnosis of breast cancer, making breast cancer the second most common cause of CNS involvement, after lung cancer.

Clinical factors such as disease stage, young age, and African-American ethnicity are associated with an increased risk of developing brain metastases (1). In patients presenting with localized, early-stage breast cancer, overall, less than 5% will ultimately be diagnosed with brain metastases. Among patients with advanced breast cancer not selected by tumor subtype, brain metastases will be diagnosed in approximately 15% (1). These figures likely are an underestimate of the true incidence, given that in autopsy studies from the 1970s and 1980s, up to 30% of patients were found to have CNS involvement at the time of death (3).

Biological risk modifiers include tumor grade, ER status, HER2 status, and *BRCA* mutation status. In studies of early breast cancer patients prior to the widespread introduction of adjuvant trastuzumab, HER2 has been shown to be a risk factor for CNS relapse (4,5). Within the HER2-positive subset, hormone receptor status appears to further influence the risk of CNS relapse, such that patients with ER-negative/HER2-positive tumors experience a higher rate of CNS involvement compared to patients with ER-positive/HER2-positive tumors (6). The risk of CNS as first site of relapse does not appear to be diminished by the use of adjuvant trastuzumab, though the absolute risk is low (<5%) (7). However, in the HERA trial, the overall risk of CNS relapse (first plus subsequent sites) was not increased with the use of adjuvant trastuzumab (8). In the advanced setting, multiple groups have reported a 25% to 55% incidence of CNS relapse among patients with HER2-positive breast cancer, which is significantly higher than historical control data of patients unselected by tumor subtype (9–11). Among deceased patients in the HERA trial, approximately half had developed brain metastases prior to death (8).

There is also increasing evidence that ER-, PR-, and HER2-negative (i.e., triple-negative) tumors are associated with a high risk of CNS relapse. In a database of 1,434 patients with early-stage breast cancer treated with breast conserving therapy, the 5-year cumulative incidence of brain metastases for patients with triple-negative tumors was 7.4%, compared with 0.1% in patients with Luminal A tumors (5). Among over 15,000 women presenting with Stage I–III breast cancer in the National Comprehensive Cancer Network breast cancer

database, triple-negative subtype was strongly associated with CNS relapse, relative to the hormone receptor-positive/HER2-negative subtype (OR 3.5, 95% CI, 2.1–5.85, $p < .001$) (12). The median time to brain metastasis diagnosis is also significantly shorter in triple-negative, compared to ER positive/HER2-negative tumors (5,13). In patients with metastatic triple-negative breast cancer, it has been reported that between 25% and 46% of patients will eventually develop brain metastases (14,15).

Of interest, deleterious *BRCA1* alterations are also associated with a high rate of CNS relapse (16). Whether this is purely attributable to the association between *BRCA1* carrier status and triple-negative breast cancer, or whether there is an additional phenotypic difference conferred by nonfunctional *BRCA1* is not clear at this time. Of note, in at least one study, *BRCA1* mutation carriers were more likely to develop brain metastases, even when compared to noncarriers with triple-negative tumors (17).

METHOD OF SPREAD AND DISTRIBUTION

Parenchymal brain metastases are thought to arise from hematogenous dissemination of tumor cells. Involvement of the cerebrum and cerebellum are common; brainstem involvement remains relatively uncommon. Older studies indicated that approximately half of patients with brain metastases presented with a single lesion. However, with the introduction of magnetic resonance (MR) imaging, a significantly more sensitive technique, current series indicate that only about one-fourth of patients with brain metastases have a confirmed single lesion at initial presentation. The term solitary brain metastasis indicates a single brain lesion in the absence of systemic metastases.

CLINICAL MANIFESTATIONS

Because brain imaging is not generally part of routine clinical care for asymptomatic patients with breast cancer, brain metastases are most commonly diagnosed in the setting of new neurological symptoms. Headaches are present in up to half of patients and are commonly bifrontal. In patients with single metastasis or a dominant lesion, there may be a predominance of the pain on the side of the metastasis. Coexisting nausea or emesis occurs in about half of patients with headaches, and is a predictive factor for the presence of brain metastases. Focal neurologic dysfunction is the presenting symptom in 20% to 40% of patients. Hemiparesis is the most common focal complaint. The distribution of symptoms depends upon the location of the metastases and the presence or absence of surrounding edema. Patients who present with cranial nerve deficits should be thoroughly evaluated for evidence of leptomeningeal or base of skull involvement.

Cognitive dysfunction, including mental status changes, memory problems, or mood or personality changes, is the presenting symptom in one-third of patients. Frequently, neurological examination will elicit additional deficits of which the patient is unaware. However, medications, metabolic abnormalities, and infections are more common causes of encephalopathy in cancer patients than brain metastases, and should be included in the differential diagnosis of altered mental status.

Seizures are the presenting symptom in 10% to 20% of patients with brain metastases, and an additional 10% to 26% will develop seizures at some time during the course of their illness. Supratentorial involvement increases the risk of seizure, whereas seizures are quite uncommon in patients with posterior fossa lesions.

In contrast to melanoma or choriocarcinoma, brain metastases from breast cancer tend not to bleed; therefore, acute cerebral hemorrhage is rarely a presenting symptom.

DIAGNOSTIC EVALUATION

In patients presenting with suspicious neurological signs or symptoms, evaluation with computed tomography (CT) or contrast-enhanced magnetic resonance imaging (MRI) is indicated. Of these approaches, MRI is the more sensitive noninvasive, diagnostic test.

MRI detects more lesions in the posterior fossa, where beam-hardening artifact can make CT difficult to interpret. MRI is also superior in defining the number of CNS lesions, a distinction that may affect clinical recommendations. For example, in a study of 23 patients who underwent both double-dose delayed CT and contrast-enhanced MRI, MRI detected more than 67 definite lesions, compared to only 37 lesions on CT (18).

The differential diagnosis of enhancing mass lesions in a patient with breast cancer includes metastasis, primary brain tumor, abscess, demyelinating disorders, cerebral infarction, hemorrhage, progressive multifocal leukencephalopathy, and posttreatment change (i.e., radiation necrosis, post-surgical change). Radiographic features that may differentiate brain metastases from other CNS lesions include the presence of multiple lesions (which helps to distinguish metastases from primary brain tumors), localization at the junction of the gray and white matter, circumscribed margins, and relatively large amounts of vasogenic edema compared to the size of the lesion. The clinical history can also be helpful in guiding appropriate diagnostic testing. For patients with advanced breast cancer who present with multiple brain lesions, further testing may not be necessary. For patients without evidence of extracranial involvement by breast cancer, consideration should be given to tissue sampling to distinguish between metastatic breast cancer versus metastasis from a non-breast primary, primary brain tumor, or nonmalignant cause. A tissue diagnosis should also be strongly considered for patients presenting with a single brain lesion. In a randomized trial evaluating the role of surgical resection for single brain metastasis, 11% of patients were found to have an alternate diagnosis on pathologic review (19). Finally, the differential diagnosis of dural-based lesions includes meningiomas. Because the incidence of meningioma has been reported to be somewhat higher in breast cancer patients than the general population, and because imaging studies may be inconclusive, tissue diagnosis may be required (20). Thus, in any patient in whom the diagnosis of brain metastases is in doubt based upon the radiographic appearance of the lesion(s), the presence of a single lesion, or the clinical history, obtaining tissue is important to establish the diagnosis conclusively.

Another diagnostic dilemma exists in distinguishing necrosis from tumor progression in patients who have previously received whole-brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS). One approach is to consider supplemental imaging with either positron emission tomography (PET), single photon emission CT (SPECT), functional MRI, or MR spectroscopy (21). With a detection rate of only 61% to 68% compared to contrast-enhanced MRI, ^{18}F-flurorodeoxyglucose (FDG)-PET does not appear sufficiently sensitive for use as a screening tool for brain metastases (22,23). However, ^{18}FDG-PET may be helpful in distinguishing radiation necrosis from tumor progression.

In a study of 32 patients with brain metastases from any solid tumor, ^{18}FDG-PET with MRI co-registration had a sensitivity of 86% and specificity of 80%, though not all groups have been able to replicate these findings (24). Others have found that a dynamic assessment of ^{18}FDG uptake with PET offered higher sensitivity and specificity (25). Another potentially useful tool is Tl-201 SPECT. In one study of 72 patients, the sensitivity was reported at 91% for differentiating between radiation necrosis and tumor progression (26). Finally, a variety of newer techniques are under evaluation, including the use of alternative PET tracers (i.e., ^{18}F-fluorocholine, ^{18}F-flurorothymidine, or L-[methyl-^{11}C] methionine) and quantification of blood vessel tortuosity (21,27). In cases in which the imaging studies remain equivocal, management options include following the patient carefully over time versus proceeding to a biopsy for tissue diagnosis. Symptomatic lesions may require steroids and/or an earlier therapeutic intervention such as surgical resection.

PROGNOSIS

Historically, CNS involvement tended to occur late in the course of metastatic breast cancer, and median survival was poor, on the order of 4 to 6 months. More recently, breast cancer-specific prognostic indices have sought to improve upon the Radiation Therapy Oncology Group (RTOG) Recursive Partitioning Analysis (RPA), a widely used, but older system which was not tumor-type specific and likely underestimated survival in breast cancer patients (28). The Graded Prognostic Assessment (GPA) examined multiple potential risk factors associated with survival in tumor-specific contexts, and found that, for patients with breast cancer, performance status was the only significant prognostic factor (29). Further refinement of the breast GPA included an analysis of the influence of tumor subtype and showed that age and tumor subtype were also prognostic in the final model, which consisted of four groups, with the most favorable group experiencing a median survival in the range of 2 years (Table 76-1) (30). Based on data from retrospective studies, it is likely that improved systemic tumor control is a major contributing factor to this difference between historical and present outcomes, particularly in patients with HER2-positive breast cancer. Although one must interpret retrospective data cautiously because of potential selection bias in terms of prescribed treatment, multiple groups have observed a substantially longer survival in patients with brain metastases who continue to receive anti-HER2 therapy following their CNS diagnosis, compared to those who received either no systemic therapy or chemotherapy without anti-HER2 therapy (31–33). In addition, it appears that death from CNS progression (in the context of controlled extracranial disease) is substantially more common in the setting of HER2-positive disease, compared to triple-negative disease, where systemic therapy is generally less effective (10,15). Together these data suggest that i) improvements in systemic therapy are allowing some patients to live longer than older historical estimates would predict, ii) continuation of systemic therapy is likely beneficial, particularly in patients with HER2-positive disease, and iii) pursuing more aggressive approaches in the CNS among breast cancer patients with well-controlled systemic disease and/or HER2-positive disease may be reasonable.

MANAGEMENT

The management of patients with brain metastases can be divided into symptomatic and definitive therapy. Symptomatic therapy includes the use of corticosteroids for the treatment of peritumoral edema and anticonvulsants for control of seizures, whereas definitive therapy includes treatments such as surgery, radiotherapy, chemotherapy, targeted therapy, and radiosensitizers directed at eradicating the tumor itself.

TABLE 76-1

Prognosis of Breast Cancer Patients with Brain Metastases According to the Diagnosis-Specific Breast GPA (DS-GPA)

	DS-GPA Scoring Criteria					
Prognostic factor	0	0.5	1.0	1.5	2.0	Patient Score
KPS	≤50	60	70–80	90–100	n/a	___
Subtype	Basal	n/a	LumA	HER2	LumB	___
Age, years	≥60	<60	n/a	n/a	n/a	
Sum total						___

GPA, graded prognostic assessment; n/a, not applicable; KPS, Karnofsky performance status; Basal, ER-/PR-/HER2-negative; LumA, ER/PR positive, HER2-negative; HER2, ER/PR negative, HER2 positive; LumB, ER/PR positive, HER2 positive.

DS-GPA Score	*Median Survival Time (Months; 95% CI)*
0–1.0	3.4 (3.1, 3.8)
1.5–2.0	7.7 (5.6, 8.7)
2.5–3.0	15.1 (12.9, 15.9)
3.5–4.0	25.3 (23.1, 26.5)
All	13.8 (11.5, 15.9)

DS-GPA, diagnosis specific grade prognostic assessment.
Modified from Sperduto PW, Kased N, Roberge D, et al. Summary report on the graded prognostic assessment: an accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* 2012;30(4):419–425.

Symptomatic Therapy

Corticosteroids

Corticosteroids are indicated in patients with symptomatic edema, and are thought to exert their effect by reducing capillary permeability, restoring arteriolar tone, and facilitating transport of fluid into the ventricular system. Most patients will improve symptomatically within 24 to 72 hours, although improvement of edema on imaging studies may not be immediately apparent. Patients who present with edema on imaging but who are asymptomatic generally do not require the prophylactic initiation of steroids.

Of the corticosteroids, dexamethasone is the most widely used because of its relatively weak mineralocorticoid activity, which reduces the potential for fluid retention. The usual starting dose is 4 mg every 6 hours, and may be preceded by a 10 mg load, depending on clinical circumstances. Because of potential adverse effects, such as myopathy, hyperglycemia, insomnia, fluid retention, gastritis, and immunosuppression, the dose of corticosteroids should be kept to the minimum effective dose and tapered during or after definitive therapy. Corticosteroid use also increases the risk of *Pneumocystis jiroveci*. In two case series, the median duration of dexamethasone therapy was only 10 weeks before onset of symptoms, and symptoms commonly appeared during tapering of steroid therapy (34,35). Therefore, *P. jiroveci* prophylaxis should be considered for patients for whom the anticipated duration of steroid use exceeds 4 to 5 weeks.

Anticonvulsants

Approximately 10% to 20% of patients with brain metastases present with seizures, and an additional 10% to 26% will develop seizures at some time during the course of their illness. For most patients, confirmation of the diagnosis with electroencephalography is not necessary, and the use of standard anticonvulsants is generally indicated.

To determine whether the routine use of anticonvulsants is indicated in patients without a prior history of seizure, the Quality Standards Subcommittee of the American Academy of Neurology reviewed the results of twelve studies that addressed this question (36). None of the individual studies indicated a significant reduction in seizure incidence between the prophylaxis and nonprophylaxis groups. A meta-analysis of the four randomized trials indicated no difference in seizure incidence (OR 1.09; 95% CI, 0.63–1.89, p = .8), seizure-free survival (OR 1.03; 95% CI, 0.74–1.44, p = .9), or overall survival (0.93; 95% CI, 0.65–1.32, p = .7). Because of the known potential for adverse effects and drug interactions, and the lack of clear benefit, the routine use of anticonvulsants is not recommended in patients without a history of seizures. A possible exception includes patients with lesions in areas of high epileptogenicity (e.g., motor cortex), though a benefit has not been clearly demonstrated in clinical studies.

In the periprocedural setting, a meta-analysis including six controlled trials of patients receiving anticonvulsant drugs in the setting of supratentorial craniotomies has been completed. It showed a non-significant trend (p = .1) for fewer postoperative seizures, though it should be noted that the included trials were generally quite small (37). High-level randomized evidence regarding the use of prophylactic anticonvulsants in the setting of SRS is not available.

Venous Thromboembolic Disease

Venous thromboembolic (VTE) disease occurs in approximately 20% of patients with brain metastases (38). Because of the concern for intracranial hemorrhage (ICH), many clinicians are reluctant to fully anticoagulate patients. However, mechanical approaches, such as the placement of an inferior vena cava (IVC) filter is reported to be associated with complications in two-thirds of patients (39). In addition, VTE recurs in up to 40% of patients with brain metastases treated with an IVC filter alone (40).

Compared to IVC filter placement, anticoagulation is associated with a lower rate of recurrent VTE, and, for most patients with brain metastases, the risk of hemorrhage appears acceptable. In a series of 42 patients treated at Memorial Sloan Kettering Cancer Center in New York who had brain metastases from a variety of solid tumors and who were anticoagulated for VTE, only three patients (7%) experienced ICH, including two patients in the setting of supratherapeutic anticoagulation (40). In a study of 25 patients with either primary or metastatic brain tumors treated with anticoagulation, only one patient experienced an incidentally found, asymptomatic focal intraventricular bleeding event (41). Consequently, the data, though limited, suggests that anticoagulation is preferable to IVC filter placement in most breast cancer patients who develop clinically significant VTE.

DEFINITIVE TREATMENT

The goals of definitive treatment of brain metastases are to relieve and/or stabilize neurological symptoms, to achieve long-term tumor control, and to extend life, while minimizing toxicity. The choice of therapy is influenced by a) the size, number, and location of lesions, b) the presence or absence of neurological symptoms, c) the patient's life expectancy, including the patient's performance status and the status of the patient's extracranial disease, d) prior treatment, e) expected toxicities of treatment, f) availability of systemic treatment options, and g) patient preference. In general, initial management will include some combination of surgical resection, stereotactic radiosurgery (SRS), and/or WBRT. Systemic therapy could be a consideration on a clinical trial, in the context of minimal disease burden in a well-informed patient with close follow-up, or in the context of progressive extracranial disease in which rapid disease control is felt necessary. Given these complex considerations, the optimal care of patients with brain metastases involves close multidisciplinary collaboration in order to avoid overtreatment of patients with a limited life expectancy, as well as potential under-treatment of patients with well-controlled systemic disease and significant CNS-related morbidity.

SURGERY

The role of surgery in patients with brain metastases is to provide relief of symptoms resulting from mass effect of the tumor, to establish a histologic diagnosis, to improve local control, and to provide a potential benefit to survival.

Three prospective, randomized trials have been conducted to evaluate the role of surgery in patients with brain metastases (Table 76-2). The first trial, reported by Patchell and colleagues, randomly assigned 48 patients with a single brain metastasis (6% with a breast primary) to either surgery followed by WBRT versus WBRT alone (19). Patients in the combined-modality arm achieved better local control (20% vs. 52%, p <.02), improved median duration of functional independence (38 weeks vs. 8 weeks; p <.005), and longer overall survival (40 weeks vs. 15 weeks; p <.01), compared to the patients who received WBRT alone. These findings were replicated in a study of 63 patients (19% with

TABLE 76-2

Summary of Selected Prospective Randomized Clinical Trials Evaluating Surgical and/or Radiotherapy-Based Approaches for Management of Brain Metastases

Trial	*Study Design*	*Population*	*N*	*# With Breast Cancer*	*Results*
Trials evaluating whole brain radiotherapy dose-fractionation schedules[a]					
Borgelt et al., 1980 (51)					
First study	30 Gy/10 fractions vs. 30 Gy/15 fractions vs. 40 Gy/15 fractions vs. 40 Gy/20 fractions	Solid tumors	910	166	More rapid symptom improvement with larger fractions (55% of patients achieved improved symptoms at 2 weeks with 30 Gy/10 fractions compared to 43% for other regimens, $p = .06$). No difference in OS among arms.
Second study	20 Gy/5 fractions vs. 30 Gy/10 fractions vs. 40 Gy/15 fractions	Solid tumors	902	146	More rapid symptom improvement with larger fractions (64% of patients achieved improved symptoms at 2 weeks with 20 Gy/5 fractions compared to 54% for the other regimens, $p = .01$). No difference in OS between arms.
Borgelt et al., 1981 (61)					
First study	10 Gy/1 fraction vs. protracted course (20, 30, or 40 Gy/10–20 fractions)	Solid tumors	26[b]	2	No difference in rate of symptom improvement or OS. Shorter duration of improvement (4 weeks vs. 10 weeks, $p = .02$) and TTP (median 8 weeks vs. 11.5 weeks, $p = .07$) with high-dose radiation.
Second study	12 Gy/2 fractions vs. protracted course (20, 30, or 40 Gy/10–20 fractions)	Solid tumors	33[a]	1	No statistically significant difference in rate of symptom improvement, duration of improvement, or OS with high-dose radiation.
Murray et al., 1997 (63)	32 Gy/20 fractions over 10 d followed by boost (24.4 Gy/14 fractions over 7 d) vs. 30 Gy/10 fractions	Solid tumors	429	43	No difference in OS with accelerated hyperfractionation ($p = .52$)
Trials evaluating the role of surgery in addition to WBRT					
Patchell et al., 1990 (19)	Surgery followed by WBRT (36 Gy/12 fractions) vs. WBRT alone	Solid tumors, single brain metastasis	48	3	Improved local control, 80% vs. 48% ($p < .02$), OS (median 40 weeks vs. 15 weeks, $p < .01$), and functionally independent survival (median 38 weeks vs. 8 weeks, $p < .005$).
Noordijk et al., 1994 (42)	Surgery followed by WBRT (40 Gy/20 fractions over 10 d) vs. WBRT alone	Solid tumors, single brain metastasis	63	12	Improved OS (median 10 months vs. 6 months, $p = .04$) and functionally independent survival (7.5 months vs. 3.5 months, $p = .06$).
Mintz et al., 1996 (43)	Surgery followed by WBRT (30 Gy/10 fractions) vs. WBRT alone	Solid tumors, single brain metastasis	84	10	No difference in OS (median 5.6 months vs. 6.3 months, $p = .24$) or proportion of functionally independent days (mean 0.32 for both arms, $p = .98$)

(Continued)

TABLE 76-2 *(Continued)*

Summary of Selected Prospective Randomized Clinical Trials Evaluating Surgical and/or Radiotherapy-Based Approaches for Management of Brain Metastases

Trial	*Study Design*	*Population*	*N*	*# With Breast Cancer*	*Results*
Trials evaluating the role of WBRT in addition to local therapy					
Patchell et al., 1998 (53)	Surgery + WBRT (50.4 Gy/28 fractions) vs. surgery alone	Solid tumors, single brain metastasis status post complete surgical resection	95	9	Improved local control (10% vs. 46%, $p < .001$) and distant control (recurrence in other sites in the brain 14% vs. 37%, $p < .01$). Decreased death due to neurologic causes (14% vs. 44%, $p = .03$). No difference in OS (median 48 weeks vs. 43 weeks, $p = .39$) or functionally independent survival (median 37 weeks vs. 35 weeks, $p = .61$).
Aoyama et al., 2006 (54)	WBRT (30 Gy/10 fractions) + SRS (with 30% dose reduction) vs. SRS alone	Solid tumors, 1–4 lesions, all ≤3 cm	132	9	Improved local control (89% vs. 73%, $p = .002$) at one year. Decreased likelihood of recurrence of tumor anywhere in the brain at 1 y (47% vs. 76%, $p < .001$). No difference in preservation of neurologic function. No difference in primary endpoint of OS (7.5 months vs. 8.0 months, $p = .42$). No difference in death due to neurologic causes (22.8% vs. 19.3%, $p = .64$).
Kocher et al., 2011 (52)	WBRT (30 Gy/10 fractions) vs. observation after either SRS or surgery	Solid tumors, 1–3 lesions, stable systemic disease	359 (199 SRS, 160 surgery)	42	WBRT vs. observation (2 years) Surgery group recurrence Local: 27% vs. 59% DR: 23% vs. 42 % SRS group recurrence Local: 19% vs. 31% Distant: 33% vs. 48% No difference in OS (10.7 months vs. 10.9 months), survival with functional independence 9.5 months vs. 10 months). Patients in observation arm reported better QOL (66).
Chang et al., 2009 (70)	WBRT (30 Gy/12 fractions) + SRS vs. SRS alone	Solid tumors, 1–3 lesions	58	8	Study stopped early due to decrease in HVLT-R total recall at 4 months in WBRT arm (primary endpoint). Local (100% vs. 67%) and distant (73% vs. 45%) control at 1-yr improved with WBRT. WBRT arm had more deaths from systemic causes leading to worse OS (5.7 months vs. 15.2 months).

Trials evaluating dose intensification of radiotherapy					
Kondziolka et al., 1999 (77)	WBRT (30 Gy/12 fractions) + SRS vs. WBRT alone	Solid tumors, 2–4 lesions, all ≤2.5 cm	27	4	Improved local control (local recurrence rate at one year 8% vs. 100%; median time to local recurrence 36 months vs. 6 months, $p = .0005$). Longer time to recurrence of tumor anywhere in the brain (34 months vs. 5 months, $p = .002$). No difference in OS (11 months vs. 7.5 months, $p = .22$).
Andrews et al., 2004 (65)	WBRT (37.5 Gy/15 fractions) + SRS vs. WBRT alone	Solid tumors, 1–3 lesions, all ≤4 cm	333	34	Improved local control at 1 y (82% vs. 71%), $p = .01$). Higher likelihood of stable or improved performance status at 6 months (43% vs. 27%, $p = .03$). No difference in primary end point of OS (6.5 months vs. 5.7 months, $p = .14$). Survival advantage observed in subgroup of patients with a single brain metastasis (median 6.5 months vs. 4.9 months, $p = .04$).
Trials evaluating radiosensitizers					
Mehta et al., 2003 (113)	WBRT (30 Gy/10 fractions) + motexafin gadolinium vs. WBRT alone	Solid tumors	401	75	No difference in OS (median 5.2 months vs. 4.9 months, $p = .48$), time to neurologic progression (median 9.5 months vs. 8.3 months, $p = .95$), or death due to neurologic causes (49% vs. 52%, $p = .60$).
Suh et al., 2006 (114)	WBRT (30 Gy/10 fractions) + efaproxiral vs. WBRT alone	Solid tumors, RPA class I or II	515	107	No difference in OS (median 5.4 months vs. 4.4 months, $p = .16$), time to neurological progression, or death due to neurologic causes. In an exploratory subgroup analysis, improved OS (HR for death 0.51, $p = .003$) and response rate (54% vs. 41%, $p = .01$) in breast cancer patients. A subsequent trial limited to breast cancer patients was negative (116).
Knisely et al., 2008 (118)	WBRT 37.5 Gy/15 fractions) + thalidomide vs. WBRT alone	Solid tumors, multiple (>3), large (>4 cm) or midbrain metastases	175	31	No difference in OS (median 3.9 months for both arms), or in deaths due to neurologic causes.

[a]All fractions given once daily unless otherwise specified.
[b]Represents number of patients assigned to the high-dose arm. These patients were compared to 143 control patients who received a more protracted course of radiation.
OS, overall survival; TTP, time to progression; WBRT, whole-brain radiotherapy; SRS, stereotactic radiosurgery; HR, hazard ratio.

breast primaries) led by Noordijk et al., in which patients treated with surgery and WBRT achieved prolonged survival (median 10 months vs. 6 months; $p = .04$) and functionally independent survival (7.5 months vs. 3.5 months; $p = .06$) compared to patients treated with WBRT alone (42). Of note, only patients with stable or absent extracranial disease appeared to derive a survival benefit from surgery; patients with progressive extracranial disease experienced a median survival of only 5 months irrespective of the allocated treatment. A third study reported no difference in either survival or functionally independent survival with the addition of surgery to WBRT (43). In contrast to the first two trials, nearly half of patients in this study were enrolled with co-existing extracranial metastases, and approximately 40% of patients had a Karnofsky performance status of 70% or less at study entry. In addition, the presence of a single brain lesion was categorized according CT rather than MRI (which could have missed multiple lesions), and 10 of 43 patients randomly assigned to radiotherapy underwent surgical resection at some point in their disease course, which may have further confounded the results.

In patients with multiple brain metastases, the role of surgery to remove all resectable lesions remains controversial, and the data are limited to retrospective series. Wronski et al. reported the largest retrospective series limited to patients with brain metastases from breast cancer (n = 70), and found no statistical difference in survival between patients with single lesions and those with multiple lesions (44). In contrast, Hazuka et al. noted that the median survival of 18 patients undergoing resection of multiple metastases was only 5 months, far shorter than that observed in 28 patients undergoing resection of a single lesion (45). In summary, although some of the retrospective data are encouraging, in the absence of randomized data, it is difficult to distinguish between a true effect from surgery versus selection bias; that is, patients with technically resectable lesions who are candidates for resection may have a better prognosis irrespective of the surgical intervention received.

The potential benefits of surgical resection must be weighed against the risks. Fortunately, advances in surgical techniques, including preoperative functional MRI, intra-operative neuronavigational devices, intra-operative cortical mapping, and intravenous sedation anesthesia have improved the safety of surgical resection of brain metastases, and in some cases, can allow resection of lesions located in eloquent areas (46). In a retrospective cohort study of 13,685 admissions for the resection of metastatic brain tumors from the Nationwide Inpatient Sample, the overall in-hospital mortality rate fell from 4.6% in 1988–1990 to 2.3% in 2000 (47). Consistent with other studies of surgical intervention, mortality and morbidity were also lower in higher-volume centers and with higher-volume surgeons.

Whole-Brain Radiotherapy

For over five decades, WBRT has played a central role in the management of brain metastases and it remains the treatment of choice for the majority of patients who present with multiple (4–5 or more) brain metastases. Early studies supported a survival benefit for brain metastases patients treated with WBRT compared to supportive care or treatment with corticosteroids only (48,49). Breast cancer brain metastases appear to be relatively responsive to WBRT in relation to other histologies such as non-small cell lung and melanoma (50). For patients with brain metastases from breast cancer, estimates of the median expected survival following treatment with WBRT alone improved to 4 to 6.5 months from 1 to 2 months with supportive care only (51). However, in patients with limited brain metastases treated with focal therapies such as surgery and/or SRS, the addition of WBRT did not produce a survival benefit in randomized trials (Table 76-2) (52–55). On the other hand, when considered as adjuvant therapy to SRS or surgery for brain metastases, WBRT has been shown to reduce of risk of elsewhere brain recurrence (52,54,55), preserve neurocognitive function in some patients (56), and prevent neurologic death (52,53). WBRT can also provide effective palliation of neurological symptoms, with durable improvement, or stability of neurological symptoms observed in approximately 70% to 90% of patients (57–59). For patients presenting with cranial nerve deficits, approximately 40% may have an improvement with WBRT (59).

A wide range of WBRT dose-fractionation schedules ranging from 2000 cGy in 5 fractions to 4000 cGy in 20 fractions have been compared for efficacy and toxicity in 2 RTOG randomized trials (Table 76-2) (51,60). While the various schedules showed no significant difference in median survival or duration of symptom palliation, symptomatic relief occurred sooner in patients treated with larger fractions. Even when breast cancer patients were analyzed in a subgroup analysis, time to progression of neurologic function or death did not differ by schedule (60). Further shortened WBRT courses such as 1000 cGy in a single fraction or 1200 cGy in 2 fractions achieve similar survival and palliative benefit as more extended fractionation schemes, but appear to be associated with inferior duration of symptom improvement and time to neurological progression (61). In addition, large fraction size may increase the risk of neurocognitive dysfunction (62). A randomized trial comparing accelerated hyperfractionated WBRT to 3000 cGy in 10 fractions showed no benefit to survival or palliation even among favorable prognostic groups (63). The current standard therapy of 3000 cGy in ten 300 cGy fractions over 2 weeks or 3750 cGy in fifteen 250 cGy fractions provides a balance between prompt palliation and control of the competing risk from brain progression with acceptably low acute side effects (64,65). Many radiation oncologists will use even longer fractionation schedules, such as 4000 cGy in 200 cGy fractions for patients with longer anticipated survival in an attempt to reduce neurocognitive sequelae.

The toxicity of WBRT is generally divided into acute, early-delayed, and late effects. The most debilitating acute and early-delayed effects are fatigue and somnolence, which can be profound. They may arise within the first week of therapy and persist for weeks or months. Other prominent acute and early-delayed effects of WBRT which impact adversely on QOL include alopecia, skin erythema, and loss of taste. For example, the EORTC 22952-26001 study demonstrated overall better health-related QOL scores among patients who did not receive WBRT, with differences most pronounced during early follow-up (e.g., physical functioning at 8 weeks, fatigue at 8 weeks). However, some toxicities were seen later after the course of treatment (e.g., global health status at 9 months, cognitive functioning at 12 months) (66). While the acute and early-delayed effects are generally reversible, the late effects are generally permanent and may be progressive. Of note are the rare, but clinically significant, risks of radiation-related leukoencephalopathy and necrosis which may manifest clinically as significant neurologic or neurocognitive dysfunction.

The potential for neurocognitive function (NCF) changes following WBRT is of substantial concern, particularly for patients who may have long survival. A landmark paper by DeAngelis et al. in 1989 described 12 cases of progressive dementia which developed at a median of 14 months following treatment in a series of 482 patients treated

with WBRT alone or surgery plus WBRT (62). All affected patients displayed cortical atrophy, ventricular dilation, and developed urinary incontinence and ataxia, with some patients showing improvement in clinical symptoms following ventriculoperitoneal shunting. Seven of the patients died of these complications with no evidence of tumor recurrence. Patients had received treatments with relatively large fraction sizes ranging from 300 to 600 cGy and total doses of 2500 to 3900 cGy. With modern radiation doses and fractionation schedules, this risk is somewhat mitigated, with broad measures of NCF often failing to demonstrate a detrimental effect of radiation (56). In terms of longer-term outcomes, a comprehensive neurocognitive assessment of patients treated with WBRT in the phase III trial PCI-P120-9801 revealed that patients with better than median local and distant tumor control displayed significantly improved preservation of executive and fine motor function relative to patients with less than median response to treatment (67). These results support the notion that optimizing local and distant brain tumor control is an important facet of preserving neurocognitive function.

Studies that have utilized in-depth neuropsychometric testing, however, have also demonstrated specific time-dependent changes following treatment, particularly with respect to short-term memory, executive functioning, and attention (55,67,68). Various approaches have been attempted to mitigate these effects. RTOG 0614 was a randomized, double-blind, placebo-controlled trial investigating the potential neuroprotective effects of memantine, a drug used to treat mild to moderate dementia, in 508 evaluable patients receiving WBRT. While not meeting the primary endpoint of improvement in delayed recall (p = .059), potentially due to low statistical power, patients receiving memantine during and after WBRT experienced longer time to cognitive decline and decreased risk of decline in multiple NCF dimensions (69).

Following surgical resection of a solitary brain metastasis, post-operative WBRT has frequently been employed with the goal of decreasing the risk of both local and elsewhere recurrence in the brain. (Local refers to a recurrence at the original site of metastasis and elsewhere to a recurrence elsewhere in the brain.) A randomized trial by Patchell et al. further clarified the effects of post-operative WBRT for patients with a surgical resected solitary brain metastasis (53). In this study, 95 patients were randomized to either WBRT or no further treatment following complete resection of a solitary brain metastasis. The addition of WBRT decreased the risk of local recurrence (10% vs. 46%, p <.01), elsewhere brain recurrence (14% vs. 37%, p <.01), and neurological death (14% vs. 44%, p = .003). No significant difference in overall survival was found, but the higher risk of neurological death observed with surgery alone has been suggested by some as a justification for combined therapy in this group of patients.

Similar results were found in the EORTC 22952-26001 study, which randomized 359 patients with 1 to 3 brain metastases to either observation or WBRT following either surgery (n = 160) or SRS (n = 199) (52). Eligibility criteria included having evidence of controlled extracranial disease or asymptomatic synchronous primary cancer. Overall, patients who received WBRT experienced fewer local (31% vs. 19%) and elsewhere (48% vs. 33%) brain relapses at 2 years, but did not experience any statistically significant gains in either overall survival or preservation of functional independence. The lack of translation of intracranial control to overall survival occurred even though the competing risk of extracranial disease was at least partially mitigated by the eligibility criteria. Among the subset treated with surgery, WBRT reduced the probability of relapse at the initial site of disease from 59% to 27% at 2 years. Of note, only 12% of patients enrolled on the EORTC study carried a primary diagnosis of breast cancer. In a separate, randomized trial evaluating SRS alone versus SRS plus WBRT in patients with 1 to 4 brain metastases reported by Aoyama et al., again, there was no difference in overall survival between the two treatment groups, though it should be noted that breast cancer patients comprised only 7% of the study population (54). There were also no differences observed in neurologic survival or functional preservation between the groups. As expected, the risk of developing a new brain metastasis was higher in the SRS alone arm versus the combined treatment arm (63.7% vs. 41.5%, p = .03). In addition, 12-month local control was greater for combined treatment than SRS alone (88.7% vs. 72.5%, p = .002), and salvage therapy was more frequently required in patients treated with SRS alone. Finally, a study conducted at the M.D. Anderson Cancer Centers and reported by Chang et al. randomized 58 patients with 1 to 3 brain metastases to SRS with or without WBRT was stopped early based on an interim analysis showing worse outcomes of the WBRT arm with respect to the primary endpoint of neurocognitive decline at 4 months based on the Hopkins Verbal Learning Test (70). The study found that the addition of WBRT had similar effects on intracranial control as had the other randomized studies: local control improved from 67% to 100% and elsewhere brain control improved from 45% to 73% at 1 year. Even though improvements in intracranial control were demonstrated, patients in the WBRT arm actually experienced worse overall survival. However, the difference in survival could be explained by excess deaths due to systemic disease progression, rather than intracranial progression or toxicity in the WBRT.

Why improvements in intracranial control do not translate into overall survival benefits is an open question. Potential explanations include the availability of effective salvage at recurrence, a dominant competing mortality risk from extracranial disease, or a combination of both. It should be noted that while patients with progressive extracranial disease at presentation were excluded from the EORTC study, two-thirds of patients developed progressive disease during the course of the study (52). The impact, however, of the elevated risk of local or elsewhere brain recurrence on QOL compared to the toxicity from the addition of WBRT, particularly in patients with long expected survival remains unclear, especially when other low morbidity salvage therapies such as SRS may be effective. In addition, localized boost therapy to the surgical resection cavity using SRS or fractionated stereotactic radiotherapy without WBRT may decrease the risk of local failure to levels comparable or less than that achieved with WBRT (71). Another approach under investigation is the use of hippocampal-sparing techniques, given the very low likelihood of hippocampal involvement in patients with brain metastases, but this hypothesis remains to be confirmed in a prospective, randomized trial (72).

STEREOTACTIC RADIOSURGERY (SRS)

SRS has come to play an increasingly important role in the management of brain metastases, in many cases offering an alternative to surgery, WBRT, or both. SRS involves the delivery of a single large dose of focused radiation to one or more tumor masses with rapid dose fall-off beyond the tumor margin. Tumors are targeted for treatment with the aid of a minimally invasive stereotactic frame, or using x-ray image guidance together with mask immobilization. Non-frame based approaches have also made multiple fraction therapy

using SRS-style set up and localization verification possible. The precise dose localization and shaping afforded by this technique minimize the treatment-related morbidity that may result from normal tissue irradiation. Overall, SRS produces a high rate of local control, which is optimal with doses greater than or equal to 1800 cGy (73). SRS has the potential for noninvasive local tumor control while allowing targeting of multiple lesions and has been evaluated for its potential to supplement, replace, or defer both WBRT and surgery.

Treatment-related morbidity using SRS depends on tumor size and location, radiosurgery dose, and prior treatment. The RTOG performed an SRS dose escalation study to determine the maximum tolerated dose (MTD) in patients previously irradiated for either a primary brain tumor or a solitary metastasis (74). Dose was escalated in 3 Gy increments such that grade 3, 4, and 5 toxicity 3 months following SRS remained less than 20%. For tumors 3 to 4 cm in diameter, the MTD was 15 Gy, for those 2 to 3 cm in diameter the MTD was 18 Gy and for those less than 2 cm the MTD was 24 Gy. On multivariate analysis, increased dose, worsening Karnofsky performance status (KPS), and increasing tumor diameter were associated with higher risk of grade 3 to 5 neurotoxicity. The actuarial incidence of radionecrosis at 12 months post SRS was 8%, and at 24 months, it was 11%. In an analysis summarizing dosimetric factors associated with the development of radiation necrosis in multiple studies using a variety of SRS applications, the volume of brain receiving 12 Gy (V12) was suggested as a potential predictive factor (75).

While surgical resection would be expected to be superior palliation for tumors with symptomatic mass effect, it is unclear if SRS is equivalent to surgery for patients with single small to medium size lesions without symptomatic mass effect. A 2003 retrospective series from the Mayo Clinic evaluated outcomes for patients with solitary brain metastases less than 35 mm treated with either surgery or SRS (76). While patients treated with either modality had similar survival, a significant improvement in local control was observed in the SRS group with no local recurrences (0/26) versus 15% (11/74) in the surgery arm. The overall recurrence rates including elsewhere brain recurrence were not significantly different: 29% in the SRS arm and 30% in the surgery arm; the use of WBRT following surgery or SRS was not significantly different between the groups. While not randomized between the modalities, the 2-year local relapse rates for surgery and SRS alone in the EORTC 22952-26001 study were 59% and 31%, respectively (52). The populations were not balanced, however, with overall larger tumors (albeit more often single rather than multiple) in the surgery cohort.

Patients with multiple brain metastases who were treated with WBRT alone in the past, with SRS reserved for failure, may now be candidates for WBRT and upfront SRS. Early data to support this view came from a single institution randomized trial reported by Kondziolka et al. which evaluated WBRT alone versus. WBRT+SRS for patients with 2 to 4 lesions less than 2.5 cm in size. Study accrual was terminated at 60% (27 patients) following interim evaluation that revealed a significant improvement in local control with combined treatment. Patients receiving both SRS and WBRT had a local recurrence rate at 1 year of only 8% versus 100% for those receiving WBRT alone. The median time to local recurrence was 6 months for WBRT alone, and 36 months following WBRT+SRS (p = .005). Despite the substantial difference in local control, no significant difference in survival between the treatment groups was found in this small study population (77).

To determine if WBRT+SRS could also result in a survival benefit, the RTOG 95-08 trial randomized a total of 333 patients with 1 to 3 brain metastases to WBRT+SRS or WBRT alone with the primary endpoint of overall survival (Table 76-2) (65). The 1-year local control was increased for the combined treatment group (82% vs. 71%, p = .01), a smaller improvement than that observed in the prior study reported by Kondziolka et al. While no significant difference in overall survival or cause of death was observed, several subgroups were identified which showed benefit from combined treatment. Patients with a solitary metastasis derived a survival benefit from the addition of SRS to WBRT, with a median survival of 6.9 versus 4.5 months (p = .04), analogous to the results observed in the first Patchell randomized trial comparing surgery + WBRT with WBRT alone. In addition, patients in RPA Class I (e.g., Karnofsky performance status ≥70, age less than 65, controlled primary cancer, and no extracranial metastases), age less than 50, or those with squamous or non-small cell histology showed significant survival benefit from combined treatment. Patients undergoing combined treatment were more likely to have stable or improved performance status at 3 (50% vs. 33%, p = .02) and 6 months (43% vs. 27%, p = .03). These results suggest that a survival benefit of combining WBRT+SRS may be limited to select patients, while the probability of maintaining a stable or increased performance status may be a more general benefit of combined treatment.

As discussed earlier, the capacity of SRS to achieve local control of multiple intracranial tumors has prompted reevaluation of the role of WBRT in palliative CNS radiotherapy, and has led to increased individualization of treatment recommendations, particularly in patients with 1 to 4 CNS lesions. There is less data to guide decisions regarding WBRT versus SRS in patients with more than 4 lesions. Bhatnagar et al. reported a retrospective review of 205 patients who underwent SRS for treatment of 4 or more metastases in the initial or re-irradiation setting (78). Median overall survival was 8 months. Of note, the total volume of metastases, rather than the total number was predictive for survival. Still, more evidence is needed to examine recurrence patterns, morbidity, and survival in order to help weigh decisions regarding the use of WBRT versus SRS in patients with a large number (>4) CNS lesions, and our general preference remains WBRT in this setting. Should SRS alone be chosen, clinical and radiographic follow-up every 2 to 4 months to detect brain recurrence is warranted.

Another clinical setting well suited for SRS is the treatment of post-WBRT intracranial recurrences. The use of WBRT re-treatment, typically with total doses of 2000 to 2500 cGy in 200 cGy fractions is associated with significant morbidity and a posttreatment median survival of only 3.5 to 5 months (57,79). Re-irradiation of less than 5 brain metastases is best accomplished with SRS, which has far less toxicity than WBRT retreatment (80,81). Kelly et al. reported on a series of 79 patients receiving SRS as salvage therapy for progressive breast cancer brain metastases, 76 of whom had received prior WBRT (82). Most patients had less than 4 lesions treated with SRS, but 23% had 4 or more metastases treated. Median survival in this population was 9.8 months. Favorable prognostic factors in this population included metastases secondary to HER2+ primary tumors and stable systemic disease at the time of SRS.

SYSTEMIC THERAPY

Chemotherapy

The delivery of chemotherapeutic agents through the blood-brain barrier (BBB) is limited by intrinsic drug characteristics, including molecular weight, lipid solubility, and plasma protein binding, as well as host and tumor characteristics, such as active efflux transport and interstitial fluid pressure. In comparison to normal brain, tumor-associated vasculature is frequently disrupted, with disordered, highly tortuous, and more permeable vessels. In preclinical models, it has

been demonstrated that a number of chemotherapeutic and targeted agents can reach brain metastases, albeit to lower levels and with more significant heterogeneity compared to non-CNS metastases (83,84).

To date, no chemotherapeutic agents have gained FDA approval for the treatment of brain metastases from breast cancer. Data are available from case reports, case series, and small prospective trials. Rosner et al. treated 100 consecutive patients with brain metastases from breast cancer with several regimens which included cyclophosphamide, 5-fluorouracil, and prednisone (85). The objective response was 50%, with a median duration of response of 7 months. Compared to the current era, patients were relatively untreated: only 7% of patients had received adjuvant chemotherapy and just under half had received any prior chemotherapy for metastatic disease. Boogerd et al. reported similar results for CMF or CAF regimens in a small case series (n = 22) (86).

The efficacy of temozolomide for brain metastases, including a broad range of solid tumors, has been evaluated in multiple phase II studies. Most of the published studies have indicated only minimal activity in breast cancer patients (Table 76-3) (87,88). In contrast, capecitabine appears to be an active agent in this setting. Rivera and colleagues evaluated capecitabine in combination with temozolomide in a phase I study of patients with brain metastases from breast cancer (89). Of 22 patients evaluable for response, 4 achieved a complete or partial response in the CNS. Given the disappointing results with temozolomide alone, it is likely that most, if not all, of the observed effect is attributable to the capecitabine (90). Platinum agents have also been evaluated, most commonly in combination with other agents, with reported response rates as high as 38% to 40% (91,92). These encouraging findings should be taken into context, however, given that, at least for extracranial disease, the response rates to platinum agents appear to fall off dramatically in later lines of therapy, compared to the first line setting (93,94).

Overall, the paucity of prospective studies evaluating systemic therapy for CNS disease makes any definitive recommendations difficult. Outside of a clinical trial, consideration of off-label use of anthracyclines, capecitabine, and platinum salts seems reasonable in patients whose disease has progressed through more standard (e.g., radiotherapy and/or surgical) approaches, or who have minimal CNS disease burden and agree to close follow-up.

Targeted Therapy

Endocrine therapies have an established role in the treatment of hormone receptor positive breast cancer. Many hormonal agents cross the blood-brain barrier. Although no prospective trials have been conducted in patients with brain metastases from breast cancer, responses in the CNS to tamoxifen and megestrol acetate have been described (95–97). Aromatase inhibitors, which act via inhibition of peripheral conversion of androgens to estrogen, also have reported anecdotal activity in the CNS (98). In animal models, fulvestrant does not appear to cross the blood-brain barrier and no reports of CNS activity have been published to date (99). Unfortunately, by the time most patients with ER-positive disease develop brain metastases, their cancer is typically refractory to further endocrine manipulations. However, endocrine therapy could be considered in patients with minimal prior endocrine therapy exposure and/or those patients who have had a history of prolonged systemic responses to endocrine treatment.

As far as other targeted approaches for brain metastases, anti-HER2 approaches have been most extensively studied (Table 76-4). A CNS objective response rate of 2.6% to 6% was reported in two phase 2 trials of lapatinib monotherapy in a pre-treated population (100,101). When given in combination with capecitabine in a similar patient population, the reported CNS response rate is higher, between 18% and 38% (101–105). Recently, results of the LANDSCAPE trial were published.

TABLE 76-3

Summary of Selected Prospective Clinical Trials Evaluating Chemotherapy for Breast Cancer Brain Metastases

Regimen	*# of Patients (# with Breast Cancer)*	*Patient Population*	*CNS ORR in Breast Cancer Subset*	*TTP/PFS*
Temozolomide (87)	19 (5)	Pre-treated with systemic therapy	0%	<2 mo
Temozolomide (88)	157 (51)	80% prior chemotherapy for MBC; 24% prior WBRT	4%	~2 mo
Capecitabine + temozolomide (89)	24 (24)	33% prior WBRT	18%	3 mo
Cisplatin + temozolomide (92)	32 (15)	~50% prior WBRT	40%	2.9 mo
Cisplatin + etoposide (91)	107 (56)	No prior CNS RT allowed; 36% chemotherapy-naive	38%	4 mo
Patupilone (119)	36 (36)	Progression after CNS RT required	19%	2.8 mo
Vinorelbine + temozolomide (120)	38 (11)	Heavily pre-treated patients	0% (1 minor response observed)	1.9 mo

CNS, central nervous system; ORR, objective response rate; TTP, time to progression; PFS, progression-free survival.

TABLE 76-4

Studies of Lapatinib for HER+ Brain Metastases

Regimen	*Number of Patients*	*Patient Population*	*CNS ORR*	*TTP/PFS*
Lapatinib (100)	39	Heavily pre-treated	2.6%	3.0 mo
Lapatinib (101)	237	Progression after CNS RT	6%	2.4 mo
Lapatinib + capecitabine (101)	50	Progression after CNS RT and through lapatinib monotherapy required	20%	3.6 mo
Lapatinib + capecitabine (103)	138	Heavily pre-treated	18%	NR
Lapatinib + capecitabine (121)	45	No prior CNS radiotherapy allowed	66%	5.5 mo
Lapatinib + temozolomide (122)	17	Heavily pre-treated	0%	2.6 mo

CNS, central nervous system; ORR, objective response rate; TTP, time to progression; PFS, progression-free survival.

In contrast to prior trials, which largely evaluated patients whose CNS disease had progressed through radiotherapy, LANDSCPAE evaluated 45 patients with previously untreated, HER2-positive breast cancer brain metastases. In this study, the CNS objective response rate (defined as at least 50% decrease in sum volume of CNS target lesions by central radiology review) was 65.9% (95% CI, 50.1 –79.5). In a secondary analysis, investigator-assessed CNS response rate by RECIST was reported as 57%. Median TTP was 5.5 months and median time to salvage radiotherapy was 8.3 months. Results of this study have prompted ongoing efforts to design a confirmatory phase 3 trial. In the meantime, the data add to the evidence of CNS activity of this regimen in patients with established metastases. However, it is not clear at this time whether lapatinib plus capecitabine could be used as primary or secondary prevention of brain metastases. Indeed, the CEREBEL trial, which compared lapatinib plus capecitabine versus trastuzumab plus capecitabine and was designed to compare the occurrence of new CNS metastases, did not meet its primary endpoint largely due to an insufficient number of CNS events in both arms (106). One notable result of the study was that patients were required to have CNS screening scans at baseline and 20% of potentially eligible patients were excluded on the basis of the detection of asymptomatic brain metastases, again underscoring the high prevalence of CNS involvement among HER2-positive patients. Notably, a number of other HER2 inhibitors, including neratinib, afatinib, and ARRY-380 are currently being evaluated for the treatment of HER2-positive brain metastases, and results are eagerly awaited.

Angiogenesis inhibitors represent another promising area for investigation. In preclinical models, treatment with anti-angiogenesis inhibitors leads to tumor regressions and improved survival in HER2 positive breast cancer (107). In the past, out of concern for intracranial hemorrhage, patients with brain metastases were excluded from nearly all trials of angiogenesis inhibitors. However, recent data support the general safety of this drug class in patients with brain metastases from solid tumors (108). At least two clinical trials (NCT01004172 and NCT01281696) combining bevacizumab with a platinum salt have been completed, and preliminary evidence of clinical activity has been observed (109).

We sense an increasing willingness to evaluate investigational agents earlier in their development cycle for the treatment of breast cancer brain metastases, and to include patients with active brain metastases in phase I and II clinical trials. Other targeted agents of potential interest in this patient population include PI3K inhibitors, mTOR inhibitors, PARP inhibitors, and cell cycle inhibitors. For example, everolimus, an orally bioavailable rapamycin analog that inhibits mTOR signaling, has clear systemic activity in ER-positive breast cancer and is being evaluated in the phase III setting in HER2-positive breast cancer. Notably, everolimus has demonstrated efficacy against subependymal giant cell astrocytoma, a rare brain tumor, suggesting its potential role in the treatment of CNS disease in breast cancer. A phase II clinical trial evaluating everolimus for breast cancer brain metastases is ongoing (NCT01305941). Anecdotal reports of CNS activity have also been reported in the phase I studies of several PI3K inhibitors, both in triple-negative and HER2-positive breast cancer patients; further exploration of the potential role of this class of agents is, thus, of considerable interest (110,111).

Radiosensitizers

Another approach to maximize the efficacy of radiation is the use of systemic agents as radiosensitizers (Table 76-2). In order to investigate the combination of anti-angiogenic therapies with radiotherapy, the RTOG conducted a phase III study of WBRT with or without thalidomide for patients with brain metastases from solid tumors. The study was closed early after an interim analysis indicated a very low likelihood of demonstrating a survival advantage in the experimental arm (112). Mehta and colleagues randomly assigned 401 patients (75 with breast cancer) to WBRT (3000 cGy) with or without motexafin gadolinium (MGd), a redox active drug that is thought to generate reactive oxygen species via futile redox cycling (113). No difference in overall survival or time to neurologic progression was noted in the overall study population. Finally, Suh and colleagues conducted two phase III trials utilizing efaproxiral (RSR13), an allosteric modifier of hemoglobin (114). Although there was a suggestion of benefit in a subset analysis of breast cancer patients enrolled in the first trial, the subsequent confirmatory trial (ENRICH) was negative.

Other agents under investigation include temozolomide, lapatinib, and the PARP inhibitor ABT-888. In two randomized phase II studies in solid tumor patients, the addition of temozolomide was associated with improvements in PFS but not overall survival (115,116). Studies limited to breast cancer patients have not been reported. A phase I study of WBRT with lapatinib in patients with HER2-positive breast cancer reported that, at the MTD of 1250 mg bid, 20 of 24 patients achieved a CNS objective response by 1 month following completion of WBRT (117). Dose limiting toxicities were found in 5 of 24 patients treated at the MTD, however, exceeding the predefined criteria for declaring feasibility. The regimen is currently being carried forward in a randomized phase II study being jointly conducted between Korean investigators and the RTOG.

In terms of PARP inhibitors, many of the investigational PARP inhibitors appear to cross the blood-brain barrier. Although the precise role of PARP inhibition in breast cancer remains to be fully defined, given the high incidence of brain metastases in patients with triple-negative breast cancer and in *BRCA1* mutation carriers, further exploration of the potential CNS activity of PARP inhibitors is warranted. In order to speed the development of potential radiosensitizers, the RTOG is developing a concept to test multiple potential radiosensitizers based on their preclinical rationale in a randomized phase II design that would involve rotating in and out various experimental arms over time, versus a control arm of WBRT alone.

CONCLUSIONS AND FUTURE DIRECTIONS

Brain metastases may lead to significant morbidity in patients with advanced cancer, and is a particularly feared site of recurrence by patients. HER2-positive and triple-negative tumors appear to be especially likely to spread to the CNS. Advances in surgery and radiotherapy have reduced treatment-related morbidity and allow for treatment of lesions that may not have previously been considered amenable to treatment. However, as patients live longer with metastatic breast cancer, it is likely that an increasing number of patients will develop CNS progression after standard first-line therapies. Thus, the optimal management of patients will increasingly require close, multidisciplinary collaborations. Furthermore, there is a greater need than ever to evaluate novel approaches to CNS metastases in the context of well-designed clinical trials.

MANAGEMENT SUMMARY

- In a breast cancer patient with signs or symptoms of brain metastases, a prompt contrast-enhanced MRI is indicated.
- Twenty percent of patients with brain metastases develop venous thromboembolic (VTE) disease. In patients with clinically significant VTE disease, anticoagulation is indicated.
- Initial treatment of brain metastases is influenced by lesion number, location, and size, and by the status of a patient's systemic disease.
- Supportive therapy includes corticosteroids for patients with symptomatic edema, and anticonvulsants for patients with a history of seizures. In patients without a seizure history, the routine use of prophylactic anticonvulsants is not recommended.
- In patients with single or solitary brain lesions, good performance status, and stable extracranial disease, surgical resection or stereotactic radiosurgery (SRS) is recommended. Surgery is preferred for lesions with symptomatic mass effect, larger lesions, diagnostic purposes, and when the risk of operative morbidity is acceptably low. Whole brain radiotherapy (WBRT) after local therapy reduces the risk of intracranial recurrence but does not appear to affect overall survival.
- For patients with a limited (2–4) number of lesions, good performance status, and favorable extracranial disease status, consideration should be given to aggressive intracranial therapy, with either WBRT followed by SRS, or SRS alone. Initial WBRT reduces the risk of subsequent intracranial recurrence and improves local tumor control in the brain but does not appear to prolong survival. The potential long-term neurotoxicities associated with WBRT must be weighed against the cognitive impairment associated with progressive disease in the CNS. Consideration should also be given to participation in a clinical trial evaluating the use of radiosensitizers or radioprotectants given in conjunction with WBRT.
- For patients with suboptimal control of extracranial disease, poor performance status, and short expected survival, therapy should be directed toward optimal palliation and consideration of hospice referral.
- For patients with recurrent or new CNS lesions after WBRT, the standard-of-care is not well-defined. Because of the complexity of potential options, including SRS, surgical resection, systemic therapy, and/or WBRT retreatment, multidisciplinary management is appropriate, particularly in patients with favorable extracranial disease status. Consideration should also be given to participation in the increasing number of clinical trials targeted to this patient population.

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CHAPTER 77

Metastatic Epidural Spinal Cord Compression

Soma Sengupta, Michael W. Groff, Nils D. Arvold, and Patrick Y. Wen

CHAPTER CONTENTS

INTRODUCTION

Epidural spinal cord compression (ESCC), resulting from tumor growth in the spinal epidural space, is an important neurological emergency that can occur in patients with breast cancer. The incidence may be increasing as a result of earlier detection and improved systemic therapy (1). Since the prognosis for good functional outcome is primarily dependent on the degree of impairment at the commencement of treatment, clinicians who care for patients with breast cancer must remain vigilant about the possible presence of ESCC. More than 91% of patients with ESCC have symptoms for longer than 1 week before a diagnosis is made (2), with pain lasting for a mean duration of 6 weeks (3). Compromise of the conus medullaris and cauda equina by epidural metastasis is generally included in a discussion of ESCC because the natural history and management of these problems are similar to those of compression of the spinal cord itself. ESCC is discussed in more detail in several recent reviews (1,4,5)

INCIDENCE

The incidence of ESCC in patients with breast cancer is approximately 4% (2). There are approximately 12,700 cases of ESCC in patients with cancer diagnosed each year in the United States (1,6). The median time from the diagnosis of breast cancer to the onset of ESCC is 42 months, with a range of 0 to 28 years (2). ESCC usually occurs in the setting of widely metastatic disease, although rarely ESCC may be the initial presentation of cancer. In some instances, biopsy of an epidural metastasis is required to establish the diagnosis of cancer.

PATHOLOGY

Epidural metastases most commonly result from hematogenous spread of metastases to the vertebral column (85%). They arise less commonly from metastases to the paravertebral space (5% to 10%) that either secondarily invade bone and then grow into the epidural space or invade the epidural space directly through the intervertebral foramen (Fig. 77-1). In rare instances, direct hematogenous spread to the epidural space or parenchyma of the spinal cord occurs (1,4), but this presentation is more likely with lymphoma than with breast cancer. If ESCC develops as the first manifestation of cancer, the absence of bony or skeletal metastases makes breast cancer an unlikely diagnosis. The vertebral column is the most common site of metastases to bone (7). Vertebral metastases occur in up to 84% in patients with advanced breast cancer (4). This high incidence is related to the fact that cancers of the breast and pelvis are in communication with Batson's vertebral plexus (8,9), a low-pressure valveless venous system that fills when thoracoabdominal pressure is raised (e.g., by maneuvers such as coughing, straining, and lifting). The presence of growth factors in bone marrow may also be a contributing factor (9). Of patients with breast cancer and ESCC, 93%

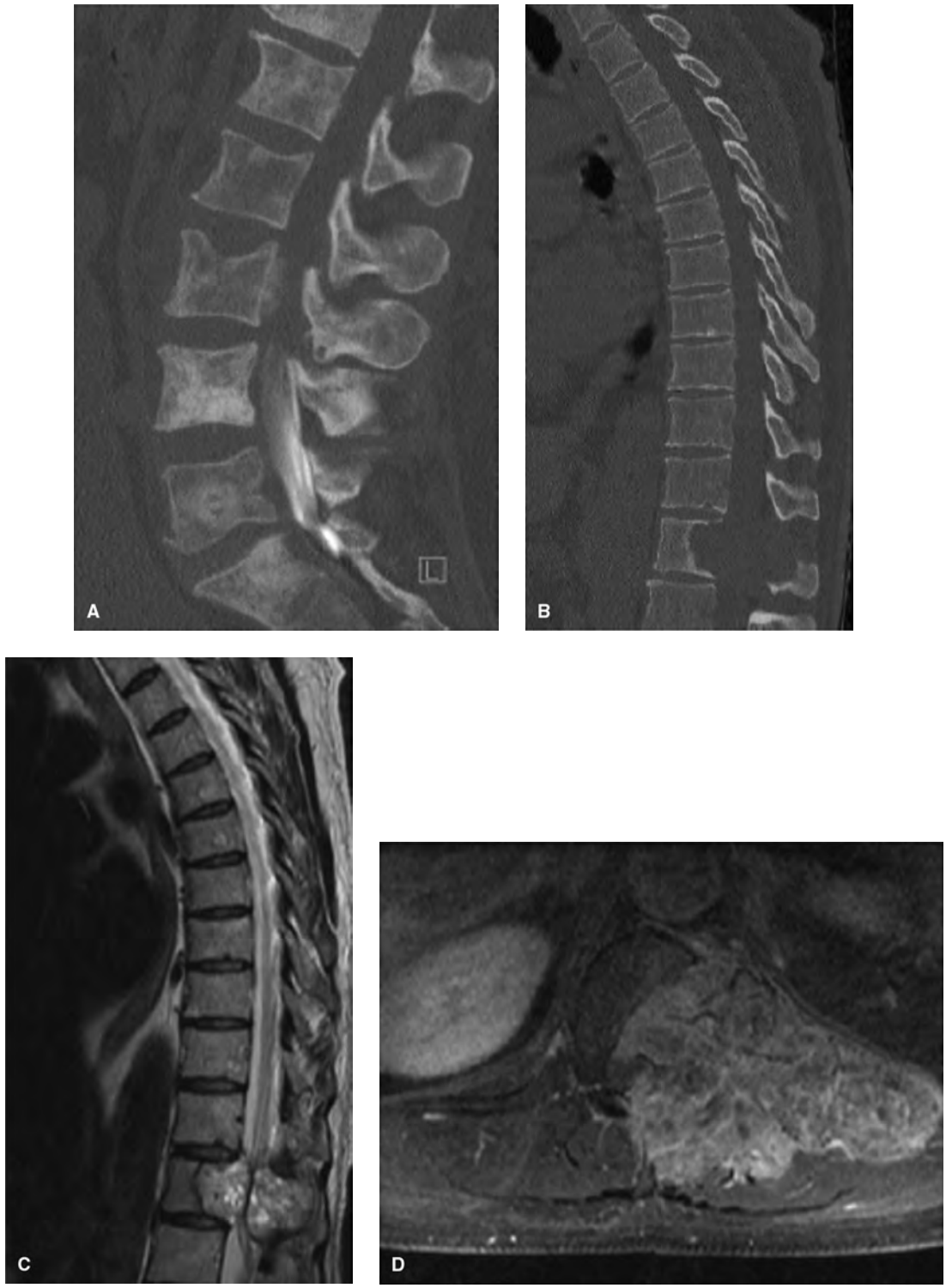

FIGURE 77-1 **(A)** Sagittal postmyelogram CT demonstrating a complete block due to epidural compression from a breast metastasis. The block, located at the L3/4 disc space demonstrates the lower extent of the mass. This was predominantly an epidural mass which occurs in a small minority of cases. **(B)** Sagittal CT scan demonstrating lytic destruction of the T12 vertebral body due to a breast metastasis. Despite the extensive destruction there is no collapse of the vertebral body or kyphosis of the spinal canal. Destruction of the posterior elements is also seen. **(C)** T2-weighted sagittal MRI demonstrating the T12 breast metastasis and the severe spinal cord compression. The spinal fluid appears white on this sequence. The tapering of the spinal fluid on the sagittal image in the region of the mass is characteristic of compression from an extradural mass. **(D)** T2-weighted axial MRI demonstrating the T12 breast metastasis and the severe spinal cord compression. The axial image demonstrates significant paraspinal extension as well.

have known bone metastases at the onset of their neurologic deficit, with a median time from the first bone metastasis to ESCC of 11 months (range, 0 to 7.5 years). Breast cancer is commonly associated with multilevel vertebral metastases, and epidural tumor is multifocal in up to 29% of patients (10). As would be anticipated from their origin in the vertebral bodies, most epidural metastases are situated anterior or anterolateral to the spinal cord (1,5), which has important implications for their surgical management. Sixty or 70 percent of epidural metastases arise in the thoracic spine, 16% to 22% in the lumbosacral spine, and 8% to 15% in the cervical spine (11). These figures are proportional to the volume of bone in each of these spinal regions (12).

Spinal cord damage in ESCC is due primarily to direct compression of the spinal cord by tumor and rarely to compression of radicular arteries that pass through the intervertebral foramen (4). Axonal swelling and white matter edema occur early in animal models of ESCC, whereas gray matter damage occur later (13). Prolonged cord compression results in necrosis of both gray and white matter. Early spinal cord damage is likely caused by venous stasis, whereas arteriolar compression by tumor is probably responsible for the late stage of tissue necrosis (13).

CLINICAL PRESENTATION

ESCC due to breast cancer occurs most commonly in the thoracic spine (9,10,25). The principal symptom of ESCC is pain (14) (Table 77-1). It is the initial symptom in 85% to 96% of patients and precedes other symptoms by a mean of 6 weeks (2,15). Pain is of three types: local, radicular, and referred. Local back pain is usually a constant ache and occurs in almost all patients. Radicular pain is caused by involvement of nerve roots by the tumor mass and is typically described as a shooting pain. It is more common with cervical and lumbosacral lesions than with thoracic lesions (16). With cervical or lumbosacral epidural metastases, radicular pain is typically unilateral. With thoracic disease, however, radicular pain is commonly bilateral, producing a band-like pain or tightness that may be felt more at the lateral or anterior chest wall than in the back itself. Referred pain occurs at a distant site from the lesion and does not radiate. For example, T12-L1 vertebral lesions may be referred to both iliac crests or both sacroiliac joints, whereas C7-T1 lesions may be referred to the interscapular region or to both shoulders (17). The pain of epidural metastasis is often worsened by lying supine, possibly because of filling of vertebral veins in this position. Patients typically report that they are unable to sleep lying down and need to sleep sitting up; this information is often not volunteered by patients but must be sought by direct questioning. The pain tends to be most prominent at night and into the morning, with resolution or improvement over the course of the day (18). The Valsalva maneuver (coughing, sneezing, or straining at stool) exacerbates the pain of epidural metastases, as it fills vertebral veins and raises intracranial pressure, which is then transmitted to the already compromised spinal canal. Pain is also worsened by stretching maneuvers, such as neck flexion in the case of cervical or upper thoracic tumors and straight-leg raising with lumbosacral or thoracic lesions. Escalating back pain in patients with cancer is a particularly ominous indicator of the possibility of ESCC. Tenderness may be present over the vertebral column at the site of the lesion, and there may be referred tenderness at the site of referred or radicular pain. Pain that worsens substantially with movement of the neck or back may be a sign of mechanical instability of the spinal column, which can occur in the setting of vertebral or epidural metastases (18).

The spinal cord usually ends at the level of L1. Therefore, ESCC above L1 will produce a myelopathy, whereas lesions below this level result in a cauda equina syndrome. Myelopathic symptoms include limb weakness in a pyramidal distribution, numbness and paresthesia, and sphincter disturbance (urinary retention, urinary urgency, constipation, or fecal urgency). At the time of diagnosis, 76% of patients complain of weakness, 87% are weak on examination, 57% have autonomic dysfunction, 51% have sensory symptoms, and 78% have sensory deficits on examination (16). In many series, fewer than 50% of patients are ambulatory at diagnosis, and up to 25% are paraplegic (2,3,16); these figures are

TABLE 77-1

Symptoms Associated with Epidural Spinal Cord Compression

Symptom	*Frequency*	*Location*
Back pain	95%	• Localized pain confined to the area with the metastases that progressively increases over time. • Radicular pain due to invasion of the nerve roots, unilateral in the cervical and lumbosacral areas, bilateral in the thoracic region. Pain is worse with Valsalva and at night. • Mechanical back pain due to pathological fractures, pain is exacerbated by any movement.
Weakness	35%–75%	• Upper motor neuron weakness—symmetric. • Lower motor neuron weakness predominantly distal extremities affected and can be unilateral.
Inability to walk	50%–68%	• Tied in with weakness but can also be linked with ataxia due to sensory problems.
Sensory deficits	50%–70%	• Pain, numbness, ataxia.
Autonomic disturbance	50%–60%	• Bowel or bladder disturbance. • High cervical cord metastases can cause respiratory problems.

Adapted from the data reviewed in Cole JS, Patchell RA. Metastatic epidural spinal cord compression. *Lancet Neurol* 2008;7(5):459–466, describing the frequency of symptoms associated with ESCC.

significant because prognosis is related to clinical deficit at presentation. Outcomes might be improved if patients were encouraged to seek treatment earlier.

Signs of a myelopathy include paraparesis or quadriparesis, increased tone, clonus, hyperreflexia, extensor-plantar responses, a distended bladder, or a sensory level. A patch of hyperesthesia may be present at the upper aspect of the sensory level. The sensory, motor, and reflex levels are only an approximate indication of the site of pathology; because sensory fibers retain their somatotopic organization as they ascend in the cord, the actual site of cord compression may be several segments above the apparent sensory level. Furthermore, there may be multiple sites of epidural disease. The entire spinal cord should, therefore, be imaged in all patients with myelopathy.

The myelopathy may be incomplete, and it is a serious error to dismiss the possibility of ESCC on the basis that any particular sign is absent. Neither a sensory level nor an extensor plantar response is necessary to make the clinical diagnosis of ESCC. Dorsal column sensation (vibration and proprioception) and spinothalamic sensation (pain and temperature) must be assessed independently in all patients with cancer and back pain. Because the subjective appreciation of light touch involves both sensory pathways, light-touch sensation may be reasonably well preserved, even in the presence of a clear cut sensory level for pain or vibration sense when these are tested separately. A hemicord or Brown-Séquard's syndrome (characterized by ipsilateral weakness and proprioception loss, and contralateral loss of pain and temperature) may occur, although this is rare in ESCC (10,16). In an oncologic population, Brown-Séquard's syndrome is more typical of intramedullary cord metastasis or radiation myelopathy (19). Involvement of spinocerebellar tracts in the spinal cord can lead to lower extremity ataxia out of proportion to the degree of weakness. Dorsal column involvement can lead to a sensory ataxia with positive rombergism while sparing power and reflexes. Both of these clinical presentations may focus the attention of the unwary examiner on the cerebellum, thereby delaying diagnosis (20). Patients may also present with herpes zoster, presumably as a result of reactivation of latent virus by compression of the dorsal root ganglion by tumor (16).

ESCC at the conus medullaris and cauda equina produces different neurologic symptoms and signs, although pain is still a prominent feature, particularly with cauda equina lesions. Conus lesions typically present with early and marked sphincter disturbance and perineal sensory loss. Anal sphincter tone may be lax, and there may be an absent anal wink. Cauda equina lesions produce patchy lower motor neuron signs related to the lumbar and sacral nerve roots—hyporeflexia or areflexia, myotomal leg weakness, and dermatomal sensory loss; sphincter disturbance tends to occur late and to be less marked than in conus lesions. When the signs include a mixture of upper and lower motor neuron features or dermatomal sensory loss as well as a sensory level, the possibility of coexistent nerve root involvement and cord compression should be considered.

INVESTIGATIONS

Epidural spinal cord compression is a medical emergency requiring expeditious investigation of all patients in whom this diagnosis is suspected. Magnetic resonance imaging (MRI) is the test of choice, although rarely other modalities may be useful.

Plain X-Rays: From 94% to 98% of patients with epidural disease will have visible vertebral metastases on plain spine films (10,21,22,23). However, these are now rarely performed given the widespread availability of MRI.

Radionuclide Bone Scan: Bone scintigraphy is more sensitive than plain radiography in the detection of epidural metastasis (24). Spinal metastases as small as 2 mm can be detected and will pick up bone metastasis 3 to 18 months before x-rays. However, it is poor in delineating the anatomy, and in cancers causing osteolytic lesions, it is less useful (23).

Positron Emission Tomography (PET)/CT: PET/CT is used to stage cancer, and is largely more sensitive and specific in detecting metastases relative to a bone scan (25).

Computed Tomographic (CT) Scanning: CT remains one of the best techniques in assessing the anatomy of the actual vertebral body prior to surgical stabilization (Fig. 77-1A, B). Its sensitivity is limited to about 66% and diagnostic accuracy to approximately 89% in detecting areas of vertebral destruction, assessment of extent of paravertebral soft-tissue extension and impingement of the actual spinal cord (26). If there is a contraindication to use MRI (pacemaker, noncompatible MR implants), CT myelography may still be employed to delineate the level of the block (27) (Fig. 77-1A).

Magnetic Resonance Imaging (MRI): Contrasted MRI is the gold standard investigation in detecting ESCC. MRI has a sensitivity of 98.5% and a specificity 98.9% with an overall accuracy of 98.7% (26) (Fig. 77-1C, D). If ESCC is suspected, the entire spine should be imaged since multifocal disease occurs frequently (28). MRI influences radiotherapy fields and in one study led to simulation alterations in 53% of patients, with 21% being major changes (28).

An unenhanced MRI scan can establish the diagnosis of ESCC. However, a contrast-enhanced scan should also be obtained to look for leptomeningeal metastasis, which may mimic the presentation of ESCC. The entire spine should be imaged, as epidural disease may be present at multiple levels, and the spinal level indicated by clinical examination may be several segments below the level of the lesion (29). It is important to obtain axial scans in addition to sagittal images. A "screening" midline sagittal scan is inadequate; multiple sagittal scans using thin slices should be performed. Coronal images of the spine are not required routinely. Adequate analgesia (including corticosteroids) should be administered before the MRI is performed because the patient must lie motionless for the scan, and lying flat may worsen the back pain. If the patient cannot tolerate the full procedure, or if there is not enough time to perform an MRI of the entire spine, the area of interest should be imaged first, followed at a later time by imaging of the remainder of the spine. When ordering radiologic investigations, a clear distinction should be made between the suspected neurologic level of involvement and the suspected vertebral level; the discrepancy between these is greatest at the inferior end of the spinal cord. Because the spinal cord terminates at the first lumbar vertebra, all of the lumbar segments and some of the sacral segments of the cord are usually situated within the thoracic spine.

EVALUATION OF INDIVIDUAL CONDITIONS

Isolated Back Pain

In patients with breast cancer and isolated back pain without neurologic abnormalities, plain spine radiographs are occasionally the appropriate first line of investigation. Definitive

imaging of the epidural space should be performed if plain films are abnormal. In patients with a clinical picture that is strongly suggestive of epidural metastasis (e.g., back pain that is significantly exacerbated by lying flat and worsened by the Valsalva maneuver), MRI of the spine with contrast should be performed. In patients with local back pain with characteristics that are not strongly suggestive of epidural metastasis, definitive imaging of the epidural space is not indicated if a plain radiograph is normal.

Radiculopathy

Radiculopathy is associated with a high incidence of epidural metastases. In one series of patients with cancer and back pain, 27 of 43 (63%) patients with radiculopathy and without signs of spinal cord involvement were found to have epidural metastases, compared with 27 of 61 (44%) patients with local back pain alone (27). When plain radiographs were abnormal, epidural metastases were found in 20 of 22 (91%) patients with radiculopathy. Similarly, in patients with abnormal findings on plain radiographs, Graus et al. found epidural metastases in 47 of 67 (70%) patients with radiculopathy, compared with 12 of 35 (34%) patients with local back pain alone (30). Importantly, in the series by Graus et al. (30) and Rodichok et al. (27), epidural metastases were found in 9% to 33% of patients with radiculopathy and normal findings on plain radiographs.

Given the high incidence of epidural metastases in breast cancer patients with radiculopathy, it is reasonable to proceed straight to MRI in all patients. It is important to remember that in the thoracic spine, which is the most common site of ESCC in breast cancer, radiculopathy commonly presents as bilateral, band-like dermatomal pain and that, in some situations, lateral or even anterior chest pain may be more prominent than back pain.

Plexopathy

The possibility of epidural metastasis must be considered in patients with breast cancer and a malignant brachial plexopathy because tumor may infiltrate directly along the plexus to the epidural space. Brachial plexus lesions present with pain (usually in the shoulder girdle with radiation to the elbow, medial side of the forearm, and medial two digits) as well as weakness and sensory symptoms in a segmental distribution. Clinical clues to the presence of epidural metastases in the setting of brachial plexopathy include a panplexopathy (as compared to the more usual lower plexopathy with involvement of C7, C8, and T1 nerve roots) and the presence of Horner's syndrome (indicating more proximal involvement). The presence of back pain also suggests that the tumor has grown proximally, but back pain may be absent with epidural extension. Patients with brachial plexopathy require imaging of the brachial plexus with CT or MRI and, if vertebral body collapse or erosion is present, at the C7-T1 levels. If a paraspinal mass is seen definitive imaging of the epidural space should be performed. If MRI is used to image the brachial plexus, the cervical and upper thoracic spine can be imaged at the same time.

Myelopathy, Conus Medullaris, and Cauda Equina Syndromes

Definitive imaging of the epidural space with MRI is required in patients with myelopathy, conus medullaris or cauda equine syndromes. If MRI is not readily available or cannot be performed (e.g., in patients with pacemakers or the occasional patient with severe claustrophobia), CT myelography should be performed.

An unenhanced MRI scan can establish the diagnosis of ESCC. However, a contrast-enhanced scan should also be obtained to look for leptomeningeal metastasis, which may mimic the presentation of ESCC. The entire spine should be imaged, as epidural disease may be present at multiple levels, and the spinal level indicated by clinical examination may be several segments below the level of the lesion. It is important to obtain axial scans in addition to sagittal images. A "screening" midline sagittal scan is inadequate; multiple sagittal scans using thin slices should be performed. Coronal images of the spine are not required routinely. Adequate analgesia (including corticosteroids) should be administered before the MRI is performed because the patient must lie motionless for the scan, and lying flat may worsen the back pain. If the patient cannot tolerate the full procedure, or if there is not enough time to perform an MRI of the entire spine, the area of interest should be imaged first, followed at a later time by imaging of the remainder of the spine. When ordering radiologic investigations, a clear distinction should be made between the suspected neurologic level of involvement and the suspected vertebral level; the discrepancy between these is greatest at the inferior end of the spinal cord. Because the spinal cord terminates at the first lumbar vertebra, all of the lumbar segments and some of the sacral segments of the cord are usually situated within the thoracic spine.

Summary

Isolated Back Pain: Definitive imaging of the epidural space should be performed if plain films are abnormal. If the patients have a clinical picture consistent with ESCC, then an MRI of the spine with contrast should be performed.

Radiculopathy: Given the high incidence of epidural metastases in breast cancer patients with radiculopathy, an MRI spine is recommended.

Plexopathy: Patients with brachial plexopathy require imaging of the brachial plexus with CT or MRI. Note that if MRI is used to image the brachial plexus, the cervical and upper thoracic spine can be imaged at the same time.

Myelopathy: Imaging of the epidural space with MRI is critical if a patient has myelopathy. If an MRI is contraindicated, then a CT myelogram should be performed.

MANAGEMENT

A multidisciplinary approach is needed to manage ESCC. Improvements in systemic therapy, surgery, and radiation have improved survival. Apart from the standard pain scales and performance status assessments, specific scales assessing neurological impairment for spinal cord issues (American Spinal Injury Association and Frankel Score) may be helpful, and these are discussed in more detail in the scoring systems section (15,31).

Pain Control

Nonsteroidal anti-inflammatory agents, narcotic analgesics, and medications for neuropathic pain such as gabapentin are the mainstay of pain control (32).

Corticosteroids

Corticosteroids, usually in the form of dexamethasone, are routinely used in the management of MESCC because they reduce pain and sometimes stabilize or improve neurologic deficits by reducing vasogenic edema (4).

One early study demonstrated that a bolus dose of 100-mg dexamethasone intravenously, followed by a tapering schedule starting with 96 mg a day in four divided doses for 3 days, had a significant and rapid effect on the pain associated with ESCC (33). In a more recent study, no difference in pain, ambulation, or bladder function was seen in 37 patients with ESCC who received either a 10- or a 100-mg bolus of dexamethasone intravenously (34). A randomized controlled trial in 1994, however, showed that in 57 patients with ESCC who proceeded to radiation therapy, high-dose dexamethasone significantly increased the proportion of patients who remained ambulatory after treatment (35).

In general, a bolus dose of 100 mg of dexamethasone is recommended for patients with suspected ESCC who present with significant deficits, followed by a maintenance dose of 24 mg every 6 hours. Steroids may then be tapered over 2 to 3 weeks while the patient receives definitive therapy. The dose may be halved approximately every 3 days if clinically appropriate. In patients who have persistent or worsening pain, steroids may need to be increased or tapered gradually. Patients with minimal deficits can probably be safely treated with a 10-mg bolus of dexamethasone, followed by an initial maintenance dose of 8 to 16 mg daily. The bolus dose of steroids should be given once the clinical diagnosis is made and before an MRI is performed. If MRI demonstrates cord compression (or if myelography shows a block of more than 80%), the high-dose regimen may be used, whereas the low-dose regimen is used for patients with epidural disease without cord compression. Oral and intravenous administration of dexamethasone are equivalent; however, systemic availability is delayed by approximately 30 minutes when given orally. Intravenous dexamethasone is recommended for the initial bolus to provide analgesia quickly, but unless the patient has gastrointestinal dysfunction, oral dexamethasone is generally appropriate. Prolonged use of high-dose dexamethasone is associated with more side effects than low-dose dexamethasone, but for short-term use, the toxicity of the doses is similar. *Pneumocystis jiroveci* prophylaxis is recommended with trimethoprim-sulfamethoxazole, one double-strength tablet once or twice a day, 3 days a week. In addition, H_2 blockers or proton pump inhibitors should be considered to reduce the risk of peptic ulceration during corticosteroid therapy.

Supportive Care

Patients with myelopathy resulting from ESCC require close attention to analgesia, bowel and bladder care, and the prevention of pressure sores. Prophylaxis against venous thromboembolism should always be considered in bedbound patients.

Hormonal Therapy

The incidence of vertebral metastases and ESCC from breast cancer can be reduced by hormonal therapy, but it is not a treatment for ESCC (36). Bisphosphonates such as zoledronate, which induce apoptosis in osteoclasts and inhibit osteoclast-mediated bone resorption (37), and denosumab, a monoclonal antibody targeting the RANK ligand which acts as the primary signal to promote bone removal, can help decrease the incidence of vertebral metastases and ESCC (38).

Scoring Systems

Several systems have been developed to help guide decisions between surgery or radiation therapy (RT) (1). Harrington (39) classified lesions on structural integrity and neurologic dysfunction, and since then there have been many scoring systems described as reviewed in Bhatt et al. (1). Rades et al. (40) described a scoring system for breast cancer involving 510 patients, half assigned to either the test or the validation group, and stratified by eight pretreatment factors (age, performance status, number of involved vertebrae, ambulatory status, other bone metastases, visceral metastases, interval from cancer diagnosis to radiation therapy of ESCC, time of developing motor deficits) plus the radiation regimen were retrospectively investigated. Factors significantly associated with survival in the multivariate analysis were included in the scoring system. This score was found to be reproducible in selecting patients for the radiation therapy group. Bilsky and Smith (18) proposed the NOMS system which considers neurologic factors (N), oncologic factors (O), mechanical instability (M), and systemic disease including comorbidities (S) in guiding treatment decisions regarding surgery versus radiotherapy which many clinicians have adopted, although it remains to be validated prospectively (Table 77-2). The National Comprehensive Cancer Network (NCCN) (41) has proposed guidelines to guide management (see Fig. 77-2). In general, patients with a prognosis of more than 3 to 6 months may benefit from surgery, while patients with a poor prognosis may be better treated with a nonsurgical palliative approach (1).

Surgery

Although the standard management of ESCC is radiation therapy with or without surgery, in reality, less than 10% of patients with ESCC undergo surgery (42). Goals of surgery in ESCC include decompression of neural structures (75% neurologic improvement); pain relief (80% to 95% improvement); debulking or removal of tumor mass; and spinal stabilization to prevent deformity and allow mobilization (reviewed in reference 1) (Fig. 77-3). Indications for surgery include the following (1):

- Progressive neurologic deficit before, during, or after radiation therapy
- Intractable pain unresponsive to conservative treatment
- Need for histologic diagnosis
- Radio-resistant tumor histology (i.e., renal cell carcinoma, melanoma)
- Spinal instability (i.e., vertebral collapse)

Recently the Spinal Instability Neoplastic Score (SINS) has been proposed by the Spine Oncology Study Group (SOSG) to identify the patients who require surgical stabilization. Spine instability is assessed by adding scores related to six factors including location of the tumor within the spine, pain, lesion bone quality, radiographic alignment, vertebral body collapse, and posterolateral involvement of the spinal elements (43,44). SINS scores range from 0 to 18. A score of 0–6 indicates stability, 7–12 indicates indeterminate instability, and 13–18 is indicative of instability. Any patient with a score greater than 7 should have a surgical consultation (43). The SINS has been shown to have a sensitivity of 95.7% and a specificity of 79.5% in identifying potentially unstable or unstable lesions (44). Decompressive laminectomies have been largely superseded by surgical approaches that have access to the anterior column for decompression and stabilization, since the vertebral body is affected in 70% of spine metastases (5). Embolization or vertebral body biopsy procedures are not often utilized in management of patients with breast cancer and rather are reserved for management of vascular lesions and unknown primary metastatic lesions respectively.

TABLE 77-2

Simplified Approach to Treatment of Epidural Spinal Cord Compression

ESCC	*Symptoms*	*Treatment*
Spine unstable or high-grade ESCC	Myelopathy or symptoms from single ESCC site	Surgery → conventional EBRT
Spine stable	Minimal or stable myelopathy	Conventional EBRT alone *or* surgery followed by conventional EBRT if very radioresistant tumor (e.g., melanoma)

This table lays out a simplified approach to NOMS. Several scoring systems have been developed to help guide decisions between surgery or radiation therapy. However, the exception is if surgery is warranted but the patient with metastatic breast cancer cannot tolerate it, then the patient goes on to EBRT directly.
Adapted from Bilsky M, Smith M. Surgical approach to epidural spinal cord compression. *Hematol Oncol Clin North Am* 2006;20:1307–1317.

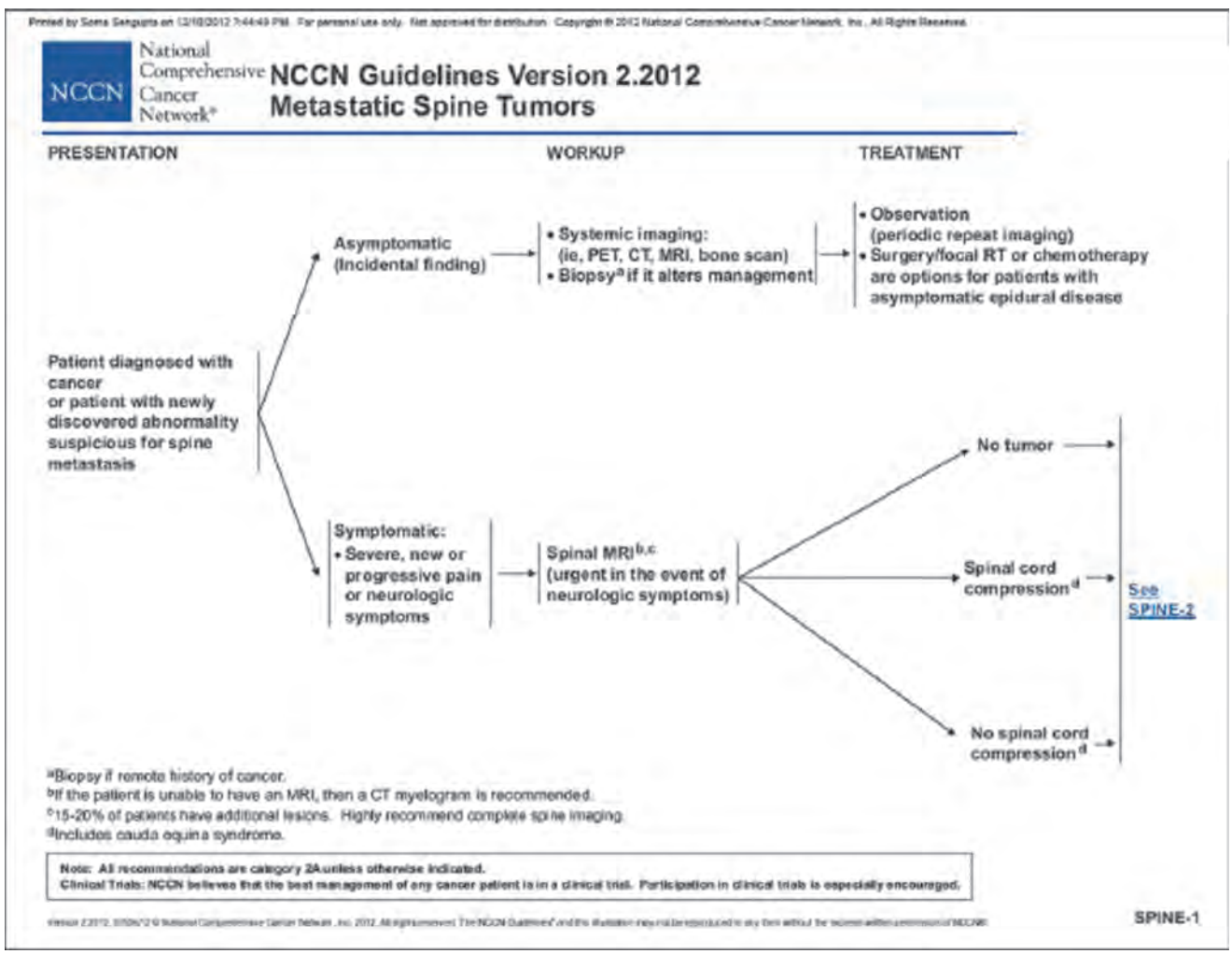

FIGURE 77-2 Three panels comprising the current NCCN guidelines Version 2.2012, Metastatic Spine Tumors. (Reproduced/Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Guideline Name V.X.201X. © 2012 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of the NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, NCCN GUIDELINES®, and all other NCCN Content are trademarks owned by the National Comprehensive Cancer Network, Inc.)

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NCCN Guidelines Version 2.2012
Metastatic Spine Tumors

PRESENTATION	TREATMENT	ADJUVANT TREATMENT
No tumor	Evaluate for other causes of pain and/or neurologic symptoms[g]	
Spinal cord compression[d] → Steroids[e]	Surgery[h,i,j] followed by RT (preferred) or Primary RT[k] or In the absence of clinical myelopathy, primary chemotherapy[l] if chemosensitive tumor (eg, lymphoma, germ cell tumor, myeloma)	
No spinal cord compression[d] → Fracture or spinal instability[f]	Surgical stabilization or Vertebral augmentation[m]	Followed by RT[k]
No spinal cord compression[d] → No fracture or spinal instability	RT[k] (preferred) or Chemotherapy[l] (if chemosensitive tumor) or Surgery[j] (selective cases) followed by RT	Consider surgery[j] or stereotactic radiotherapy[k] if: • Deterioration during RT • Intractable pain • Tumor progression

[d]Includes cauda equina syndrome.
[e]The recommended minimum dose of steroids is 4 mg of dexamethasone every 6 hours, although dose of steroids may vary (10-100 mg). A randomized trial supported the use of high-dose steroids (Sorensen PS, et al. Eur J Cancer 1994;30A:22-27).
[f]Spinal instability is grossly defined as the presence of significant kyphosis or subluxation (deformity), or of significantly retropulsed bone fragment.
[g]Consider alternative diagnosis of leptomeningeal disease (See LEPT-1).
[h]Tumor resection with or without spinal stabilization. Surgery should be focused on anatomic pathology.
[i]Regarding surgery, note the following:
- Category 1 evidence supports the role of surgery in patients with epidural spinal cord compression willing to undergo surgery. (Patchell RA, et al. Lancet 2005;366(9486):643-648)
- For surgery, patients with hematologic tumors (lymphoma, myeloma, leukemia) should be excluded, life expectancy should be ≥ 3 mo, and the patient should not be paraplegic for > 24 h.
- Surgery is especially indicated if the patient has any of the following: spinal instability, no history of cancer, rapid neurologic deterioration during RT, previous RT to site, and single site spinal cord compression.

[j]See Principles of Brain Tumor Surgery (BRAIN-B).
[k]See Principles of Brain Tumor Radiation Therapy (BRAIN-C).
[l]See Principles of Brain Tumor Systemic Therapy (BRAIN-D).
[m]Vertebral augmentation: vertebroplasty, kyphoplasty.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SPINE-2

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2012
Metastatic Spine Tumors

NCCN Guidelines Index
CNS Table of Contents
Discussion

FOLLOW-UP	PRESENTATION (Symptom or MRI based)	TREATMENT FOR RECURRENCE OR PROGRESSIVE DISEASE
MRI/CT 1-3 mo after treatment, then every 3-6 mo as clinically indicated →	Progressive disease or Recurrent disease → If previously treated with: RT or Surgery and RT	Consider surgery[j] Consider re-irradiation if recurrent
	Progressive disease or Recurrent disease → If previously treated with: Chemotherapy	Consider RT[k]

[j]See Principles of Brain Tumor Surgery (BRAIN-B).
[k]See Principles of Brain Tumor Radiation Therapy (BRAIN-C).

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

SPINE-3

FIGURE 77-2 *(Continued)*

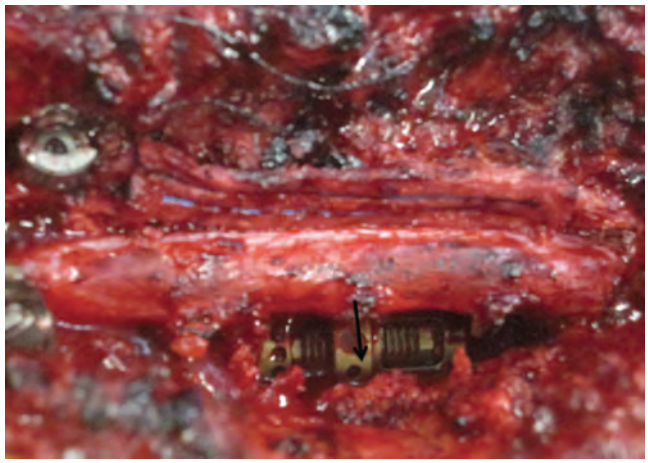

FIGURE 77-3 Intraoperative picture demonstrating exposure obtained with an advanced posterolateral approach, in this case a costotransversectomy. Circumferential decompression has been achieved, the ipsilateral T12 nerve root has been ligated to facilitate exposure of the ventral disease, vertebral body resection and reconstruction with an expandable cage has been performed. Pedicle screws at the left side of the image are part of the posterior instrumented fusion yet to be completed.

In 2005, Patchell et al. reported a phase III prospective, randomized controlled trial that compared surgical decompression followed by radiation therapy to radiation therapy alone in patients with solid tumor ESCC (45). Patients with at least one neurological symptom of ESCC (including pain) and evidence of a solitary epidural metastasis following whole spine MRI were given high-dose steroids and then randomized to receive surgery followed by radiation therapy (n = 50) versus radiation therapy alone (n = 51). Patients with multiple lesions, nerve root compression, radiosensitive tumors (lymphoma, leukemia, multiple myeloma, and germ cell tumors), and paraplegia more than 48 hours prior to entry were excluded. As a result the findings are applicable only to a minority of patients with ESCC.

Most of the previous studies had used a posterior approach, whereas in the Patchell study the approach was chosen by the surgeon based on the location of the tumor (anterior, lateral, or posterior) (45). The study population included 13 breast cancer patients, equally distributed between groups (7 had surgery plus radiation therapy, 6 had radiation therapy alone). The primary end point was the ability to walk immediately following radiation, with duration of ambulation and survival time among the secondary end points. In the group who received surgery, 84% were able to ambulate at the end of radiation therapy, compared to 57% of those who received radiation therapy alone (p = .001). The median duration of ambulation was 122 days with surgery plus radiation therapy, compared to 13 days with RT alone (p = .003). Stability of Frankel Functional Scale and American Spinal Injury Association (ASIA) motor scores, as well as decreased need for opiates and corticosteroids were seen more often in those who underwent surgery. Overall survival was better in the surgery plus radiation therapy group (126 days vs. 100 days with radiation therapy alone; p = .033). Importantly, surgery did not result in prolonged hospitalization; the median hospital stay was 10 days in both the surgery group (interquartile range 2 to 51 days) and the radiation group (0 to 41 days; p = .86). Based on superior posttreatment ambulatory rate in the surgically treated group, the study was stopped at the midpoint analysis and concluded that surgery plus radiation therapy is superior to radiation therapy alone in the treatment of ESCC.

This study suggests that patients with ESCC treated with radical direct decompressive surgery plus postoperative radiation therapy retained the ability to walk longer than patients treated with radiation alone. Surgery permitted most patients to remain ambulatory and continent for the remainder of their lives, whereas patients treated with radiation alone spent approximately two thirds of their remaining time unable to walk and incontinent. In patients with multiple metastases, or in institutions without surgical resources to perform emergency anterior decompression in patients with ESCC routinely, the benefit of surgery is less clear. Also, whether the benefit of surgery applies to radiosensitive tumors such as breast cancer remains to be seen, since breast cancer patients comprised only 13% of the study group. Nonetheless, this is an important study that provides evidence to support surgical decompression in certain patients with ESCC (45).

In contrast to the Patchell study (45), a retrospective study carried out by Rades et al. (46) did not show any benefit from surgery. In this study, 108 patients receiving surgery plus radiation therapy were matched to 216 patients (1:2) receiving radiation therapy alone. Thirteen percent of patients in each group had breast cancer. Groups were matched for 11 potential prognostic factors and compared for posttreatment motor function, ambulatory status, regaining ambulatory status, local control, and survival. Subgroup analyses were performed for patients receiving adequate surgery (direct decompressive surgery plus stabilization of involved vertebrae), patients receiving laminectomy, patients with solid tumors, patients with solid tumors receiving adequate surgery, and patients with solid tumors receiving laminectomy. The outcomes of the end points evaluated after radiation therapy alone appeared similar to those of surgery plus radiation therapy. This study therefore did not confirm the benefit of adding surgery to radiation therapy and suggests that further randomized studies examining the benefit of surgery is needed.

A recent study by Rades et al. (47) suggests that patients older than 65 do not benefit from surgery in addition to radiation therapy as determined by functional outcome, local control of ESCC, or survival. This is in part due to the increased risks of anesthesia or due to the surgery itself (47).

In summary, surgery is recommended for patients whose disease progresses or relapses despite radiation therapy, for spinal instability due to fracture dislocation of the vertebrae, and for patients in whom the spinal cord compression is largely caused by bony fragments in the epidural space rather than tumor. Surgery for patients who are nonambulatory at presentation is probably beneficial, although the data are inconclusive (48). In patients who were treated soon after the onset of paraplegia (less than 48 hours), the Patchell et al. (45) study showed improved outcomes in those who underwent surgery with radiation therapy. Of those who entered the study unable to walk (32 patients), 10 of 16 (32%) regained the ability to walk in the surgery group compared to 3 of 16 (19%) who received radiation therapy alone (p = .012). Additionally, the surgical group maintained ambulation for a median 59 days, compared to 0 days in those receiving only radiation therapy (p = .04). Treatment decisions therefore must be individualized, taking into account the risk of surgery and the patient's overall condition and ability to tolerate therapy.

Radiation therapy is usually administered following surgery to improve local tumor control. Ideally it is performed 2 to 3 weeks after surgery to allow wound healing (49).

Kyphoplasty and Vertebroplasty

Kyphoplasty is a technique that involves percutaneous curettage of the affected vertebral body followed by inflation of a balloon in the body and subsequent injection of cement into the newly formed cavity. In contrast, vertebroplasty involves injection by fluoroscopic guidance of polymethylmethacrylate cement directly into the compromised vertebral body and requires an intact vertebral body. Both techniques help with stabilization and strengthening of compromised vertebrae, and due to stabilization of the anterior column, are thought to relieve pain (50). The SOSG has reviewed the data and literature related to kyphoplasty and vertebroplasty and deemed these procedures as safe in improving pain and functional outcomes in patients with vertebral body metastases, although the outcome is highly operator dependent (50). However, these procedures are relatively contraindicated in patients with ESCC with compression of neurologic structures.

Radiation Therapy

Radiation therapy alone is the most common treatment for ESCC. Although all patients with ESCC should undergo RT, patients with expected survival of less than 3 to 6 months, inability to tolerate an operation, total neurological deficit for more than 24 to 48 hours and multilevel or diffuse disease should probably not undergo surgery and should receive RT alone (1).

In general, patients with breast cancer undergoing focal radiation therapy receive a dose of up to 3,000 cGy (30 Gy) administered over 2 weeks to the metastases plus one or two vertebral bodies above and below. Three- and four-week regimens administering up to 4,000 cGy have also been described, without benefit in motor function, local control of disease, or survival over the standard 2-week regimen (51). Short-course radiation therapy involving two doses of 800 cGy has also been proposed, producing results comparable to those obtained with higher doses in uncontrolled studies (52,53). Single fraction radiation for pain relief has also been proposed for patients with uncomplicated metastases (54). No dose fractionation schedule has proven to be significantly more efficacious than others (1,4,52), but shorter courses may have a higher rate of local recurrence and need for further treatment.

Rades et al. (52) performed a retrospective review of 335 breast cancer patients who received radiation to determine significant prognostic factors. They found that slower development of motor deficit (more than 14 days) and ability to ambulate prior to initiating radiation therapy was associated with a better functional outcome. A short course of radiation (800 cGy in one dose vs. 3,000 to 4,000 cGy over 3 to 4 weeks) did not significantly impact functional status after treatment, but was associated with a higher in-field rate of recurrence (20% at 2 years vs. 10% with standard course RT). Median overall survival was 20 months, but was decreased in patients with visceral metastases, deterioration of motor function after radiation therapy, rapid development of motor deficits (1 to 7 days), and poor performance status. An updated recent analysis from the same group found that an additional favorable prognostic factor on functional outcome was having no visceral metastases, and that additional factors associated with improved survival were having only one or two vertebral metastases, and no other bony metastases (55).

One approach is to recommend the course of radiation based on the patient's expected survival and ability to tolerate treatments. Short-course radiation therapy may be most appropriate for those with an estimated survival of less than 6 months, since the main benefit of long-course RT is reduced local recurrence (52,56).

Radiation therapy should be initiated urgently. It is known that rapid deterioration within 48 hours of the start of RT predicts a poor outcome, and patients who were ambulatory before treatment are likely to remain ambulatory or improve in their performance status overall. In situations in which patients present in the middle of the night, when it is logistically difficult to obtain neuroimaging or commence radiation therapy, the high-dose steroid regimen may be commenced; the radiation oncologists can be notified about the patient, and a spine MRI and radiation planning session performed first thing the following morning.

Reirradiation

The use of radiation therapy for recurrent ESCC, when this involves reirradiating a previously treated segment of spinal cord, poses a potential risk of producing radiation myelopathy (57) and historically has been used sparingly. However, with increasingly effective systemic treatment options, reirradiation of the spine for either recurrent ESCC or recurrent vertebral body metastases is becoming more prevalent, with many reports describing favorable outcomes in selected patients (58,59). Myelopathy is less likely to occur within the limited life expectancy of this population, but since this is a potentially devastating complication of retreatment, particular attention should be paid to cumulative radiation dose to the spinal cord. Nieder et al. (59) examined outcomes of patients who underwent spinal cord reirradiation, recalculating the cumulative doses they received according to the biologically effective dose (BED). With a median follow-up of 17 months, the risk of myelopathy was extremely small if the cumulative BED was not greater than 135.5 Gy in 2-Gy equivalents, the interval between initial radiation and reirradiation was at least 6 months, and the dose for each course of radiation was not greater than 98 Gy in 2-Gy equivalents. Patients who have previously received a maximal dose of radiation therapy to the spine may have an option to undergo decompressive surgery if indicated. Alternatively, in selected cases, reirradiation can be performed using highly conformal techniques, such as stereotactic radiosurgery (SRS), to markedly reduce any further dose to the spinal cord.

Stereotactic Radiosurgery (SRS) and Stereotactic Body Radiotherapy (SBRT)

Recently there has been growing interest in more conformal techniques such as SRS and SBRT, terms that are used interchangeably for treatment of spinal metastases (1,5) and typically refer to treatment courses of between one and five total fractions. SRS/SBRT achieve accurate targeting with multiple highly conformal radiation beams delivering a high dose of radiation to a small target, with rapid dose fall-off to avoid injury to adjacent critical structures (1). SRS/SBRT is typically used for vertebral body metastases at least 3 mm away from the spinal cord and much less commonly for actual ESCC, given that tumor abuts the cord in ESCC and therefore risk of myelopathy may be increased. One clinical trial at Henry Ford Hospital used SRS with a median dose of 1,600 cGy to "decompress" the epidural tumor in patients with ESCC, finding improvement in neurologic function in 81% of patients with a median follow-up of 11.5 months and no cases of SRS-related myelopathy (60). However SRS/SBRT alone for ESCC is considered highly experimental, and if used in the management of ESCC is more often done only after surgical decompression. SRS/SBRT for vertebral body metastases is more technically complex to plan and each treatment takes longer to deliver, but has several potential advantages over conventional radiation: it can avoid irradiating excess marrow; it may interfere less with concurrent chemotherapy; it is accomplished in fewer total

treatments; it can safely deliver a higher dose which may be important for radioresistant tumors; and it may provide a higher degree of pain relief, which is currently being evaluated in the phase II/III clinical trial RTOG 0631, comparing spine SBRT to conventional radiation.

Chemotherapy and Hormonal Therapy

Chemotherapy does not play a significant role in the treatment of ESCC caused by metastatic breast cancer, although Boogerd et al. (61) describe protracted remission of epidural metastases in four patients with breast cancer who received chemotherapy. Chemotherapy may be a more important treatment modality in highly chemosensitive tumors, such as germ cell tumors, lymphoma, and neuroblastoma (12,62,63).

PROGNOSIS

The outcome of ESCC is directly related to the patient's clinical condition at the commencement of treatment. Patients who are ambulant are far more likely to remain ambulant after treatment: 79% to 100% of patients who are ambulant before treatment remain so, whereas only 18% to 69% of nonambulant patients regain the ability to walk (12,16,59,64–66,68). In most series, fewer than 10% of patients who are paraplegic or quadriplegic before treatment regain the ability to walk (12,16,62–65,67), although vertebral body resection has been associated with ambulation rates of 24% to 56% in initially paraplegic patients (45,48).

The prognosis for patients with breast cancer treated with radiation therapy alone has been characterized by Maranzano et al. (66). In this study, the likelihood of responding to radiation therapy was dependent on the pretreatment ambulatory status, whereas duration of response is dependent on the post-treatment ambulatory status. Eighteen of 26 (69%) patients who were nonambulant before treatment became at least partially ambulant with treatment (walking alone or with support). Only 1 ambulant patient of 30 (3%) became nonambulant despite treatment, underscoring the value of early diagnosis.

The median survival of patients with breast cancer in whom ESCC develops is 5 to 14 months (2,64–65). The time from diagnosis of breast cancer to the development of ESCC has been found to be a predictor of survival, with patients who develop ESCC after 3 or more years having a better survival (2). The Patchell study (45) suggests that the addition of surgery to radiation therapy increased absolute survival (126 days vs. 100 days; $p = .033$), as well as the duration of ambulation 122 days vs. 13 days). However, as this study selected radioresistant tumors and only 13% of patients had breast cancer, the role of surgery remains controversial.

Posttreatment ambulatory status is the most important factor influencing survival in patients with breast cancer (2,66). In the study by Maranzano et al. (66), the median survival was 13 months for all patients, 17 months for patients who were ambulant after treatment, and only 2 months for those who were nonambulatory after treatment. The 1-year survival of posttreatment ambulant patients in this study was 66% versus 10% for nonambulant patients. However, local control at the site of spinal metastasis did not appear to be responsible for the improved survival in ambulant patients because most deaths were due to progression of systemic disease rather than relapse in the irradiated spine. In another series reported by Maranzano et al. (65), which included patients with ESCC due to other cancer types, median survival was improved in patients with breast cancer (12 months) than in patients with other tumor types (3 to 7 months). This relatively long survival, in association with the fact that early diagnosis may preserve ambulatory status, underscores the potential value of prompt investigation and treatment of ESCC in patients with breast cancer. Putz et al. (69) examined biological, patient-related, mechanical, and time-dependent aspects influencing functional outcome following treatment of ESCC and found four different prognostic factors with a significantly positive or negative impact on postoperative ambulatory status. The negative factors included vertebral compression fracture, high Tokuhashi score (70) which is based on the Karnofsky Performance Status, number of metastases in the bone, vertebral bodies, internal organs, primary site of cancer, and the presence of neurologic deficits. The positive factors included early decompression (less than 48 hours) and ambulation before treatment. However, given the lack of standardized prognostic tools, prediction of ambulatory outcome after primary surgery in ESCC patients is currently limited. There is an ongoing NIH clinical trial to evaluate whether the Tokuhashi score can be validated. The current NCCN guidelines algorithm can be used to guide in the management of metastatic spinal cord tumors (41) (Fig. 77-2).

MANAGEMENT SUMMARY

- Early diagnosis and treatment of epidural spinal cord compression is very important in preventing serious neurologic disability. Functional outcome is primarily dependent on the degree of neurologic impairment at the commencement of treatment. Optimal outcomes occur when no neurologic findings are present at the time of diagnosis.
- Epidural spinal cord compression should be suspected in any breast cancer patient with back or neck pain, particularly if there is myelopathy or radiculopathy.
- In patients with pain and myelopathy, dexamethasone 100 mg intravenously should be administered immediately, followed by 24 mg orally every 6 hours, with a spine MRI obtained urgently.
- In patients with pain and radiculopathy or with highly suspicious symptoms, dexamethasone 10 mg intravenously should be administered immediately followed by 4 mg orally every 6 hours (or 8 mg orally every 12 hours) and a spine MRI obtained within 24 hours.
- In patients with pain and a low index of suspicion for epidural spinal cord compression, plain spine radiographs or a bone scan should be obtained.
- If epidural spinal cord compression is confirmed on MRI, and any neurologic deficit is mild or stable, treatment is generally radiation therapy to a dose equivalent to 3,000 cGy in 10 treatments.
- Surgical decompression is recommended for patients with a symptomatic single lesion, or an unstable spine, and paraplegia for less than 48 hours.
- Chemotherapy has a limited role in epidural spinal cord compression due to metastatic breast cancer.
- Patients with neurologic compromise should receive adequate analgesia, bowel and bladder care, and prevention of pressure sores. Prophylaxis against venous thromboembolism should be considered in bed-bound patients.

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CHAPTER 78

Leptomeningeal Metastasis

Eli L. Diamond and Lisa M. DeAngelis

CHAPTER CONTENTS

Leptomeningeal metastasis (LM) occurs when tumor spreads to the subarachnoid space and cerebrospinal fluid (CSF) that surround the brain and spinal cord. It may be the sole site of central nervous system (CNS) metastasis or may coexist with brain, dural, or parenchymal spinal cord metastases. LM is an increasingly important neurologic complication of solid tumors in addition to its well-recognized association with hematopoietic malignancies. Enhanced clinical detection with improved neuroimaging and prolonged patient survival with better control of systemic cancer contribute to the increased frequency of LM in patients with solid tumors, particularly breast cancer (1).

The frequency of LM in clinical series of patients with breast cancer is estimated at 8%; however, autopsy series of these patients reveal an incidence of 3% to 40% (2). LM usually coexists with disseminated systemic disease, but it can also occur as an isolated site of relapse. The CNS may be a sanctuary site for metastatic disease in patients with breast cancer whose systemic tumor has been controlled with effective systemic therapies (3), particularly HER2-positive breast cancer treated with trastuzumab (4). The repertoire of active agents to treat breast cancer consists mainly of water-soluble drugs that do not penetrate the blood–brain barrier (BBB). There are numerous efflux transporters that comprise the BBB, including P-glycoprotein, other multidrug resistance-associated proteins (MRP), and the breast cancer resistance protein (ABCG2) that extrudes chemotherapeutic agents such as anthracyclines, taxanes, and vinca alkaloids (5). These agents can eradicate disease in systemic sites, but if a microscopic tumor resides in the CNS, they do not cross the intact BBB; thus, these agents allow the CNS tumor to grow, leading to subsequent brain or leptomeningeal metastases. Once a CNS tumor reaches a macroscopic size, the BBB is typically disrupted and, occasionally, systemically administered drugs can be effective against CNS metastases. However, sequestration of a microscopic tumor behind an intact BBB is likely a major explanation for the rising frequency of brain and leptomeningeal metastases in patients with otherwise well-controlled breast cancer.

Determining the diagnosis of LM is often difficult because the presenting neurologic symptoms can be confused with other CNS complications of breast cancer. Neuroimaging and laboratory tests aid in establishing the diagnosis but are limited by a lack of sensitivity, specificity, or both. Optimal therapy has not been defined; difficulties of drug distribution in the CSF, intrinsic drug resistance of the metastases, and neurotoxicity are important factors that limit the success of standard therapies. Nevertheless, in some patients, an aggressive approach is rewarding, and prolonged control of both disease and symptoms is possible. This chapter reviews the clinical presentation of this disorder, the methods of diagnosis, and the recommended therapeutic approaches.

CLINICAL SETTING

CNS metastases in breast cancer have been associated with younger age, premenopausal status, infiltrating ductal histology, estrogen- and progesterone-receptor negativity, aneuploidy, altered p53, and epidermal growth factor receptor (EGFR) overexpression (6). Lobular type breast cancer has a predilection for LM compared to other histologic types of breast cancer, with one autopsy study showing LM to occur in 14% of all cases of lobular carcinoma (2). In a study done by Altundag et al. (7), 3.8% of 420 breast cancer patients with CNS metastases had a tumor of lobular histologic type, but 31.6% of these patients presented with isolated LM, compared to 7% of all patients in the series. Studies have shown an increased incidence of CNS metastases in women with HER2-positive breast cancer as high as 25% to 40% (8). This increase may be multifactorial and includes biologic factors as well as treatment-related factors. The use of trastuzumab, a monoclonal antibody directed against the HER2 receptor, is associated with increased systemic response rates, prolonged disease-free survival, and overall survival for patients with HER2-positive breast cancer. Due to its high molecular weight, it does not cross the BBB, which may explain the emergence of CNS metastases. It has been postulated, however, that trastuzumab does not increase the risk of CNS relapse directly but rather improves systemic control and overall survival, leading to

an unmasking of occult brain metastases that would otherwise remain clinically silent (9). In fact, other studies do not support a direct association between treatment with trastuzumab and increased CNS metastases (10). One study observed a lower rate of LM in patients with brain metastases and HER2-positive disease compared to HER2-negative patients with brain metastases (11).

A wide time interval between the diagnosis of breast cancer and the occurrence of LM has been reported; in large series, it ranges from a few weeks to more than 15 years (2). In rare instances, LM is the initial manifestation of breast cancer. Many patients with a solid tumor have widespread metastatic disease when LM is diagnosed but, in patients with breast cancer, the systemic tumor may be inactive or responding to chemotherapy. Of 48 patients diagnosed with LM reported by de Azevedo et al. (1), 34 (56.7%) had been treated with 3 or more chemotherapy regimens prior to the diagnosis of LM, and 51 (85%) had metastatic disease at the time of diagnosis.

PATHOPHYSIOLOGY

The cerebral and spinal meninges are composed of the dura mater, arachnoid, and pia mater. The leptomeninges include the arachnoid and pia mater. The pia mater is a thin lining, closely adherent to the surface of the brain and spinal cord, separated from the arachnoid by fine trabeculae. It follows the sulci of the cerebral cortex and penetrates the parenchyma of the CNS in association with arterioles. The associated parenchymal perivascular space is termed the Virchow-Robin space (Fig. 78-1). Pathologic evidence suggests several methods by which tumor cells reach the leptomeninges:

1. Hematogenous spread to the vessels of the arachnoid or to the choroid plexus of the ventricles (the latter produces dissemination of malignant cells to the leptomeninges by normal CSF flow);
2. Direct extension from adjacent metastasis in the cerebral parenchyma or dura or the lymphatic paraspinal region;
3. Retrograde access to the subarachnoid space by tumor cells infiltrating the venous system from adjacent calvarial or spinal metastases; or
4. Iatrogenic spread after resection of a brain metastasis.

Tumor dissemination into the CSF after surgical procedures is primarily associated with removal of metastases from the cerebellum, in which the subsequent development of leptomeningeal disease may be as high as 67% (2). The risk of LM after posterior fossa surgery is increased in the setting of piecemeal as opposed to en bloc resection. There does not seem to be a relationship between radiosurgery of a cerebellar metastasis and the development of LM (12).

Autopsy studies demonstrate that leptomeningeal tumor grows in a sheet-like fashion along the surface of the brain, spinal cord, cranial nerves, and nerve roots (2). It usually disseminates widely, but it may be limited to portions of the cerebral or spinal leptomeninges. When tumor cells are closely adherent to one another, multifocal nodules may form, particularly on the cauda equina or ventricular surface of the brain. LM is usually accompanied by a fibroblastic proliferation of the meninges. An inflammatory response may be seen pathologically in the leptomeninges and, occasionally, reactive lymphocytes accompany malignant cells in a CSF specimen. Tumor may ensheathe meningeal arteries and veins within the subarachnoid space and may extend into the Virchow-Robin spaces, with resulting perivascular tumor cuffing and parenchymal invasion; tumor cells may invade into the cranial nerves and spinal roots as well. Invasion may interfere with blood supply to neurons, causing ischemic changes and even frank infarction (2). Neuronal dysfunction may also be caused by local metabolic derangement because of competition between tumor cells and neurons for glucose and other critical nutrients.

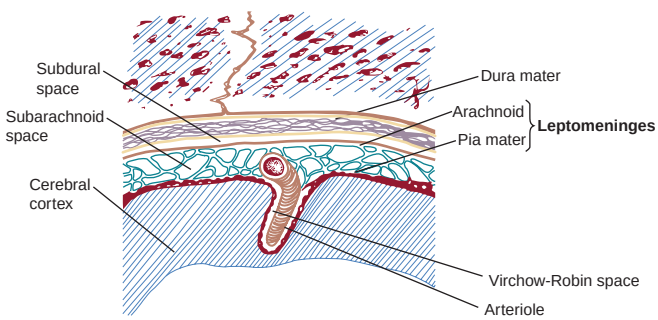

FIGURE 78-1 Relation of the cerebral meninges to the brain.

CLINICAL MANIFESTATIONS

The clinical hallmark of LM is the simultaneous occurrence of multifocal abnormalities at more than one level of the neuraxis (cerebral, cranial nerve, and spinal). A careful neurologic examination often reveals more signs than suggested by the clinical symptoms. Spinal symptoms are the most common presentation of LM (Table 78-1); limb weakness is frequent, usually involving the legs, and may be accompanied by paresthesias and pain in the affected limb. Neurologic examination may reveal asymmetric depression of deep-tendon reflexes, radicular limb weakness, and sensory loss. Signs of meningeal irritation, such as nuchal rigidity, are rare. The most common finding of cerebral dysfunction is a change in mentation. Seizures occur in fewer

TABLE 78-1

Presenting Symptoms and Signs of Leptomeningeal Metastases

Symptom or Sign	*Percentage*
Cerebral symptoms or signs	
Headache	38
Mental change	25
Nausea and vomiting	46
Gait difficulty	46
Cranial nerves	8
Visual loss	8
Diplopia	2
Hearing loss	2
Dysphagia	2
Spinal symptoms	
Pain	25
Paresthesias	10
Limb weakness	22

From DeAngelis LM, Posner JB, Posner JB. *Neurologic complications of cancer.* New York: Oxford University Press, 2009.

than 10% of patients. Cerebral symptoms of LM often result from the obstruction of CSF flow and include headache, changes in mentation (lethargy, confusion, and memory loss), nausea and vomiting, and ataxia. These symptoms often indicate elevated intracranial pressure, which may occur with or without hydrocephalus. The most common cranial nerve symptom is diplopia. Hearing loss, visual loss, and facial numbness also occur. Paresis of the extraocular muscles is the most common cranial nerve abnormality, followed by facial weakness and diminished hearing (2).

METHODS OF DIAGNOSIS

The diagnosis of LM often requires a high index of suspicion. Initial testing may not reveal the diagnosis, and the physician must often resort to a variety of tests combined with clinical findings to establish the diagnosis. Occasionally, a presumptive diagnosis is made and treatment is initiated if the clinical picture is typical, other diagnoses are excluded, and the CSF is abnormal despite a negative CSF cytologic examination (Table 78-2).

Neuroimaging with gadolinium-enhanced MRI should be the first test obtained for a patient with cancer who has new neurologic symptoms. Specific findings on MRI may be sufficient to establish the diagnosis of LM and may eliminate the need for CSF analysis. Neuroimaging is also essential to exclude parenchymal brain (Chapter 76) or spinal epidural lesions (Chapter 77), which may produce a similar clinical picture and may coexist with LM. Gadolinium-enhanced T1-weighted MRI is the best technique for either cranial or spinal imaging. Definitive imaging findings that establish the diagnosis of LM include:

1. Enhancement of the leptomeninges over the convexities or within the cerebral or cerebellar sulci;
2. Tumor nodules or diffuse enhancement of the brainstem, spinal cord, or cauda equina (Figs. 78-2 through 78-4);
3. Enhancement of the cranial nerves; and
4. Enhancement of the basal cisterns or subependymal area.

Despite the sensitivity of MRI, it is negative in 33% of patients with positive CSF cytology, but it is negative in only

TABLE 78-2

Diagnosis of Leptomeningeal Metastases

Neuroimaging: magnetic resonance imaging or computed tomography
Enhancement of cerebrospinal fluid in sulci
Tumor nodules on cauda equina
Enhancement of spinal cord surface
Enhancement of basal cisterns
Enhancement of ependymal surface
Cerebrospinal fluid
Positive cytology
Tumor markers
CA-15-3
Carcinoembryonic antigen
Circulating tumor cells, biomarkers of angiogenesis (VEGF, tPA)[a]

[a]In development.

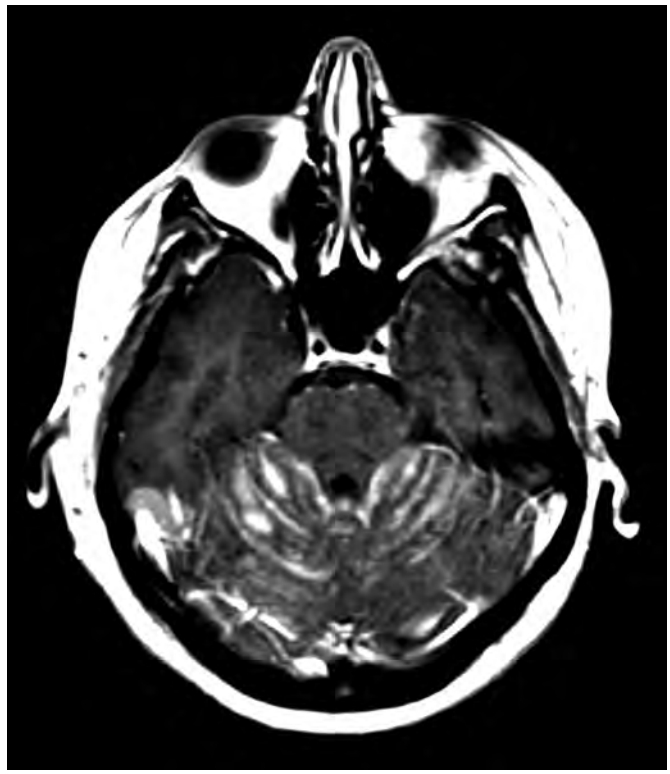

FIGURE 78-2 Leptomeningeal metastases from breast cancer. Axial gadolinium-enhanced brain magnetic resonance imaging reveals diffuse nodular enhancement in the prepontine cistern as well as the cerebellar folia. This image is diagnostic.

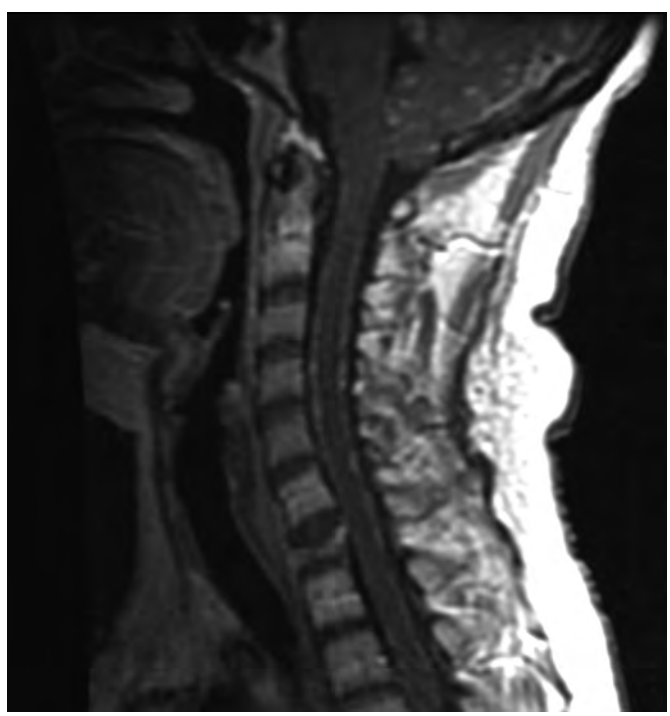

FIGURE 78-3 Sagittal gadolinium-enhanced spine magnetic resonance imaging reveals thickening and nodular enhancement of the leptomeninges adjacent to the cervical spinal cord.

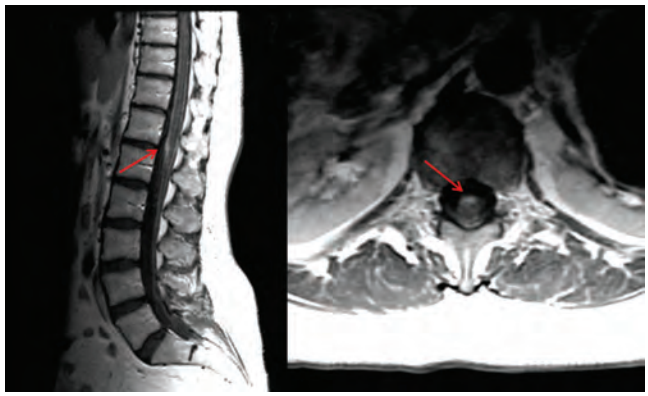

FIGURE 78-4 Sagittal and axial gadolinium-enhanced spine magnetic resonance imaging reveals leptomeningeal enhancement with a nodule (*red arrow*) overlying the upper cauda equina.

10% to 25% of patients with solid tumors compared with 48% to 55% of patients with hematologic malignancies (2,13). The radiologic diagnosis of LM may be missed in a patient receiving bevacizumab because of diminution of post-gadolinium enhancement (14). Rarely, ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) CT may establish a diagnosis of LM (15).

In the absence of diagnostic radiographic abnormalities, other imaging findings that suggest LM include hydrocephalus or small superficial metastases deep in sulci. Patients clinically suspected of having LM need to undergo CSF analysis to establish the diagnosis when neuroimaging is negative or inconclusive. The presence of "definitive" radiographic findings in patients not known to have cancer cannot be attributed automatically to metastasis because primary leptomeningeal tumors, infection, postoperative conditions, or even changes after lumbar puncture can mimic subarachnoid metastases. These patients require documentation of malignancy to establish the diagnosis.

The established gold standard to diagnose LM is the demonstration of malignant cells in the CSF, typically obtained by lumbar puncture. Malignant cells are not identified in the CSF of patients with parenchymal, dural, or epidural metastasis, and they indicate metastasis to the subarachnoid space (2). The initial lumbar CSF cytologic examination gives positive results in up to 50% of patients with LM, but the yield increases to 90% if three lumbar punctures are performed (2). Nevertheless, 10% of patients with LM will still have a negative CSF cytologic examination after 3 lumbar punctures. The detection of malignant cells can increase when larger volumes (>10 mL) of CSF are available for analysis and occasionally when a CSF sample is taken from an alternate site; examination of cisternal CSF can be more sensitive, particularly in those patients with cerebral or cranial nerve symptoms (2). The failure to detect malignant cells in the CSF may be a sampling error because tumor cells are not equally distributed throughout the CSF due to adherence of the cells to CNS structures, or it may indicate that the tumor is localized. In an autopsy study of 30 patients with LM (2), there was a positive CSF cytologic evaluation in 76% of patients with multifocal or disseminated LM, but in only 58% of those with focal disease (2).

Because of the relatively low sensitivity of CSF cytology, newer technologies have been used to improve detection of malignant cells in the CSF. *In vitro* methods include immunocytochemistry, flow cytometry, fluorescence *in situ* hybridization (FISH) for aneusomy of chromosome 1, and polymerase chain reaction (PCR) (in which genetic alterations of the tumor cells are used for amplification) (16). Furthermore, the CellSearch (Veridex) detection platform has demonstrated potential for identification and enumeration of circulating tumor cells in the CSF of patients with breast cancer (17).

The CSF of most patients with LM has abnormalities in the routine chemistries and white blood cell count. An elevated protein concentration is the most common abnormality but is usually less than 100 mg/dL; there is a normal gradient of protein along the CSF axis, and a normal ventricular CSF protein concentration is less than 20 mg/dL. Up to one-half of patients have pleocytosis, usually mononuclear. About one-third of patients have a low CSF glucose concentration, defined as less than 70% of a simultaneous serum glucose concentration. Measurement of intrathecal tumor markers has also been used to diagnose LM. Carcinoembryonic antigen (CEA) and the breast cancer antigen (CA15-3) are elevated in the CSF of some patients with breast cancer (18), but the CSF levels must be compared with serum concentrations because extremely elevated serum levels can cross the BBB and be detected in the CSF. For CEA and CA15-3, the expected serum:CSF ratio is 100:1, and therefore, concentration in the CSF of these markers greater than 1% of the serum concentration is suggestive of LM (2). Like CSF protein levels, tumor marker values are lower in the ventricular than lumbar CSF, thus making interpretation from this region difficult. Elevation of β-glucuronidase, total lactic acid dehydrogenase (LDH), or the percentage of the LDH-5 isoenzyme are established tumor markers and can be indirect indicators of LM. However, these biomarkers are nonspecific and may be elevated in infections and other disorders of the CNS (2).

Proteins associated with angiogenesis have been studied as potential CSF biomarkers of LM. Increased concentration of vascular endothelial growth factor (VEGF) in the CSF is reported to be sensitive and specific for the diagnosis of LM from breast cancer (19), as well as decreased concentration of tissue plasminogen activator (tPA); combining these two markers predicted LM with 100% sensitivity in one study, although with a false-positive rate of up to 27% (20). CSF protein profiles of soluble adhesion molecules, cytokines, and chemokines have been used to discriminate between LM and other processes (21). Mass spectrometry–based methods have investigated protein expression patterns in CSF from breast cancer patients with and without LM and have found reproducible peptide profiles that might assist in diagnosing LM (22).

CSF is usually sampled in patients suspected of LM to establish the diagnosis with the demonstration of malignant cells. However, lumbar puncture may be necessary to measure the intracranial pressure (ICP). Headache, nausea, vomiting, and lethargy may be clinical indicators of increased ICP in patients with LM. Plateau waves, which are marked increases in ICP often triggered by a change in body position, may be manifest as transient decreased consciousness, visual disturbances, or gait difficulties; they are often confused with seizures because of their brief duration. Elevated ICP may be a consequence of hydrocephalus resulting from impairment of CSF flow. Hydrocephalus is almost always communicating in this situation and is easily diagnosed on cranial imaging. However, marked elevation of ICP can occur in patients with LM in the *absence* of hydrocephalus. These patients may have normal or small-appearing ventricles on MRI or CT scans. In these patients, lumbar puncture is needed to detect the elevated ICP. Increased ICP requires specific therapeutic intervention and is an absolute contraindication to intrathecal

chemotherapy until the condition is corrected (discussed below). Failure to diagnose increased ICP is a common mistake in the management of patients with LM and can be the cause of persistent neurologic symptoms, failure to respond to treatment, and treatment-related neurotoxicity.

TREATMENT

There is no standard treatment that has been demonstrated to prolong overall survival in LM, and numerous controversies remain regarding the role and timing of different treatment modalities. Sustained remissions are rare, and patients usually succumb to their neurologic disease. However, vigorous treatment of LM can, in some patients, palliate symptoms, achieve disease control, and prevent further neurological deterioration for a meaningful period of time. Supportive care involves anticonvulsant medications, treatment of painful radiculopathy, and the use of corticosteroids to ameliorate symptoms of elevated ICP. Corticosteroids are usually ineffective in reversing neurologic deficits from LM because there is little edema in the underlying CNS parenchyma. The following are general principles regarding the implementation of radiotherapy (RT), intrathecal chemotherapy, and systemic chemotherapy in the treatment of LM.

All patients with LM should undergo enhanced MRI of the entire neuraxis to search for bulky disease. Radiation should be administered to symptomatic areas (i.e., cranial irradiation for cranial neuropathies), whether or not structural disease is identified on imaging, and possibly to bulky disease because RT is usually the most effective modality for treating focal LM nodules. It is also the most reliable modality for the relief of symptoms such as cauda equina syndrome and pain.

Complete neuraxis RT is discouraged even for diffuse bulky tumor because it does not control the disease and is associated with acute morbidities such as esophagitis and severe myelosuppression, particularly in patients who are heavily pretreated or who are receiving systemic chemotherapy. Whole brain RT can enhance the neurotoxicity of chemotherapy administered into the CSF and should be reserved for patients with symptoms from the brain or cranial nerves. Bulky tumor deposits seen on MRI impair CSF flow and cause an accumulation of drugs proximal to the flow obstruction; focal RT can occasionally restore normal CSF dynamics if it also shrinks the tumor nodules (2). Intrathecal chemotherapy should not be administered concurrently with whole brain RT to reduce the risk of neurotoxicity. Radiotherapy is effective at palliating a region of LM, but the process involves the entire subarachnoid space and, therefore, treatment must encompass that whole compartment. Chemotherapy is often used to accomplish this.

Bulky leptomeningeal tumor develops its own vascular supply, which has a disrupted BBB. Therefore, intravenous chemotherapy may reach an enhancing subarachnoid nodule, but most systemic drugs do not achieve sufficiently high levels in the CSF and cannot eradicate tumor cells floating in the CSF or clusters less than 1 mm thick that do not generate their own blood vessels. For this reason, chemotherapy has been administered directly into the CSF. Direct CSF instillation achieves a higher concentration of drug in the subarachnoid space because the initial volume of distribution is smaller than the vascular compartment and the clearance half-life is longer in the spinal fluid for some agents. In addition, intra-CSF instillation often reduces or spares systemic toxicity, although the CSF can act as a reservoir for some drugs, such as methotrexate, that can slowly leak into the peripheral circulation and cause mucositis and myelosuppression. A disadvantage of chemotherapy administration into the CSF is the frequent occurrence of CSF flow abnormalities, which may result in nonuniform distribution of the drug throughout the CSF pathways, thereby reducing efficacy and increasing local toxicity; flow obstruction can cause a drug instilled in the ventricle to penetrate slowly into the periventricular tissue and cause leukoencephalopathy (2). Moreover, intra-CSF chemotherapy does not penetrate into bulky tumor deposits or infiltrated roots or cranial nerves and therefore cannot treat nodular disease effectively.

Despite these limitations, there is still a role for intrathecal chemotherapy, particularly in patients with minimal bulky disease. However, there must be normal CSF flow before the drug is instilled. CSF flow abnormalities usually correlate with bulky disease identified by neuroimaging, and flow disruption should be presumed in these patients. However, impaired CSF flow can be present despite normal neuroimaging. Radionuclide CSF flow studies using indium may be performed prior to intrathecal chemotherapy administration because they often demonstrate abnormalities of CSF dynamics that result in compartmentalization of CSF pathways. Involved-field RT to a site of bulky tumor may restore normal CSF flow and thus permit normal distribution of intra-CSF chemotherapy throughout the subarachnoid space.

Intra-CSF chemotherapy can be instilled directly into the lumbar subarachnoid space or the ventricular system through an Ommaya reservoir. Intraventricular administration is recommended because this approach ensures delivery of a drug into the CSF and allows for simple repetitive administration. Lumbar punctures result in inadvertent epidural or subdural injection in 10% of procedures. Most important, delivery of a drug into the ventricular system ensures more reliable and uniform drug distribution. Three agents are routinely instilled into the CSF: methotrexate, thiotepa, and cytarabine (including liposomal cytarabine or DepoCyt). Only methotrexate and thiotepa have intrinsic activity against breast cancer. Intra-CSF administration of methotrexate usually is performed twice a week initially, and the frequency is gradually tapered. The dose is fixed at 12–15 mg because the volume of CSF is identical for all patients regardless of size. Intra-CSF thiotepa has been studied in patients with LM from solid tumors, including breast carcinoma. The dosage is usually 10 mg and is administered twice weekly initially. The frequency is decreased over 1 to 3 months. In a comparative randomized study of intraventricular methotrexate versus thiotepa in 52 patients with solid tumors, 25 of whom had breast carcinoma, there was a slight survival advantage with methotrexate (23). Thiotepa has a rapid half-life in the CSF that may limit its effectiveness. No evidence shows that combination intra-CSF chemotherapy is better than single-agent therapy, and toxicity is additive (24).

Liposomal cytarabine (DepoCyt) is a sustained-release form of cytarabine that maintains cytotoxic levels in the CSF for 10 days or more. The dose is 50 mg twice monthly, and then it is decreased to monthly treatments. Adverse side effects include arachnoiditis and headaches which can be severe. All patients must be treated with dexamethasone 4 mg twice a day beginning 2 days prior and continuing at least 2 days following each dose of DepoCyt. In an open label trial of DepoCyt, 110 patients, 34% of whom had breast cancer, had a response rate comparable to twice weekly methotrexate. An increased time to neurological progression was seen, favoring DepoCyt; this may be due to prolonged tumor exposure to cytotoxic concentrations of drug (25).

A new area of investigation is intrathecal trastuzumab for LM from HER2-positive breast cancer. There have been reports of clinical and radiographic response to both

monotherapy with intrathecal trastuzumab (26,27) and combination intrathecal treatment (28), and this is currently being explored. Another therapeutic approach in development is tumor selective radioimmunotherapy, including intrathecal iodine-labeled monoclonal antibodies; these targeted therapies may inhibit leptomeningeal tumor growth, but none have been developed specifically for breast cancer (29).

An increasingly important approach to the treatment of LM is the use of systemic chemotherapy, which is either lipophilic and can penetrate into the subarachnoid space or is administered in high doses to reach the leptomeninges (30,31). This approach has the benefits of reaching the entire CSF, regardless of CSF flow dynamics, and treating both bulky and microscopic disease. However, it can subject patients to the systemic toxicities of chemotherapy, and many patients have been extensively pretreated by the time LM emerges. Lassman et al. (32) studied high-dose methotrexate at 3.5 g/m^2 in 32 patients with or without radiotherapy and intrathecal chemotherapy, 29 of whom had breast cancer. Patients had recurrent parenchymal or leptomeningeal metastases. An objective response or stable disease was seen in 9 patients (28%), and median overall survival was 19.9 weeks with 1 patient alive more than 135 weeks; most of these patients had breast cancer and LM with or without brain metastases and had stable or improved disease with reasonable toxicity. Treatment with higher doses of methotrexate (8 g/m^2) has been associated with 84% cytologic clearing of CSF and survival of 23.7 weeks (33).

Capecitabine, an oral analog of 5-flurorouracil (5-FU), has been effective despite limited penetration of 5-FU into the CNS. In one study, patients with parenchymal or LM from breast cancer received 1,000 mg/m^2 capecitabine twice daily for 14 days in a 21-day treatment cycle; 43% of patients had a complete response, and 43% had stable disease. Treatment was well tolerated, with no observed neurological toxicity. Median overall survival was 13 months, and the median progression-free survival was 8 months (34). Successful treatment of LM with a combination of capecitabine and trastuzumab has also been described (35). Wilson et al. (36) reported resolution of extensive LM with weekly docetaxel therapy.

There may be a role for newer targeted therapies in the treatment of LM, but this has yet to be studied. Lapatinib, a dual tyrosine kinase inhibitor targeting EGFR and HER2, is thought to penetrate the BBB and has been shown to have activity against cerebral metastases of HER2-positive breast cancer in combination with capecitabine (37), but this has yet to be reported in the treatment of LM. Other targeted treatments that demonstrate potential to cross the BBB are under investigation, including poly (adenosine diphosphate ribose) polymerase (PARP) inhibitors, histone deacetylase (HDAC) inhibitors, polo-like kinase 1 (Plk1) inhibitors, and the microtubule-stabilizing agent sagopilone (38). Novel second-generation analogs of eribulin are being studied for their potential to enter the CNS as well (39).

Elevated ICP can rarely be corrected with whole brain RT, but usually antitumor treatment cannot restore adequate CSF dynamics to normalize ICP. Many of these patients must be treated with a ventriculoperitoneal (VP) shunt to correct the elevated pressure. Omuro et al. (40) examined 640 patients with LM, and 6% had VP shunt placement; 62% of these patients had breast cancer. After VP shunt placement, 77% had symptomatic improvement with decreased headache, decreased nausea and vomiting, and improved level of alertness. Three patients had shunt malfunction, and one developed a subdural hematoma. No deaths were attributed to complications of the procedure.

Placement of a VP shunt can be lifesaving; however, it can complicate subsequent treatment for LM, particularly involving the administration of intrathecal chemotherapy. A subcutaneous reservoir with an on-off device may be placed in series with the shunt valve, but these devices often function poorly. The newer programmable shunts can be opened and closed easily, but they are programmed with an external magnet, and each time the patient has an MRI scan, the shunt must be reprogrammed to ensure flow through the shunt. More important, when a VP shunt is turned off, CSF flow dynamics remain impaired and unable to distribute intrathecal chemotherapy adequately. Therefore, once a shunt is placed, intrathecal chemotherapy should never be administered into the ventricular compartment again. It may be administered by lumbar puncture, but it will not reach the entire CSF compartment, and this is likely useful only for those with predominately spinal disease. In patients with a shunt, systemic chemotherapy or RT are better options because they do not require normal CSF flow to distribute the agent throughout the subarachnoid space.

PROGNOSIS

Response criteria in LM are not standardized. Most reported studies define response to treatment as the normalization of CSF and improvement of clinical symptoms, and there is some evidence that cytologic response is associated with clinical improvement (41). The concentration of tumor markers in the CSF may also be associated with response to treatment, and their rise may herald disease progression even in the setting of normalization of the CSF cytology (41).

The median survival in patients with untreated LM is 1.5 to 2 months (2). Early diagnosis and treatment may improve clinical outcome although there are conflicting data regarding the efficacy of intrathecal or systemic chemotherapy or RT in the treatment of LM. Of solid tumors, breast cancer responds best to treatment with a median survival of 6 months, and 15% of patients survive more than 1 year. Many reports suggest that a patient's clinical condition at diagnosis is a key determinant of outcome. A study of 85 patients with LM from solid tumors (42) suggests that radiographically apparent LM may portend a worse prognosis; another study (11) suggests that LM of triple-negative breast cancer may be associated with shorter survival and greater likelihood of CNS death. There is currently no evidence that elevated ICP is of prognostic significance, but this has not been studied.

Systemic and intrathecal chemotherapy are the only treatment modalities shown to improve survival in LM when compared to spinal and whole brain RT (31); however, RT relieves symptoms more effectively. Intrathecal methotrexate seems to provide improved survival compared with no therapy in most studies, with a median survival of 3–6 months in general and a median survival of 15 months in those who respond (2). Boogerd et al. (43) randomized 35 patients to receive appropriate systemic therapy and RT to clinically relevant sites, with or without intrathecal methotrexate. Patients who received intrathecal chemotherapy did not have additional survival benefit or improved neurological response but did have an increased risk of neurotoxicity.

TOXICITY

Toxicity from treatment of LM is primarily neurologic, and systemic toxicities (typically myelosuppression) arise primarily from systemic chemotherapy. Systemic complications of intrathecal methotrexate include stomatitis and myelosuppression. Low-dose oral leucovorin protects

against these toxicities in patients receiving intrathecal methotrexate, and the authors typically administer 10 mg of leucovorin twice daily for eight doses to all patients receiving intrathecal methotrexate. Intra-CSF thiotepa can cause myelosuppression, particularly when concurrent systemic chemotherapy is administered.

Spinal RT can contribute to depressed bone marrow function, particularly if the patient is heavily pretreated or receiving concurrent systemic therapy. Mucositis can also occur with radiotherapy to the cervical or upper thoracic region. Fatigue is almost universal and can be exacerbated by any of the treatment modalities used against LM.

Neurotoxicity after irradiation of the nervous system or after intra-CSF or systemic chemotherapy is a significant obstacle to treating patients with LM aggressively. The most common neurologic complication of intra-CSF chemotherapy is transient aseptic meningitis, which develops within hours of injection and produces headache, fever, stiff neck, and confusion. It does not necessarily recur on subsequent injections, and corticosteroids can prevent or ameliorate the reaction (2). While any drug delivered into the CSF can cause aseptic meningitis, it is most severe with liposomal cytarabine. Intra-CSF methotrexate causes leukoencephalopathy, but so can any drug instilled into the subarachnoid space. The risk of leukoencephalopathy rises with increasing total methotrexate dose, prolonged CSF methotrexate levels, and concurrent cranial RT (2). Leukoencephalopathy can often be identified first on cranial MRI in which increased signal, predominantly in the periventricular white matter, can be seen on T2-weighted or fluid-attenuated inversion recovery (FLAIR) images (Fig. 78-5). Patients develop apathy, memory loss, gait disturbance and, later, urinary incontinence. Clinical abnormalities correlate loosely with the severity of changes seen radiographically. Focal leukoencephalopathy can result from high local cerebral concentrations of methotrexate around an Ommaya reservoir catheter, particularly if inadvertent separation of the catheter occurs or if intraventricular pressure is elevated (2). Clinically significant complications related to the Ommaya reservoir are uncommon but include infection of the reservoir, bacterial meningitis, and intracerebral hemorrhage. Any drug can also cause myelopathy after lumbar injection.

If neurologic decline occurs, treatment-related toxicity must be distinguished from progressive leptomeningeal tumor. If the latter occurs, the chemotherapy agent should be changed, RT administered to bulky areas, or both. Patients must also be monitored for progression of their systemic disease although most patients with breast cancer die of progressive LM.

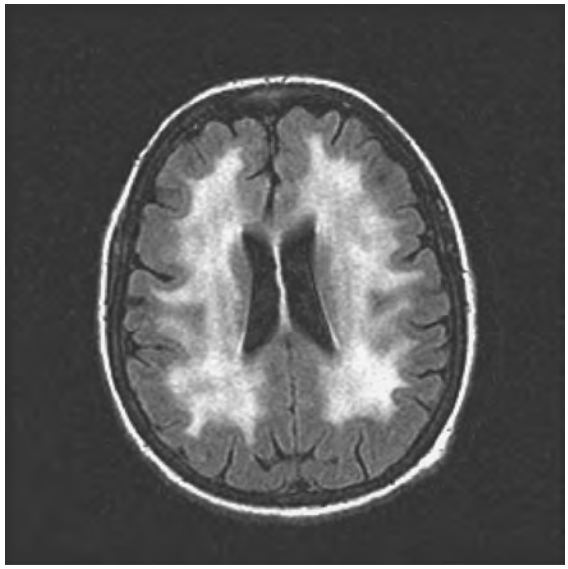

FIGURE 78-5 Leukoencephalopathy. Fluid-attenuated inversion recovery (FLAIR) magnetic resonance image of a patient with breast cancer treated with intrathecal methotrexate only for leptomeningeal metastasis. There is extensive white matter hyperintensity that is bilateral and symmetric. She had no cognitive impairment.

MANAGEMENT SUMMARY

- Leptomeningeal metastasis is an increasingly common complication of breast cancer.
- Early diagnosis is important before the patient develops severe neurologic deficits that cannot be reversed with treatment, and good performance status is associated with a better response to therapy.
- Diagnosis can be established by the demonstration of tumor nodules or enhancing disease in the subarachnoid space on MRI or the finding of tumor cells in the CSF. Serial CSF cytology and measurement of tumor markers may aid with diagnosis and monitoring responses to treatment.
- Treatment usually requires focal RT to symptomatic sites or areas with bulky disease followed by chemotherapy.
- The optimal choice of chemotherapy depends on a thorough assessment of the neurologic and systemic extent of disease. Patients with multiple nodules may be treated best with systemic chemotherapy, whereas those with positive CSF cytology but negative imaging can be treated with intra-CSF chemotherapy alone and thus spared the toxicity of systemic drug administration. Intrathecal methotrexate, thiotepa, and cytarabine have all been reported to have some efficacy.
- For patients with advanced disease and poor performance status, it is often appropriate to pursue management of symptoms with supportive medications and potentially palliative focal RT but not to proceed with chemotherapy.
- Despite treatment, most patients do poorly, and the median survival is about 4–6 months although some survive for years with vigorous treatment.

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CHAPTER 79

Brachial Plexopathy in Patients with Breast Cancer

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CHAPTER CONTENTS

The brachial plexus is a somatic nerve plexus formed by intercommunications among the ventral rami of the lower four cervical nerves (C5–C8) and the first thoracic nerve (T1). The brachial plexus, which provides motor and sensory innervation of the upper extremity, is subdivided into roots, trunks, divisions, cords, and branches. Nerve roots exit through the vertebral interspaces joining to form the superior (C5–6), middle (C7), and inferior (C8–T1) trunk. The plexus trunks are located between the anterior and middle scalene muscles, bifurcating into anterior and posterior divisions within the supraclavicular fossa. These merge to form cords which pass over the first rib, coursing under the clavicle into the axilla. The terminal branches, located at the lateral border of the pectoralis minor muscle, include the axillary, musculocutaneous, radial, median, and ulnar nerves.

In patients with cancer, symptoms and signs of brachial plexus injury may be attributable to acute brachial neuritis, trauma to the plexus during surgery or anesthesia, metastatic spread of tumor, transient or permanent radiation injury, or radiation-induced tumors. In patients with breast cancer, metastatic spread of tumor, iatrogenic injury from radiation therapy and surgery, and second primary cancers are the most common causes of such signs. Careful evaluation of the clinical history, symptoms and signs, as well as electrodiagnostic and imaging studies are helpful in diagnosing the cause of a brachial plexopathy.

TUMOR INFILTRATION OF THE BRACHIAL PLEXUS (METASTATIC BRACHIAL PLEXOPATHY)

Despite the proximity to the draining axillary lymph nodes, tumor infiltration of the plexus is relatively uncommon. Even among specialist consultation services in a major cancer center, this diagnosis represented only 5% of the neurologic consultations evaluated by the neurology consultation service (1) and only 4% of patients referred to a cancer pain service (2). Early and accurate diagnosis is critical to prevent

irreversible nerve damage and chronic neuropathic pain and to determine the prognosis and treatment of the tumor.

Clinical Symptoms and Signs

Pain

Eighty-five percent of patients with tumor infiltration present with pain that is moderate to severe, often preceding neurologic signs or symptoms for up to 9 months (3,4). The pain distribution depends on the site of plexus involvement. Typically, the pain radiates in the sensory distribution of the lower plexus, usually involving the shoulder girdle and radiating to the elbow, medial side to the forearm, and the fourth and fifth fingers (consistent with involvement of the lower plexus C7, C8, T1) (3,4).

Other, less common clinical presentations are occasionally observed, including pain localized to the posterior aspect of the arm or to the elbow, a burning or freezing sensation and hypersensitivity of the skin along the ulnar aspect of the arm, or pain referred to either the shoulder girdle or the tip of either the index finger or thumb (consistent with infiltration of the upper plexus C5–6 by tumor rising in the supraclavicular nodes).

By the time of diagnosis of a brachial plexus lesion, 98% of patients have pain that is most often reported as severe. In Kori's series (3), 2 of 78 patients with malignant brachial plexopathy had pain as the only symptom or sign of tumor recurrence and required exploration and biopsy of the plexus to establish the diagnosis.

Paresthesias

Paresthesias occur as a presenting symptom in 15% of patients with tumor, in an ulnar distribution from infiltration of the lower plexus, or with a median nerve distribution in lesions of the upper plexus.

Lymphedema

Lymphedema is rarely a presenting symptom of tumor infiltration of the brachial plexus (3,4), but it does occur in about 10% of patients, most often in patients who received previous radiation therapy to the plexus and who subsequently develop recurrent tumor.

Weakness

Focal weakness, atrophy, and sensory changes in the distribution of the C7, C8, and T1 roots occur in more than 75% of patients. In one series of patients with brachial plexopathy arising from any tumor type, 25% of patients presented with whole-plexus motor weakness (panplexopathy) (3).

Horner's Syndrome

Patients with a panplexopathy or a Horner's syndrome have a higher likelihood of epidural extension and should undergo imaging of the epidural space as part of their evaluation.

Palpable Masses

Careful physical examination commonly reveals palpable supraclavicular or axillary lymphadenopathy. Occasionally, tumor infiltration in the distal plexus is associated with a palpable mass or fullness in the clavipectoral triangle. In all cases, these areas need careful evaluation.

Relationship to Natural History

In 12 of 78 patients with tumor infiltration of the brachial plexus included in the Kori series, the plexus lesion was the only evidence of tumor, and other metastases appeared only after several months (3). In two patients, the plexus lesion was the only sign of recurrence for 4 years. In one patient, surgical exploration after 2 years of plexopathy signs proved to be normal, but because of progressive worsening of neurologic signs, a second exploration was carried out, confirming tumor recurrence.

RADIATION INJURY TO THE BRACHIAL PLEXUS

Regional Nodal Radiation Therapy

Radiation therapy (RT) plays an important role in the curative treatment of women with early stage breast cancer. Randomized trials and meta-analyses have demonstrated that, in patients with node-positive disease, the addition of adjuvant radiation therapy to the regional lymph nodes improves locoregional control and survival compared to radiation to the breast or chest wall alone. Regional nodal radiation therapy generally includes the axillary and supraclavicular lymph nodes in patients with high risk disease. Late adverse effects from breast/chest wall RT, generally appearing months to years after treatment, may include skin and soft-tissue fibrosis, cardiac and lung injury, rib fracture, and secondary malignancies. Although very little of the plexus is usually exposed in radiation treatment of the breast or chest wall, the addition of radiation to the regional nodes can expose substantial portions of the plexus to the potential for radiation damage (5).

Pathophysiology of Radiation Injury

Factors that can contribute to radiation injury of the brachial plexus include age, total radiation dose, dose per fraction, radiation treatment volume, length and volume of the plexus receiving radiation, and combined chemotherapy (6,7).

There are three possible types of peripheral nerve damage after radiation therapy:

1. A very high dose of radiation may cause severe vascular damage to the blood vessels supplying a segment of a nerve. This type of peripheral nerve damage occurs within months to years after irradiation.
2. Extensive fibrosis of the adjacent and overlying connective tissues may damage a peripheral nerve trunk situated within intact tissue. This tends to be a very late phenomenon, occurring many years after radiation.
3. Extensive fibrosis of the adjacent and overlying connective tissues may damage a peripheral nerve trunk situated within tissues previously subjected to surgical dissection. The microvascular disruption caused by the previous dissection makes these tissues more vulnerable, and, consequently, fibrosis may develop more rapidly, after a few months to years.

Fibrosis and decreased vascularity may destroy peripheral nerves and prevent the regeneration of their proximal normal portions. The degree of connective tissue injury at the time of or preceding radiation therapy may be important in influencing the subsequent development of connective tissue fibrosis.

Clinical Syndromes of Radiation-Induced Brachial Plexopathy

Three distinct clinical syndromes of brachial plexopathy related to radiation therapy have been reported in patients with breast cancer: (i) reversible or transient radiation injury, (ii) ischemic brachial plexopathy, and (iii) radiation fibrosis of the brachial plexus. All three are uncommon

clinical entities, each with a characteristic clinical presentation and course.

Transient Radiation Injury

Transient brachial plexopathy has been described in breast cancer patients immediately following radiotherapy to the chest wall and adjacent nodal areas. In retrospective studies, the incidence of this phenomenon has been variably estimated as 1% to 20% (8–10).

In a retrospective study of 63 patients, Fulton et al. reported radiation-induced plexopathy in 19 cases, including 14 with transient and 5 with permanent injury (8). Transient plexopathy did not appear to predispose patients to the development of permanent plexopathy. In a review of 565 patients treated with adjuvant radiation doses of 50 Gy in 5 weeks using megavoltage radiation therapy, Salner et al. identified 8 (1.4%) cases of transient brachial plexopathy (9), with the onset of symptoms occurring 3 to 14 months (median 4.5 months) following irradiation. Seven of 8 patients received adjuvant chemotherapy; in 6 patients, symptoms began following drug treatment. There was a temporal clustering of these cases, suggesting a possible neurotropic viral component. The symptoms and signs of paresthesia and weakness did not conform to any anatomical pattern, but most commonly affected the distribution of the lower plexus. Weakness occurred in 5 of 8 patients, and was profound in two cases. All patients regained full strength. In 3 patients, residual paresthesias persisted.

In contrast to older series, clinical experience in the modern era suggests that lower estimates are more accurate. In a long-term follow-up study of 1,624 patients, Pierce et al. found that radiation-induced plexopathy was transient in 16 cases. Mild symptoms, with minimal pain and weakness, were predictive of resolution (11). Similarly, in a series of 419 patients who received radiation to the axillary nodal region, Galper et al. reported that 5 (1.2%) developed a transient brachial plexopathy (10).

Radiation-Induced Ischemic Brachial Plexopathy

Case reports during the era of extensive nodal surgery and outdated radiation techniques have described radiation-induced ischemic brachial plexopathy arising decades after treatment. Gerard et al. reported a case of subclavian artery occlusion occurring 19 years after radiation to the breast and axillary nodes following radical mastectomy (12). The patient's symptoms occurred acutely after carrying a heavy object and holding her left arm outstretched above the shoulder. The syndrome was acute in onset, nonprogressive, and painless, in contrast to the typical progressive nature of radiation fibrosis. Rubin et al. described one case of radiation-induced arteritis of large vessels and brachial plexopathy occurring 21 years after local radiation for breast cancer. Arteriography revealed arteritis, with ulcerated plaque formation at the subclavian-axillary artery junction, consistent with radiation-induced disease, and diffuse irregularity of the axillary artery. The risk of this uncommon entity in contemporary practice is unclear but is likely rare with the use of less extensive nodal surgery and modern techniques in radiation therapy planning, which optimize dose homogeneity and limit normal tissue exposure.

Radiation Fibrosis

Radiation fibrosis of the brachial plexus is a well-described clinical entity characterized by progressive and irreversible neurologic dysfunction of the brachial plexus. The risk of developing chronic brachial plexopathy has been estimated as 0.6% to 14%, varying with study era, radiation therapy prescription and techniques, and other treatment factors, including extent of nodal surgery and the use of chemotherapy (3,13–15).

Symptoms and Signs: Symptoms of radiation fibrosis, including weakness, paresthesia, and pain, typically develop months to years after radiotherapy (13,16,17) though in many cases no latency is apparent (18). The natural history of brachial plexus fibrosis is variable. Motor dysfunction may be incomplete or may progress to a severe paresis (18). Even with advanced radiation fibrosis, severe pain is relatively uncommon at presentation and its presence should prompt evaluation for recurrent tumor (3).

Weakness Arm weakness is the dominant symptom of radiation fibrosis. Motor weakness typically involves the muscles innervated by the upper plexus alone or both the upper and lower plexus (3,4,16,18). Weakness in a distribution of the lower plexus alone is uncommon (18).

Pain Although pain is a presenting symptom in less than 20% of patients with radiation injury to the brachial plexus, its prevalence increases with time (3,18,19). The pain is commonly described as mild discomfort associated with aching pain in the shoulder or hand. At the time of diagnosis, 65% of patients will report discomfort or pain in the arm; in 35%, it is severe (3).

Parasthesias In over 50% of affected patients, paresthesias are a prominent symptom (3). They are commonly reported to occur in the thumb and forefinger but often involve the entire hand. These symptoms are often confused with carpal tunnel syndrome but may be differentiated clinically and by electrodiagnostic studies.

Lymphedema Lymphedema of the ipsilateral arm was observed in 16 of 22 patients with radiation fibrosis in Kori's series (3) and in a substantial proportion of those reported by others (4). Olsen et al. found that lymphedema is a common late consequence of radiation therapy that occurs in approximately 25% of patients, and that it was not predictive of brachial plexus fibrosis (20).

Radiation Skin Changes Radiation skin changes were noted in approximately one-third of the patients with radiation injury, but these changes were not predictive of an underlying plexopathy (3).

Uncommon Osteoradionecrosis of the ribs and, rarely, of the humeral head can be noted on plain radiographs (21). Horner's syndrome is occasionally present (4,18).

Radiobiology and Dose Fractionation Considerations

Tumors and normal tissues differ in their sensitivities to radiation therapy. The therapeutic ratio of radiation therapy, which represents the balance between maximizing tumor control versus minimizing normal tissue complication, is affected not only by the total radiation dose, but also by the fraction size or dose per fraction, overall treatment time, and volume of normal tissue exposure. Radiobiological models based on cell culture experiments and clinical studies have been developed to describe the sensitivities of tumor and normal tissues to different fractionation schedules (22). The most widely used model is the

linear-quadratic equation, in which the Biological Effective Dose (BED) = Total Dose (TD) × (1 + Dose per Fraction/α/β ratio). This model, which assumes dual mechanisms for cell kill resulting in nonrepairable (α) and repairable (β) damage, predicts that the biological effect of radiation will be directly proportional to the total dose and dose per fraction (22,23). In the evaluation of different dose fractionation regimens, this equation can be used to calculate the biological effective dose and determine the isoeffective dose in tumors and normal tissues with similar kinetics.

Much of the data reporting high rates of radiation-induced brachial plexopathy in patients with breast cancer were from older eras that used techniques that result in field overlap, equipment such as orthovoltage and Cobalt units, and dosing schedules that would be considered suboptimal by modern standards.

The most commonly used fractionation schedules in North America for adjuvant radiation therapy for breast cancer deliver 1.8 to 2 Gy per fraction, 5 days a week to total dose of 45 to 50 Gy over 5 weeks. The risk of brachial plexopathy associated with conventional fractionation nodal irradiation using 2 Gy per fraction delivering a biological effective dose of 50 Gy or less to the plexus is approximately 1% (11,24). In a series of 1,624 patients treated with breast conserving surgery and adjuvant radiation therapy with a median follow-up time of 79 months, Pierce et al. reported that nodal radiation therapy, chemotherapy use, and total radiation dose to the axilla were factors significantly associated with the development of brachial plexopathy. Among patients treated with nodal irradiation, the incidence of brachial plexopathy was 1.3% with total doses of 50 Gy or less to the axilla, compared to 5.6% with total doses greater than 50 Gy (11). In a study with 449 patients treated with postoperative radiation therapy to the breast and lymph nodes who were followed for 3 to 5.5 years, Powell et al. reported that the incidence of brachial plexopathy was 5.6% in 338 patients who received 45 Gy in 15 fractions (dose per fraction 3 Gy, BED 56 Gy in 2 Gy fractions) and 1% in 111 patients who received 54 Gy in 27 to 30 fractions (dose per fraction 1.8 Gy, BED 51 Gy in 2 Gy fractions) (24). Although the difference was not statistically significant (p = .09), the observation of a higher risk of brachial plexopathy in association with the use of both a higher dose per fraction and a higher biological effective dose is in keeping with radiobiological principles described by the linear-quadratic model.

The last decade has witnessed renewed interest and debates regarding the safety and efficacy of altered fractionation regimens, in particular hypofractionation or the delivery of a higher dose per fraction and smaller number of total fractions. Radiobiological modeling suggests that if the α/β ratio of a tumor is similar or less than that of the critical normal tissue, then hypofractionation with a concomitant reduction in total dose may confer similar tumor control and normal tissue effects compared to conventional fractionation (25). Hypofractionation is supported by data from randomized controlled trials compared to conventional fractionation radiation therapy in women with early breast cancer (26–29). In the Standardization of Breast Radiotherapy (START) B trial from the United Kingdom, 2,215 women with early-stage breast cancer were randomized between 1999 and 2001 after primary surgery to radiation therapy 50 Gy in 25 fractions with 2 Gy per fraction over 5 weeks versus 40 Gy in 15 fractions using 2.67 Gy per fraction over 3 weeks. Regional nodal radiation was delivered in 7% of enrolled subjects (29). Brachial plexopathy was prospectively evaluated and was reported if damage to the brachial plexus was suspected and the patient had symptoms of pain, paresthesia, numbness, or other sensory symptoms graded on a 4-point scale. Suspected cases of brachial plexopathy were subject to confirmation by neurophysiological assessment and MRI. At a median follow-up of 6 years, locoregional control was equivalent, and there were no cases of brachial plexopathy in 82 women who received 40 Gy in 15 fractions or in 79 women who received conventional fractionation 50 Gy in 25 fractions to the regional nodes (29).

Older studies using a large dose per fraction (greater than 3 Gy) without adequate reductions in the total dose have resulted in high rates of brachial plexopathy (5%–70%). In a review of the literature evaluating brachial plexus injury with different hypofractionated radiation schedules, Galecki et al. reported that the risk of brachial plexopathy was less than 1% with regimens using dose per fraction between 2.2 and 2.5 Gy with reductions in total dose to 34 to 40 Gy to ensure that the biological effective dose to the brachial plexus is less than 50 Gy in 2 Gy fractions. In contrast, even when the dose per fraction was lower (between 2 and 2.17 Gy), but the total dose was not reduced, yielding biological effective doses greater than 55 Gy, the risk of brachial plexopathy increased steeply from 2% to 15% (7). These findings suggest that the hypofractionated nodal radiation regimen used in this trial is associated with low risks of brachial plexopathy; however, larger patient samples receiving regional nodal irradiation and using longer follow-up times are essential to fully assess this risk.

Advances in Radiation Therapy Planning and Delivery

In contemporary practice, the goal of safe and effective implementation of nodal irradiation in women with high risk breast cancer has been advanced by technological innovations in radiation therapy planning and delivery. Overlaps between breast or chest wall fields with the supraclavicular and/or axillary fields can be readily avoided with isocentric techniques. Optimizing dose homogeneity and reducing hot spots and brachial plexus exposure can be achieved with tools including image-based 3D-conformal radiation therapy planning, multileaf collimation, mixed megavoltage beam energies, intensity-modulated radiation therapy, and rigorous adherence to normal tissue dose-volume constraints. Standardized methods to delineate the brachial plexus in image-based radiation therapy planning have been developed and validated (30). Computer-assisted image segmentation methods to allow rapid and accurate identification of the brachial plexus are now available (31). Guidelines in data collection and reporting on radiation dose-volume parameters and clinical outcomes have also been formulated (32). These resources will be useful in the design of future prospective trials examining the risk of radiation-induced brachial plexopathy in women with breast cancer.

POSTAXILLARY DISSECTION NEUROPATHIC PAIN (POSTMASTECTOMY SYNDROME)

Prevalence

Chronic neuropathic pain of variable severity is a common sequela of surgery for breast cancer. Although chronic pain has been reported to occur after almost any surgical procedure on the breast from lumpectomy to radical mastectomy, it is most common after procedures involving axillary dissection, occurring in 25% to 70% of patients (33–35,36).

The risk for, and severity of, pain is correlated positively with the number of lymph nodes removed (36) and the presence of tumor in the upper outer quadrant of the breast (35) and is inversely correlated with age (36). There is conflicting data as to whether preservation of the intercostobrachial nerve during axillary lymph node dissection can reduce the incidence of this phenomenon (37).

The incidence is reduced, but not avoided, when axillary dissection is avoided either by sentinel node excision without full dissection (36) or when nodes are irradiated without dissection (38).

Clinical Features

The pain is usually characterized as a constricting and burning discomfort localized to the medial arm, axilla, and anterior chest wall. Pain may begin immediately or as late as many months following surgery. The natural history of this condition appears to be variable, and both subacute and chronic courses are possible (39). The onset of pain later than 18 months following surgery is unusual, warranting careful evaluation to exclude recurrent disease. On examination, there is often an area of numbness within the region of the pain. Chronicity of pain is related to the intensity of the immediate postoperative pain (40), postoperative complications, and subsequent treatment with chemotherapy and radiotherapy (41).

Etiology

It is most commonly associated with neuropraxia of the intercostobrachial nerve during the process of axillary lymph node dissection (42,43). There is marked anatomic variation in the size and distribution of the intercostobrachial nerve, and this may account for some of the variability in the distribution of pain observed in patients with this condition (44).

Differential Diagnosis

This syndrome must be differentiated from postmastectomy phantom breast pain (45), neuroma pain (46), postmastectomy frozen shoulder (47), axillary web syndrome (48), and breast cellulitis (49). In some cases of pain after breast surgery, a trigger point can be palpated in the axilla or chest wall.

OTHER CAUSES OF BRACHIAL PLEXOPATHY AND NEUROPATHIC ARM PAIN

Second Malignant Primaries

Uncommonly, a malignant peripheral nerve tumor or a second primary tumor in a previously irradiated site can account for pain recurring late in the patient's course (50). Primary tumors of the brachial plexus are uncommon (51), and nerve sheath tumors that occur years after radiation therapy are generally thought to be a late effect of radiation therapy (52). This condition must be differentiated from recurrence of breast cancer, which may also occur in a plexus previously damaged by radiation fibrosis (53).

Carpal Tunnel Syndrome

Among patients with a past medical history of breast cancer who were referred for evaluation of arm pain, 4 of 30 were found to have carpal tunnel syndrome (4). Although electrophysiological abnormalities that are consistent with carpal tunnel syndrome occur twice as frequently ipsilateral to the resection among women who have undergone mastectomy (54), it is an infrequent cause of arm pain in this population, and the diagnosis requires demonstration of a prolonged sensory latency that is greater than that recorded for the radial and ulnar nerves (55,56).

Lymphedematous Brachial Plexus Compression

Some authors have suggested that lymphedema alone can produce a compression injury of the brachial plexus (4,54). Ganel et al. performed a series of electromyographic studies on women who had undergone mastectomies with or without subsequent radiation therapy. On the basis of an increased prevalence of "F" wave latency abnormalities ipsilateral to previous mastectomy in women with lymphedema, lymphedema was suggested to be the cause of an entrapment brachial plexopathy (54). Vecht inferred this diagnosis in one of 28 patients evaluated for arm pain on the basis of negative imaging studies and a nonprogressive neurological deficit in a patient with lymphedema (4). In the absence of demonstrable reversibility of the neurologic deficit with effective management of the lymphedema or surgical evaluation of the plexus to exclude recurrent tumor or radiation fibrosis, this diagnosis should be approached with clinical skepticism.

Pathologic Fracture of the Humerus

Pathological fractures or fracture dislocations of the humerus may traumatize adjacent nerves of the infraclavicular plexus (57). Fractures or dislocations of the neck of the humerus may cause axillary nerve compression, whereas midshaft fractures, which are less common, may damage the radial or ulnar terminal nerves.

DIAGNOSTIC INVESTIGATIONS

There are many potential causes of plexopathy in cancer patients, the most common of which are tumor infiltration and radiation fibrosis. In patients with symptoms suggestive of plexopathy with a history of previous radiotherapy, it is critical to distinguish between tumor infiltration and radiation-induced fibrosis. When radiological findings are nondiagnostic, electrophysiological studies may assist in making the distinction.

Cross-sectional imaging is essential in all patients with symptoms or signs compatible with plexopathy. Both MRI and CT scanning are commonly used in these settings.

Magnetic Resonance Imaging (MRI)

Although there are few comparative data on the sensitivity and specificity of MRI to CT in evaluating lesions of the brachial plexus, MRI is widely thought to be the best choice for evaluating the anatomy and pathology of the brachial plexus (58). MRI is a noninvasive procedure that can assess the integrity of the vertebral bodies and may differentiate tumor from radiation fibrosis as well as fully visualize the adjacent epidural space. Additional advantages include its superior soft-tissue resolution and the ability to readily reconstruct images in multiple planes.

As illustrated in Figure 79-1A and B, T1-weighted images best define the relationship of tumor to the surrounding structures. Both tumor and radiation fibrosis generate intense images. The most common findings observed with radiation fibrosis are thickening and diffuse enhancement of the brachial plexus without a focal mass and/or soft-tissue changes with low signal intensity on both T1- and T2-weighted images, with or without enhancement of

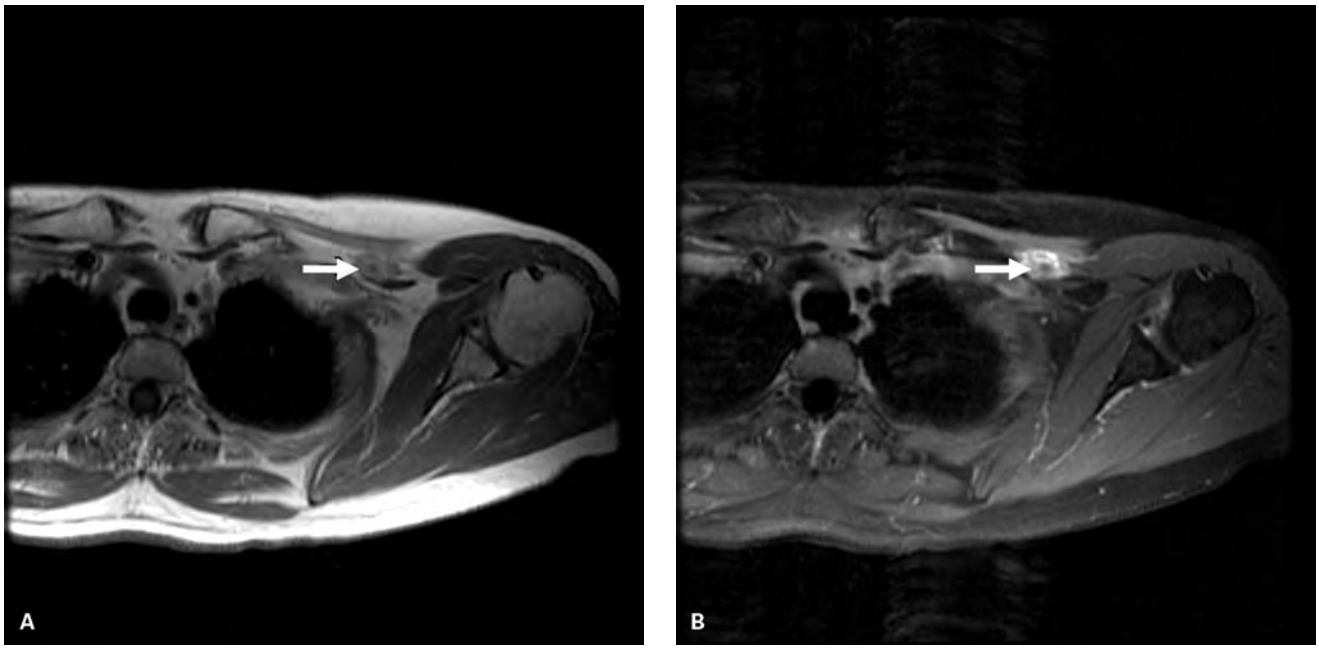

FIGURE 79-1 **(A)** Pre-contrast T1 MRI image of a brachial plexus tumor (*arrow*). **(B)** Post-gadolinium contrast T1 MRI image of a brachial plexus tumor (*arrow*).

multiple plexus elements (58). A prospective study using MRI for detection of malignant brachial plexopathy yielded a sensitivity of 96%, specificity of 95%, positive predictive value of 96%, and negative predictive value of 95% (59).

Because patients with brachial plexus lesions are at high risk for developing epidural cord compression from direct tumor infiltration along the plexus into the epidural space or from hematogenous spread of tumor to the vertebral body (3), imaging should include the adjacent epidural space. Imaging of the epidural space is essential if spinal cord compression is suspected and in the evaluation of patients who have any of the clinical findings that are commonly associated with this complication, including panplexopathy, Horner's syndrome, vertebral body erosion or collapse at the C7-T1 levels, or a paraspinal mass detected on CT scanning. Accurate imaging with MRI determines the extent of epidural encroachment (which influences prognosis and may alter the therapeutic approach) and defines the appropriate radiation target volumes.

Computed Tomography (CT) Scan

Recent years have witnessed tremendous improvements in the techniques of CT imaging, which have enhanced the value of this modality in imaging of the brachial plexus. Modern spiral CT enables simultaneous x-ray source rotation and patient table translation as well as retrospective multiplanar and three-dimensional reconstruction. In many cases, these approaches are very helpful, particularly in the identification of mass lesions in the plexus and adjacent infiltration of the neural foramina. Modern CT imaging is often a very useful initial modality, particularly in situations when MRI is not readily available.

CT scanning techniques to image the brachial plexus should include both bone and soft-tissue windows and should be contrast enhanced to give clear definition of vascular structures. Adequate imaging requires scanning from C4 to T6 vertebral bodies using a large gantry aperture to include both axillary fossae so that the symptomatic plexus may be compared with the normal contralateral side. Vascular enhancement allows for identification of vascular structures that relate to the plexus. Because a high concentration of contrast can produce a streaking artifact, some experts recommend that intravenous contrast should be administered contralateral to the suspected lesion. The elements of the brachial plexus are depicted as nodular or linear areas of soft-tissue density that can be difficult to identify.

The typical appearance of radiation fibrosis of the plexus on CT studies is a diffuse infiltration and loss of tissue planes without a mass lesion. There is often associated arm lymphedema, evident on CT, and, occasionally, radiation necrosis of the clavicle, rib, or humeral head may be identified at the adjacent level (21). Tumor infiltration of the plexus cannot be differentiated from radiation fibrosis by CT studies when diffuse infiltration is noted. In such cases MRI, PET/CT, or image-guided biopsy of the brachial plexus mass should be considered.

Positron Emission Tomography (PET) Scanning

Compared to conventional imaging techniques, PET and PET/CT scanning have both greater sensitivity and specificity in detecting metastases from breast cancer (60). As illustrated in Figure 79-2, the fused ^{18}F-fluorodeoxyglucose (FDG)-PET and CT images give two pieces of critical information within a single study: the extent of viable tumor and its exact location. Because it provides biological and functional information, FDG-PET often is complementary to CT or MR. This is particularly true when trying to differentiate between radiation fibrosis and recurrent tumor.

Despite these generalizations, published information specific to the detection of brachial plexopathy is remarkably limited (61–63). In a study of 19 patients with symptoms suggestive of brachial plexopathy, 14 had abnormal uptake of ^{18}FDG in the region of the symptomatic plexus. Of those with abnormal findings in the plexus, only 33% had a lesion identifiable on CT imaging (63).

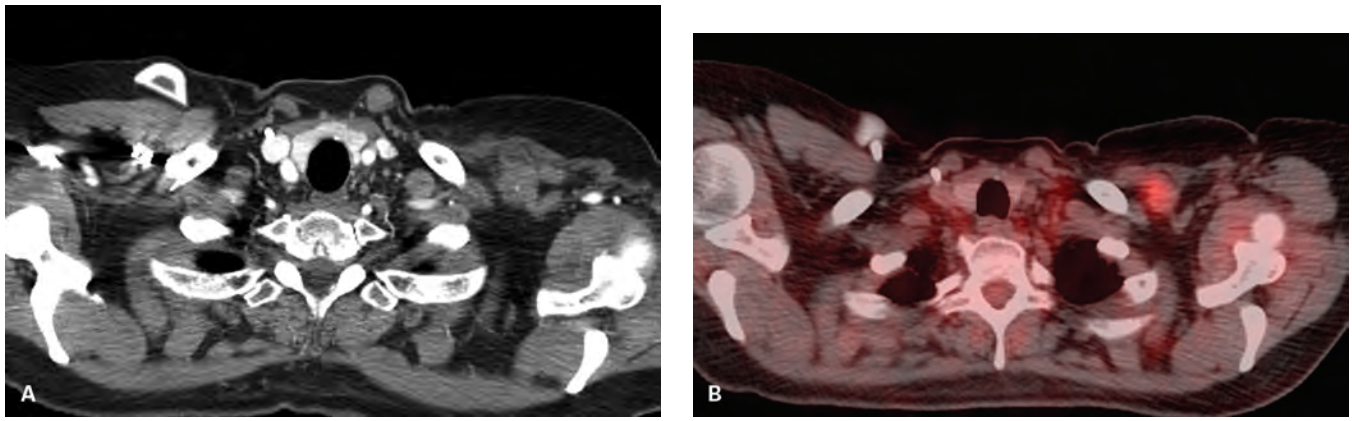

FIGURE 79-2 **(A)** image of right brachial plexus tumor infiltration. **(B)** Overlay PET/CT scan of right brachial plexus tumor.

Electrophysiologic Studies

Electrophysiologic studies may be useful in distinguishing tumor infiltration from radiation fibrosis (64). Electrodiagnostic studies in patients with radiation fibrosis typically include widespread infraclavicular demyelinating conduction blocks on motor nerve conduction studies and myokymic discharges and fasciculation potentials on needle electrode examination. Widespread myokymia is strongly suggestive of radiation-induced plexopathy.

In malignant plexopathy, electromyography (EMG) typically reveals fibrillation potentials and positive waves characteristic of denervation in the distribution of the brachial plexus that is consistent with plexus signs and symptoms. A normal EMG in the cervical paraspinal muscles is usually adequate to exclude the presence of root disease. In the rare instances that myokymia is observed in patients with tumor infiltration of the brachial plexus, it is localized and may be isolated to one muscle group alone (65); this contrasts with the widespread myokymic discharges seen in radiation-induced plexopathy.

Surgical Exploration

The differential diagnosis of tumor infiltration from radiation injury to the plexus may be made in the majority of cases using the clinical criteria, imaging, and electrophysiologic studies. However, if these diagnostic approaches fail to define the nature of the neurologic disorder, exploration of the plexus may occasionally be diagnostic (66). In additional to traditional open exploration, minimally invasive laparoscopic methods have been developed and described (67). Such exploration should be undertaken only under the following circumstances:

1. The CT, MRI, and PET scans are normal or show no evidence of change from before the onset of symptoms.
2. A work-up, including tumor markers establishing the full extent of disease, has been completed and shows no evidence of diffuse metastatic disease.
3. The site of neurologic involvement is certain (for example, a lesion that can be localized to either the upper or lower plexus). This factor is important in determining the appropriate surgical approach. Upper plexus dysfunction may best be assessed through a supraclavicular approach, whereas involvement of the lower plexus is best assessed through a posterior scapular approach or a high posterior thoracotomy, commonly used to explore apical tumors of the lung (68).

TREATMENT OF BRACHIAL PLEXOPATHY IN BREAST CANCER

The care of patients with brachial plexopathy requires an integrated approach involving primary therapy appropriate to the specific cancer diagnosis along with symptomatic pain management.

Primary Therapies

Treatment of Radiation Fibrosis

The management of patients with radiation fibrosis begins with the establishment of an accurate diagnosis to rule out metastatic disease. There are no proven methods to reverse neurologic damage. Splinting the arm at the chest wall, preventing subluxation of the shoulder joint, and using intensive physical therapy to manage lymphedema are common approaches to managing the musculoskeletal pain syndromes associated with this disorder.

Evidence-based treatments other than symptomatic care are lacking. There is some data that antioxidant therapy with a combination of pentoxifylline and vitamin E may partially reverse radiation fibrosis, particularly when treatment is started soon after the initial radiation insult (69). No specific experience has been reported using this approach in radiation-induced plexopathy. Hyperbaric oxygen therapy has been suggested to reduce radiation damage. However, a double-blinded randomized trial of hyperbaric oxygen therapy did not yield substantial relief in patients with radiation-induced brachial plexopathy (70). Finally, some authors have suggested the use of neurolysis with pedicle omentoplasty to treat radiation fibrosis (71). Anecdotal data suggests that this procedure frequently results in reduced pain and that progression of neurologic deficit can be arrested in some cases (71). In the largest series, Le-Quang reported on 60 patients followed from 2 to 9 years and advocated early surgery as soon as possible after the onset of paresthesias (71). Surgical exploration of the brachial plexus is difficult and may risk iatrogenic injury to the nerve, leading to worsening pain syndrome.

Treatment of Tumor Infiltration

The treatment of tumor infiltration of the brachial plexus depends on the status of the patient's disease, the extent of neurologic involvement, and any prior history of radiation therapy to the brachial plexus. There is compelling clinical evidence to suggest that steroids provide pain relief in patients with tumor infiltration of the brachial plexus, and they are often used to provide analgesia during therapy (72).

Antitumor therapy with either systemic therapy (chemotherapy or hormonal therapy) or radiation therapy may provide tumor shrinkage with symptomatic improvement (73). Radiation therapy is the treatment of choice for patients with rapidly progressive neurologic signs, patients unresponse to systemic treatment, or patients with epidural spinal cord compression. High-quality CT and MRI should be used to define the target volume in these cases. The dose of radiation therapy employed varies. In the reported series, a dose of 30 Gy delivered over a 3-week period or 50 Gy delivered over a period of 5 weeks represents the most commonly used dose ranges (3,9,74,75).

There is conflicting data about the likelihood of benefit from palliative radiotherapy for malignant brachial plexopathy in breast cancer. In a review of the published experience and his own experience, Ampil reported that the total delivered dose, rather than the width of the therapy port, was the most important factor in achieving optimal symptomatic palliation (75). In his series of 23 patients, significant pain relief was achieved in 77.2% of patients for a median of 3 months; the observed objective response rate was 46%. In another series, Nisce and Chu reported that 12 of 47 patients (25.5%) with metastatic brachial plexopathy and breast cancer had complete pain relief for a mean duration of 15 months, and 23 (49%) had partial pain relief for a mean duration of 6 months (76). These researchers suggested that higher radiation doses (50 Gy) were more effective than lower doses. In Kori's retrospective review, radiation doses of 20 to 50 Gy delivered to the plexus relieved pain in 46% of cases (3). Neurologic improvement was minimal, and persistent, chronic pain was the most significant problem. In Fulton's experience with 44 breast cancer patients with definite (n = 31) or probable (n = 13) brachial plexopathy, 9 of the 17 patients treated with radiation therapy improved (8).

In patients with tumor infiltration of the brachial plexus with evidence of metastatic disease in other sites, systemic chemotherapy is a reasonable approach. In patients who have received previous radiation therapy to the region, systemic therapies with either cytotoxic or hormonal agents may offer the only reasonable antitumor treatment. Chemotherapy or hormonal therapy may provide sustained relief from malignant brachial plexopathy in responding patients (73). Since most responses are partial and subsequently followed by relapse, pain often returns when disease recurs. Indeed, worsening pain is often the earliest indicator of recurrence or progression.

THE MANAGEMENT OF PAIN ASSOCIATED WITH BRACHIAL PLEXOPATHY

Analgesic Pharmacotherapy

Primary antitumor therapies should be considered for patients with tumor invasion of the brachial plexus. All patients with pain should initially be treated with analgesic pharmacotherapy in accordance with the World Health Organization (WHO) three-step analgesic ladder (77).

Opioids in the Management of Brachial Plexus Pain

A trial of opioid therapy should be administered to all patients with pain of moderate or greater severity, irrespective of the pathophysiological mechanism underlying the pain. Patients who present with severe pain are usually treated with a pure agonist opioid. Until recently, patients with moderate pain have been conventionally treated with a combination product containing acetaminophen or aspirin plus codeine, dihydrocodeine, hydrocodone, oxycodone, and propoxyphene. Recent years have witnessed the proliferation of new opioid formulations that may improve the convenience of drug administration for patients with moderate pain. These include controlled-release formulations of codeine, dihydrocodeine, oxycodone, morphine, and tramadol in dosages appropriate for moderate pain. Opioid analgesics should be used in accordance with usual standards of practice (78). The persistence of inadequate pain relief should be addressed through a stepwise escalation of the opioid dose until adequate analgesia is reported or unmanageable side effects supervene. The severity of the pain should determine the rate of dose titration. An understanding of the strategies used to prevent or manage common opioid toxicities is needed to optimize the balance between analgesia and side effects.

Adjuvant Analgesics

Even with optimal management of adverse effects, some patients do not attain an acceptable balance between pain relief and side effects. Several types of noninvasive interventions including adjuvant analgesics, a switch to another opioid, and the use of psychological, physiatric, or noninvasive neurostimulatory techniques should be considered for their potential to improve this balance by reducing the opioid requirement. Adjuvant analgesics are drugs that have a primary indication other than pain but have analgesic effects in some painful conditions. The use of adjuvant analgesics can contribute substantially to the successful management of pain caused by brachial plexopathy.

Corticosteroids

Corticosteroids are frequently used in the management of neuropathic pain due to infiltration or compression of neural structures by tumor. Patients with advanced cancer who experience pain and other symptoms that may respond to steroids are usually given relatively small doses (e.g., dexamethasone 1–2 mg twice daily). A very short course of relatively high doses (e.g., dexamethasone 100 mg I.V. followed initially by 96 mg per day in divided doses) can be used to manage a severe exacerbation of pain associated with malignant brachial plexopathy (72). The dose should be gradually lowered following pain reduction to the minimum needed to sustain relief.

Centrally Acting Adjuvant Analgesics Used for Neuropathic Pain

Neuropathic pain is generally less responsive to opioid therapy than nociceptive pain, and, in many cases, the outcome of pharmacotherapy may be improved by the addition of a centrally acting adjuvant analgesic. This subject has been recently reviewed by the neuropathic pain working group of the International Association for the Study of Pain (79). Several antidepressants and calcium channel $\alpha 2\text{-}\delta$ ligands are included in their list of first-line medications.

Antidepressant drugs are commonly used to manage neuropathic pain, and the evidence for analgesic efficacy is greatest for the tertiary amine tricyclic drugs such as amitriptyline, doxepin, and imipramine. The secondary amine tricyclic antidepressants (such as desipramine, clomipramine, and nortriptyline) have fewer side effects and are preferred when concern about sedation, anticholinergic effects, or cardiovascular toxicity is high. Duloxetine, a selective serotonin and norepinephrine reuptake inhibitor (SSNRI), has demonstrated potential efficacy in neuropathic pain. It is generally well tolerated, and dosing is simple, starting at 30 mg/day

and titrated after 1 week to 60 mg/day. The potential efficacy of venlafaxine, another SSNRI, has also been demonstrated at dosages of 150 to 225 mg/day.

Gabapentin and pregabalin both bind to the α2-δ subunit of voltage-gated calcium channels, decreasing the release of glutamate, norepinephrine, and substance P. Gabapentin is generally well tolerated, and the main adverse effects are somnolence and dizziness. Several weeks can be required to reach an effective dosage, which is usually between 1,800 and 3,600 mg/day (administered in three divided doses). When it is effective, pain relief may be seen as early as the second week of therapy, but peak effect usually occurs approximately 2 weeks after a therapeutic dosage is achieved. Pregabalin produces dose-dependent side effects similar to those of gabapentin. Treatment can be initiated at 75 mg twice daily and can be titrated up to 300 mg twice daily. The onset of pain relief with pregabalin can be more rapid than with gabapentin.

The so-called second-line adjuvant analgesics all have less evidence of potential efficacy. Second-line anticonvulsants include carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproic acid. Second-line antidepressant medications include bupropion, citalopram, and paroxetine. Other agents that may be considered in this setting include mexiletine and baclofen.

Anesthetic and Neurosurgical Techniques

Invasive anesthetic and neurosurgical techniques should only be considered for patients who are unable to achieve a satisfactory balance between analgesia and side effects from systemic analgesic therapies. Techniques such as intraspinal opioid and local anesthetic administration (80), locoregional infusion of local anesthetic (81), intrapleural local anesthetic (82), or intraventricular opioid administration (83) can potentially achieve this end without compromising neurological integrity. The use of neurodestructive procedures such as brachial plexus neurolysis (84); chemical, surgical, or radiofrequency rhizotomy (85); or dorsal root entry zone (DREZ) lesioning (86) should be based on an evaluation of the likelihood and duration of analgesic benefit, the immediate and long-term risks, the likely duration of survival, and the anticipated length of hospitalization.

Rarely, patients have been treated with a forequarter amputation of the limb for relief of the discomfort of a lymphedematous, functionless arm. This extreme approach is often not successful in providing significant pain relief but does improve patient complaints of a heavy lymphedematous useless extremity.

MANAGEMENT SUMMARY

- Early diagnosis of tumor infiltration of the brachial plexus is important to institute prompt cancer therapy and prevent the development of chronic neuropathic pain and neurological dysfunction.
- Evaluation consists of a careful history, a detailed neurological examination, and MRI or CT imaging. Electrodiagnostic studies should be performed if the radiographic studies are negative for both soft-tissue and bony disease. An evaluation to assess for evidence of metastatic disease should follow, and, if negative, surgical exploration should be considered to allow for biopsy of adjacent lymph nodes and soft tissue.
- In patients presenting with brachial plexopathy after previous radiation therapy, the history and physical findings and follow-up on CT and MRI may be helpful to distinguish tumor recurrence from radiation fibrosis but none of these may be definitive. When uncertainty remains, biopsy should be considered to provide tissue confirmation to guide the treatment decision (e.g., in a patient with progressive symptoms of brachial plexopathy but without other evidence of distant metastases in whom documentation of recurrent disease will result in a decision to initiate anticancer treatment).
- Radiobiological modeling and clinical data suggest that the risk of brachial plexopathy may be kept acceptably low (<1%) by not exceeding a biologically effective dose (BED) of 50 Gy in 2 Gy fractions. Hypofractionation regimens using a modestly increased dose per fraction with concomitant reductions also have low likelihood of brachial plexopathy. Hypofractionation using a high dose per fraction (greater than 3 Gy) without appropriate reductions in total dose should be avoided.
- Prospective studies are needed to establish the risk of brachial plexopathy in women with breast cancer treated in the contemporary era of sentinel node staging, adjuvant chemotherapy, image-based radiation treatment planning, and altered fractionation schedules.

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CHAPTER 80

Ophthalmic Metastases

Christopher A. Barker, Beryl McCormick, and David H. Abramson

CHAPTER CONTENTS

Ophthalmic metastases refer to secondary malignant neoplasms occurring in or around the eye. The uvea is the highly vascular middle layer of the eye and the most frequent site of metastasis. The choroid comprises the majority of the uvea and is the predominant location for uveal metastasis. Less frequently, metastases can arise in other parts of the uvea (ciliary body and iris), as well as extraocular structures (bones and soft tissues of the orbit, eyelids, extraocular muscles, and optic nerve). Importantly, metastases in any of these locations can dramatically affect vision. The contribution of vision to quality of life is significant; therefore, ophthalmic metastases can be a disabling sequela of breast cancer. This chapter presents concepts related to the epidemiology, biology, diagnosis, management, and outcome of ophthalmic metastases in patients with breast cancer.

EPIDEMIOLOGY

The true prevalence of ophthalmic metastases from breast cancer has been difficult to precisely determine, but necropsy and clinical series have provided estimates. Studies performed in the 1970s suggested that 10% to 37% of patients dying with, or of, metastatic breast cancer harbored orbital and/or ocular metastases on post mortem histologic examination (1,2). However, a similarly designed study from a more recent era suggest 0% to 8% of patients harbor ocular metastases (3). Many have suggested that improvements in systemic therapy have led to a decreased prevalence of ophthalmic metastasis. These studies have clearly demonstrated that breast cancer metastasizes to the eye more frequently than other carcinomas.

Because of the prevalence of ophthalmic metastases noted in necropsy studies, several prospective screening studies have been carried out in visually asymptomatic patients with contemporary ophthalmic assessment methods (visual acuity assessment, slit-lamp examination, indirect ophthalmoscopy, with or without ultrasonography, see Table 80-1). Two of the studies were unable to identify any patients with ocular metastases, and concluded that screening was not worthwhile (4,5). Another study found choroid metastases in 5% of screened patients (6). Of note, the latter study involved a younger group of patients with greater burden of disease and took place in an earlier time period than the former studies. The prevalence of ophthalmic metastases among patients with vision problems is likely higher than asymptomatic patients. One study reported that of 152 metastatic breast cancer patients with ophthalmic symptoms or signs, 58 (38%) were found to harbor choroid metastasis (7).

Risk factors for the development of ophthalmic metastases are ill-defined. Some studies suggest that early age at initial diagnosis of breast cancer may be associated with higher risk (8). Others have noted a higher risk of ophthalmic metastasis in patients with greater disease burden (having metastasis in more than one organ, or the presence of brain or lung metastasis, but not liver or bone metastasis), but not initial tumor stage or presence of estrogen receptor on the primary tumor (6). Gender does not appear protective as men with breast cancer have been reported to develop ophthalmic metastasis.

BIOLOGY

The reason that breast carcinoma has a predilection to metastasize to the eye is unknown. Researchers investigated a small group of patients with ocular metastases from breast cancer, and found no clear aggregation of breast cancer in the family of affected patients, or any associations with common *BRCA1* or *BRCA2* gene mutations. However, the investigators noted that most women with ocular metastases were younger than 51 years at the time of initial diagnosis, suggesting an as of yet unidentified genetic relationship (8). The association of specific genetic aberrations and organ metastases from breast cancer has been described previously, and may explain the predilection (9).

Using animal models, investigators have reported that more than 50% of mice receiving an intracardiac injection of the r3T breast cancer cell line develop choroidal metastases. Pigmented abnormalities in the brain of mice with choroid metastases were frequently noted, suggesting a common mechanism in the development of brain and choroid

TABLE 80.1

Contemporary Prospective Ophthalmic Metastasis Screening Studies of Metastatic Breast Cancer Patients without Visual Symptoms

					Ophthalmic Metastases		*Extra-Ophthalmic Metastases*		
Study Origin	*Time Period*	*Patients Screened (n)*	*Diagnosis to Screening (Years)*	*Patient Age (Years)*	*Choroid (n [%])*	*Orbit (n [%])*	*1 organ (n [%])*	*>1 organ (n [%])*	*Frequency*
Germany	1995–1997	120	mean N/R median = 3.6	mean N/R median = 55	6 [5%]—5 unilateral; -1 bilateral	0 [0%]	68 [57%]	52 [43%]	Bone [79%] Lung [23%] Liver [22%] Other [22%] Brain [15%]
United Kingdom	January 2001–June 2001	68	mean = 6.3 median = 5	mean = 60 median = 62	0 [0%]	1 [2%]	31 [46%]	37 [54%]	Bone [54%] Lung [29%] Soft tissue [27%] Liver [21%] Brain [4%]
Israel	January 2002–December 2003	77	mean = 5.7 median N/R	mean = 62 median N/R	0 [0%]	N/R	64 [83%]	13 [17%]	Bone [most] Soft tissue [2nd most] Lung [3rd most] Liver [4th most] Brain [least]

N/R, not reported.

metastases. Moreover, in mice with choroid metastases, metastasis in the bone and lung metastases were observed in 71% and 92% of the animals. However, only 29% of the mice with choroid metastasis harbored liver metastasis. Animals with bone metastasis were not significantly more likely to harbor choroid metastasis. It was hypothesized that CXCR4 expression on r3T cells might explain the predilection for choroidal metastases, but this was not supported by experimental data (10).

DIAGNOSIS

Most patients diagnosed with ophthalmic metastases present with symptoms and signs listed in Table 80-2. In a study of 264 patients evaluated at a single ophthalmic oncology center for uveal metastases from breast cancer, the most frequently noted symptoms were blurred vision (88%), floaters (5%), and photopsia (5%) (11). These or other unexplained problems listed in Table 80-2 should prompt referral to an ophthalmologist for further evaluation.

Ophthalmic evaluation should include indirect ophthalmoscopy with photography (Fig. 80-1). Common features of choroid metastasis from breast cancer include: yellow color (99%), plateau configuration (77%), lack of retinal exudate (97%) or hemorrhage (98%), and presence of subretinal fluid (64%). Uveal metastasis is bilateral in 38% of patients, unilateral in 62%, and multifocal in 48% (11). Pain is a feature of metastasis, which is rare in primary eye tumors. Ophthalmic ultrasonography may be a helpful diagnostic adjunct to detect the metastatic tumor if secondary exudative retinal detachment is present. Uveal metastases typically demonstrate thickened, dome-shaped choroid lesions with moderately high internal acoustic reflectivity. Fluorescein angiography may be a useful diagnostic adjunct and typically demonstrates early hypofluorescence and diffuse late staining in uveal metastases. Biopsy by fine needle aspiration is rarely required by experienced clinicians because of the characteristic appearance, and can be complicated by hemorrhage, tumor seeding, and vision loss.

Extraocular metastases in the orbit may lead to ptosis, proptosis, enophthalmos, heterotropia, or diplopia (Fig. 80-2). Palpation of the orbit may reveal a mass or indurated periorbital skin and orbital firmness with resistance to retropulsion of globe. For suspected orbital metastases in the bones, computed tomography of the orbits is recommended. Contrast-enhanced magnetic resonance imaging is superior for the evaluation of soft tissue abnormalities.

Most uveal metastases can be identified with ophthalmic assessments without sophisticated imaging. However, a prospective study of patients with choroidal metastases revealed that 26% of patients harbored asymptomatic brain metastases on contrast enhanced CT of the brain (12). MRI of the brain is the most sensitive diagnostic test for brain

TABLE 80.2

Symptoms and Signs of Ophthalmic Metastases

Site	*Symptoms*	*Signs*
Iris	Asymptomatic	Iris mass (usually superior)
	Blurred vision	Uveitis
		Glaucoma
		Pseudo-hypopyon
Ciliary body	Asymptomatic	Dome-shaped or sessile mass (usually inferior)
	Blurred vision	Uveitis
	Pain	Glaucoma
		Sectorial cataract
		Lens subluxation
		Shallow anterior chamber
Vitreous	Floaters	Vitretis
	Blurred vision	
Choroid	Asymptomatic	Yellow placoid lesions (usually superior and temporal)
	Blurred vision	Serous retinal detachment
	Metamorphopsia	Alteration of retinal pigment epithelium
	Pain	Choroidal detachment
	Diplopia (rare)	Glaucoma
Retinal	Blurred vision	Vitretis
	Floaters	Black infiltrative retinal mass with retinitis-like appearance
Optic disc	Asymptomatic	Diffuse or localized disc swelling
	Blurred vision	Disc hemorrhage
		Disc edema
Extraocular	Diplopia	Proptosis
		Enophthalmos
		Heterotropia
Cerebral	Field defects	Strabismus
	Hemineglect	Field loss
	Abnormal color vision	
	Blurred vision	
	Diplopia	

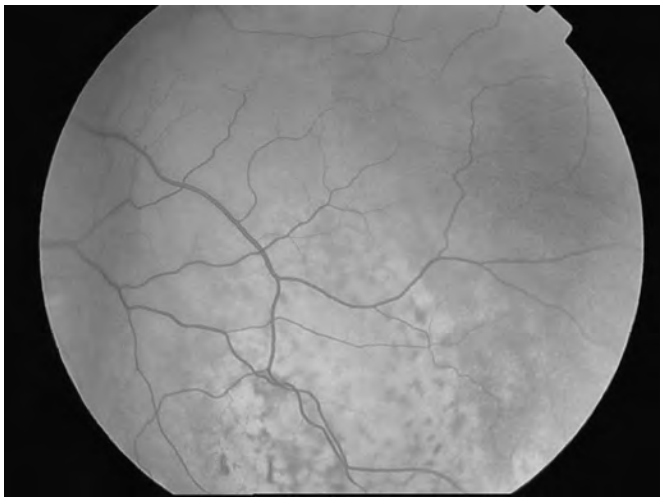

FIGURE 80-1 Ophthalmoscopic photograph of diffuse intraocular breast cancer metastases causing blurred vision.

metastasis and should be undertaken in any patient with newly diagnosed uveal metastasis because of the high likelihood of brain metastasis and implications for treatment planning. Systemic imaging should be considered for the patient with previously unrecognized metastases to characterize the extent of disease.

MANAGEMENT AND OUTCOME

The goal in managing ophthalmic metastasis is palliation. For patients that present without symptoms, careful observation can be considered. Otherwise, therapy to reduce vision impairment and alleviate pain should be undertaken. Therapy can be systemic and non-specific or local and targeted. The extent of disease and necessity for extra-ophthalmic treatment frequently guides the modality employed. Most data comes from retrospective clinical studies, with the notable exception of two prospective studies.

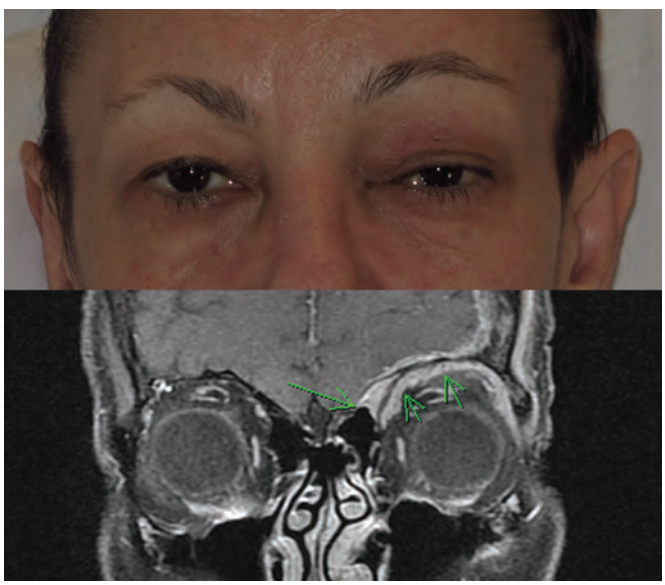

FIGURE 80-2 Clinical photograph and T1 contrast enhanced fat saturated magnetic resonance image of the orbits in the coronal plane demonstrating left superior orbital metastasis causing proptosis and diplopia.

Observation

In the largest series of patients with uveal metastases from breast cancer published, observation was employed in 18% of patients with choroid metastasis and 9% of patients with iris metastasis. Remarkably, regression during observation was noted in 50% of choroid metastases, but none of the iris metastases. Recurrence was noted in 9% of choroid metastases, and 50% of iris metastases (11). Appropriate selection of patients for this management strategy is challenging.

Systemic Therapy

Systemic therapy is often employed in the presence of extra-ophthalmic disease that is progressive or symptomatic. Hormonal therapy, cytotoxic chemotherapy, and biologic therapy have all been reported in small studies. In the largest series of patients with uveal metastases from breast cancer reported, 9% and 29% or 5% and 27% of patients with choroid or iris metastasis received hormone therapy or chemotherapy, respectively. Metastasis regression and stability was noted in 65% and 16% of patients with choroid metastasis and in 50% and 33% of patients with iris metastasis treated with hormone therapy or chemotherapy, respectively. Recurrence of the metastasis was noted in 11% and 17% of patients with choroid and iris metastasis treated with hormone therapy or chemotherapy, respectively (11).

Little data exists on the relative efficacy of different systemic therapeutics for ophthalmic metastases. Although it is likely that ophthalmic metastasis will respond to agents that specifically target the primary tumor phenotype, this has not been well documented. Hormone therapy generally has a slower time to response than chemotherapy, and, therefore, may not be a good initial therapy for patients with rapidly progressing symptoms. HESA-A is a novel compound that was reported to yield a 100% rate of vision improvement in a prospective double-blind placebo-controlled study of patients with choroid metastasis from breast cancer, the reported details of which are limited (13).

Radiation Therapy

Radiation therapy for ophthalmic metastasis is most commonly used with high-energy photon teletherapy (external beam), but proton teletherapy and brachytherapy are other effective treatment modalities. In the largest series of patients with uveal metastases from breast cancer reported, external beam radiation therapy was the most commonly used management strategy and given to 59% and 64% of patients with choroid and iris metastasis (11).

A single center prospective study (95-08) carried out by the Arbeitsgemeinschaft Radiologische Onkologie (ARO) of the German Cancer Society provides the best evidence regarding the safety and efficacy of external beam radiation therapy for choroid metastasis (14). In this study, 50 patients underwent treatment of 65 eyes with choroid metastasis between 1994 and 1998; the majority of the patients (n = 31, 62%) had metastatic breast cancer. All patients received 40 Gy in 20 fractions of 2 Gy with 6 MV photons using a lens-sparing beam arrangement; a single lateral field was used for unilateral metastasis, while parallel opposed lateral fields were used for bilateral metastases. Median survival after treatment was 10 months in patients with breast cancer. Acute side effects were mild: 50% of patients experienced grade 1 dermatitis or conjunctivitis. Late side effects were noted in 2 patients: one patient experienced optic

neuropathy 2 years after radiation therapy and the other patient developed retinopathy concurrent with tumor recurrence. One patient underwent enucleation for painful glaucoma caused by tumor recurrence. Of the 50 symptomatic eyes, visual acuity increased in 36%, stabilized in 50%, and decreased in 14%. Of 15 asymptomatic eyes, visual acuity improved in 20% and stabilized in 80%. By ultrasonography, 38% of metastases completely regressed, while 44% partially regressed, and 17% remained unchanged. Complete regression was significantly more common among breast cancer patients. Regression rates were higher in patients that underwent chemotherapy after radiation therapy. Recurrence was noted in 13% of breast cancer patients 5 to 16 months after radiation therapy. Of note, no patient receiving unilateral irradiation experienced recurrence in the fellow eye, suggesting that bilateral irradiation is unnecessary for patients with unilateral involvement. Some have hypothesized that exit dose to the fellow eye from unilateral irradiation may be sufficient to control subclinical disease (15).

Radiotherapeutic alternatives to conventional photon teletherapy have been reported. Proton therapy is typically delivered in fewer fractions than photon therapy. In one study of patients with choroid metastasis from various primary cancers (the majority being breast cancer), 2 fractions of 14 Gy yielded a tumor regression rate of 84%, with 47% of eyes demonstrating stable or improved visual acuity (16). Brachytherapy involves placement of a radiation emitting source near the metastasis. This typically entails a procedure under anesthesia, but may be completed within a few days. Moreover, reirradiation of the ocular metastases may be facilitated using the precise doses delivered with brachytherapy. In a series of 13 patients treated with plaque brachytherapy for uveal metastases from breast cancer (31% of whom had received prior ocular teletherapy), 93% of patients demonstrated tumor regression (17).

Other Local Therapies

Other local therapies have been reported in small series of patients with choroid metastases from breast cancer. Transpupillary thermotherapy (TTT) may be useful for small tumors with minimal subretinal fluid, and was reported to be successful in a patient with breast cancer (18). Likewise, photodynamic therapy (PDT) has been reported to have a successful outcome in a patient with choroid metastasis from breast cancer (19). Laser therapy was reported to induce regression with associated improved visual acuity in a series of 7 patients with choroid metastasis from breast cancer (20).

MANAGEMENT SUMMARY

- Ophthalmic metastases have been reported in 0% to 37% of patients dying with, or of, breast cancer, in 0% to 5% of visually asymptomatic patients with metastatic breast cancer, and in 38% of breast cancer patients with vision problems.
- Most patients presenting with ocular metastases report blurred vision, photopsia, and floaters.
- Clinical evaluation by an experienced ophthalmologist is necessary to establish the diagnosis. Upon detection of uveal metastasis, brain imaging should be performed given the high frequency of concurrent brain metastasis and implications for therapy.
- Management of ophthalmic metastasis can consist of systemic therapy, radiation therapy, or other local therapy, and is commonly dictated by severity and progression of symptoms and presence and burden of extra-ophthalmic disease.
- Conventional photon external beam radiation therapy is the most frequently used local therapy and has proven to be safe and effective when given to 40 Gy in 2 Gy fractions.
- Ipsilateral eye irradiation provides good tumor control and may spare ophthalmic morbidity in patients without evidence of bilateral metastases.

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CHAPTER 81

Management of Isolated Liver Metastases

Rebecca Miksad, Douglas W. Hanto,
Robert D. Timmerman, and Steven Come

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INTRODUCTION

About half of patients with metastatic breast cancer develop liver metastases, a finding that generally portends a poor prognosis (1): median overall survival (OS) of 4 to 22 months (1,2). Since liver metastases commonly occur in the setting of concurrent extrahepatic metastases, liver involvement is generally considered to be a manifestation of disseminated disease, and patients are usually treated with systemic therapy (2) (see Chapters 33 and 34). However, in modern studies a minority of patients manifests metastatic breast cancer limited to the liver (1,2). Localized, liver-directed treatments have achieved some success in other cancers, especially when disease is limited to the liver, and these approaches have been applied to breast cancer patients. Published studies have evaluated the safety and benefit of a range of liver-directed treatments: hepatic resection (Table 81-1), radiofrequency ablation (RFA), transarterial chemoembolization (TACE) with and without drug-eluting beads, radioembolization, intraarterial chemotherapy, stereotactic body radiation therapy (SBRT), brachytherapy, and interstitial laser therapy (ILT) (Table 81-2). However, the comparative efficacies of these approaches remain unknown because there are limited prospective studies and no randomized controlled trials (Table 81-3). Furthermore, identifying appropriate patients remains a challenge, and the carefully selected patients in published series may represent good prognosis subgroups independent of the therapeutic approach.

Nevertheless, studies suggest that treatment of metastatic breast cancer limited to the liver may benefit some patients. In addition, as improvements in systemic therapies offer better control of metastatic disease and longer survival, more patients may need localized management of liver metastases. This chapter reviews localized, liver-directed treatment of hepatic metastases in breast cancer, details specific clinical considerations for each treatment option, and describes the available data for common and emerging approaches.

GENERAL SELECTION CRITERIA FOR LIVER-DIRECTED TREATMENT OF METASTATIC BREAST CANCER IN THE LIVER

Careful patient selection is essential to optimize the risk-benefit ratio of liver-directed approaches for all cancers with liver involvement (Table 81-4). The patients most likely to benefit from liver-directed approaches have a good overall prognosis (see Chapters 30 and 31) such that progression of other disease sites and/or comorbidities do not negate any disease control achieved in the liver. General criteria are controlled primary disease, limited metastatic disease in the liver (both number and size of lesions), longer disease-free intervals, a younger age, and a higher performance status (1–3). On the basis of the more extensive experience of liver metastases in colorectal cancer, the presence of extrahepatic metastatic or residual primary breast cancer is commonly (4), although not always (5,6), considered a contraindication to liver-directed therapy.

Evaluation before proceeding with liver-directed therapy for metastases from breast cancer should define the extent of disease as well as the potential responsiveness to systemic therapy. These factors may aid risk assessment and decision making regarding the role of liver-directed and/or systemic therapy. Commonly used imaging studies are (i) computed tomography (CT) of the chest to rule out pulmonary and mediastinal disease; (ii) triphasic CT scan of the abdomen and pelvis to evaluate the number and location of liver metastases in order to facilitate procedure planning and to rule out other intraabdominal disease; and (iii) a bone scan to rule out bone metastases. A PET scan may be useful to identify extrahepatic disease (see Chapters 33 and 34), and magnetic resonance imaging (MRI) may provide more detailed evaluation of the liver.

TABLE 81-1

Data for Hepatic Resection of Metastatic Breast Cancer to the Liver (selected)

Authors	*Year*	*Type of Study*	*No. of Breast Cancer Patients (n)*	*Postoperative Mortality (%)*	*Median Survival (mos)*	*5-Year Survival (%)*
Maksan et al. (7)	2000	CS	90	0	—	51
Selzner et al. (10)	2000	CS	17	6	25	22
Yoshimoto et al. (15)	2000	CS	25	—	34	27
Elias et al. (9)	2003	CS	54	0	34	50 (3 yrs)
Vlastos et al. (4)	2004	CR	31	0	63	61
D'Annibale et al. (3)	2005	CS	18	0	32	30
Adam et al. (6)	2006	CR	85	0	32	37
Martinez et al. (19)	2006	CR	20	—	32	33
Caralt et al. (60)	2008	CR	12	0	35.9	33
Lubrano et al. (16)	2008	CR	16	0	42	33
Thelen et al. (18)	2008	CR	39	—	—	42
Hoffmann K (14)	2010	CS	41	0	58	48
Abbott et al. (13)	2012	CS	86	0	57	43.6
van Walsum et al. (12)	2012	CR	32	0	55	37

Dash (—) represents unknown/not reported; CS, case series; CR, chart review; mos, months; n, number; yrs, years.

The need for thorough staging was highlighted in a series of 90 breast cancer patients evaluated for resection of liver metastases: 60% were deemed ineligible preoperatively because of extrahepatic metastases, 22% had unresectable extrahepatic disease at exploratory laparotomy, and only 10% ultimately underwent resection (7).

Palliative liver-directed treatment may also be beneficial if liver metastases impair quality of life. However, recent improvements in outcomes for endocrine-responsive, *HER2/neu*-amplified cancers and palliative single-agent chemotherapy have improved the effectiveness and tolerability of systemic therapy (8). Therefore, the risks and benefits of liver-directed therapies should be evaluated in context of potential systemic treatment options (2) (see Chapters 72–79).

SURGICAL APPROACH

Hepatic Resection

Hepatic resection (metastectomy) is the most commonly available liver-directed option for breast cancer patients. The morbidity and mortality of hepatic resection has declined significantly over the past two decades because of improvements in (i) understanding of intrahepatic segmental anatomy; (ii) imaging techniques (three-dimensional CT and intraoperative ultrasound) to characterize the tumor; (iii) anesthetic management; (iv) surgical techniques (preoperative portal vein embolization, segmental and anatomic resections, vascular inflow occlusion, maintenance of low central venous pressure, devices for safer division of the liver parenchyma and for maintenance of hemostasis); (v) laparoscopic hepatic resection approaches; (vi) understanding of negative risk factors (steatosis, remnant liver volume, and preoperative chemotherapy); and (vii) postoperative care. As a result, surgical resection is a technically safe option for most patients with metastatic breast cancer limited to the liver.

Patients deemed to be surgical candidates after preoperative screening undergo additional evaluation in the operating room. Prior to hepatic resection, patients are often explored to rule out extrahepatic, intraabdominal disease. Intraoperative ultrasound may identify additional liver lesions not imaged preoperatively, characterize the exact location of the lesion(s), and define the proximity of lesions to venous structures. The value of this additional exploration was demonstrated by a series of 108 breast cancer patients considered for hepatic resection after extensive preoperative evaluation with imaging (6). Over a 20-year period, 23% were found to have unresectable extrahepatic or hepatic disease during abdominal exploration, and an additional 13% had unexpected, but resectable, intraabdominal disease (6). Of the 85 patients who ultimately underwent hepatic resection, an R0 (microscopically negative margin) resection was attained in only 65%, while an R1 microscopically positive margin) resection was achieved in 18%, and an R2 resection (macroscopically positive margin) was carried out in 17% (6).

Selection Criteria for Hepatic Resection

In addition to the general selection criteria outlined above, hepatic resection candidates must have lesions that can be completely resected while leaving an adequately sized liver remnant along with its hilum (i.e., vascular and ductal continuity to the body). Because the function and architecture of the liver are integrated, adequate liver function can be maintained if there is a critical volume of intact liver and a contiguous bile duct system (20% of a normal liver, 40% of the liver if steatosis is present). If a small liver remnant is anticipated, a patient may benefit from preoperative portal vein embolization (right or left) of the lobe to be resected. This causes hypertrophy of the opposite lobe (the lobe that will become the liver remnant), thereby decreasing the risk of postoperative hepatic insufficiency.

Although there are limited data, the combination of hepatic resection and RFA has been explored for metastatic disease in both lobes or when one or more lesions are technically unresectable (4). In addition, while patients with extrahepatic metastases are traditionally excluded from resection, some series include patients with controlled extrahepatic disease (6).

TABLE 81-2

Data for Nonsurgical Locoregional Treatments for Metastatic Breast Cancer to the Liver (selected)

Authors	*Year*	*Type of Study*	*No. of Breast Cancer Patients with Liver Metastases (n)*	*Median Survival (mos)*	*Survival (Time point)*
Radiofrequency Ablation (RFA)					
Livraghi et al. (34)	2001	NRT	24	—	96% (4 to 44 mos)
Lawes et al. (35)	2006	NRT	19	—	41% (2.5 yrs)
Gunabasham et al. (36)	2007	NRT	14	—	64% (1 yrs)
Sofocleous et al. (5)	2007	CR	12	60	30% (5 yrs)
Meloni et al.[a] (33)	2009	CR	52	29.9	27% (5 yrs)
Jakobs et al. (37)	2009	CR	43	58.6	—
Carrafiello et al. (38)	2011	CR	13	10.9 (mean)	—
Transarterial Chemoembolization (TACE)					
Li et al. (27)	2005	CR	TACE = 28 SC = 20	TACE = 28 SC = 18	TACE = 13.01% (3 yrs) SC = 11.29% (3 yrs)
Buijs et al. (20)	2007	CR	14	25	35% (3 yrs)
Cho et al. (61)	2010	CR	10	12	—
Vogl et al. (24,25)	2010 (2011)	NRT	208 (TACE + LITT: 161)	18.5 (TACE + LITT: 32.5, mean)	33% (3 yrs) (TACE + LITT: 36.6% [3 yrs])
Duan et al. (26)	2011	CR	TACE + SC = 44 SC = 43	—	TACE + SC = 47.6% (3 yrs) SC = 7.4% (3 yrs)
Martin et al. (22)[b]	2012	CS	40	47	—
Hepatic Arterial Infusion (HAI)					
Fraschini et al. (28)	1987	NRT	31	11	—
Ikeda et al. (62)	1999	NRT	28	25.3	—
Camacho et al. (29)	2007	NRT	10	—	—
Radioembolization					
Bangash et al. (63)	2007	NRT	27	<25% tumor burden: 9.4 mos >25% tumor burden: 2.0 mos	—
Hoffmann et al. (59)	2010	CR	16	—	—
Stereotactic Body Radiation Therapy (SBRT)					
Wulf et al. (52)	2001	NRT	6	—	—
Herfarth et al. (47)	2004	NRT	14	—	—
Katz et al. (54)	2007	CR	16	—	about 50% (2 yrs)
Milano et al. (51)	2012	NRT	39 breast cancer patients with 13 liver metastases treated with SBRT	—	47% (6 yrs) for all breast patients
Brachytherapy					
Wieners et al. (58)	2011	NRT	41	—	60% (18 mos)
Collettini et al. (57)	2012	CR	37	18	—
Interstitial Laser Therapy (ILT)					
Mack et al. (55)	2004	NRT	232	4.3 yrs	41% (5 yrs)

[a]Includes 9 patients from Livraghi study (34).
[b]TACE with drug-eluting beads loaded with doxorubicin.
Dash (—) represents unknown/not reported; NRT, nonrandomized trial; CS, case series; CR, chart review; mos, months; yrs, years; TACE, transarterial chemoembolization; SC, systemic chemotherapy; LITT, laser-induced chemotherapy.

TABLE 81-3

Liver-Directed Therapy for Metastatic Breast Cancer: Summary of the Evidence

Liver-Directed Therapy		
Surgical resection	Pro	• Data available from a large number of case series over 20+ years • Compared to other liver-directed treatment options, more extensive data suggesting a 5-year survival benefit in appropriately selected patients • Relatively available
	Con	• Invasive procedure requiring hospitalization • Risk of postoperative complications and decreased liver function • Many patients not eligible because of comorbidities and extent of liver disease • Best results obtained for patients with small and/or few lesions
Nonsurgical liver-directed therapies	Pro	• Less invasive than surgical resection • More patients may be eligible • Compared to surgical resection, decreased risk of postprocedure complications and decreased liver function • Procedure may be accomplished in outpatient setting or with short hospital stay • Efficacy may be improved by combining modalities • Approaches supported by data for colorectal and hepatocellular cancer
	Con	• Data in breast cancer limited to relatively few, heterogeneous case series • Data for survival and tumor control are mixed • Treatment modalities and operator expertise may not be readily available • Despite generally good safety results, serious complications have been reported

Outcome of Hepatic Resection for Metastatic Breast Cancer

Most published series of outcomes after hepatic resection for metastatic breast cancer involve small, nonuniform patient populations. The survival data reflect this heterogeneity: median overall survival in 26 published series (more than 600 patients) ranges from 15 to 63 months, and the 5-year survival rate ranges from 18% to 61%, with more modern series reporting rates from 30 to 40% (3,4,6,9). Postoperative mortality is commonly zero (3,4,6), although rates up to 6% (n = 17) (10) in small series have been reported. Significant or severe morbidity rates range from 0% (11) to 44% (12).

Despite the limits of case series data, several favorable prognostic factors have emerged for hepatic resection of metastatic breast cancer. Consistent with the colorectal and primary liver tumor literature, a better prognosis for resection is observed when patients have a smaller tumor burden in the liver (12). In addition, a longer length of time between

TABLE 81-4

Summary of Patient Selection Guidelines for Liver-Directed Therapies

General Selection Guidelines Associated with Best Outcomes	• Good overall prognosis • Good performance status and few comorbidities • Documented response to preprocedure systemic therapy • Smaller lesions and fewer number of lesions in the liver • Metastatic disease isolated to the liver only • Longer disease-free interval between treatment of primary cancer and development of hepatic metastasis • Liver lesions that can be completely eradicated by the procedure
Procedure-Specific Guidelines	
Resection	• Adequate anticipated liver remnant (may be able to enhance with preoperative embolization) • Good operative risk
RFA	• Lesion size less than 3 to 5 cm in diameter • Limited number of lesions (usually 3 or fewer)
TACE	• Adequate liver function • No portal vein thrombosis or other contraindication
SBRT	• Well-demarcated lesion • Adequate anticipated liver remnant

initial diagnosis and the development of liver metastases (7,13,14) is associated with improved survival in some series (13,14), but not all (4,6,12,15,16). The type of resection attained may also be important: An R0 resection (22%–61% 5-year survival) is associated with improved survival compared to an R2 resection (0%–16% 5-year survival) (6,17,18). However, an earlier series of 54 patients did not demonstrate the same benefit: median survival was 40 months for R0 resections, and 31 months for R1 and R2 resections (p = .56) (9). In this series, the only significant prognostic predictor of median survival was hormone receptor status: 44 months if positive and 19 months if negative (9). This result was substantiated for 5-year and median survival in a subsequent study (6): 3.52 years for estrogen-receptor- (ER-) positive primary tumors compared to 1.5 years for ER negative (p < .02). A similar result was found for the ER status of the metastatic tumor in a series that also reported improved survival for *HER2/neu*-positive metastases (p = .02) (19).

A large (n = 85) contemporary series of liver resection for metastatic breast cancer demonstrated a median survival of 32 months and a 5-year survival of 37% (6). Multivariate analysis identified three factors correlated with poor outcome: (i) the absence of response to pre-resection chemotherapy (p = .008); (ii) an R2 resection (p = .0001); and (iii) a lack of repeat resection for recurrent liver disease (p = .01). The most important predictor of survival in this series was the completeness of the resection, with only 10% of R2 resection patients surviving 5 years, compared with 42% of R1 and 43% of R0 patients. Patients who developed recurrent liver metastases and then underwent re-resection had a 5-year survival of 81%, while those who did not had a 5-year survival of 29%. Although the presence of extrahepatic disease did not affect prognosis in this multivariate analysis, the subset of patients with extrahepatic disease at the time of hepatectomy had a lower 5-year survival (16%) compared to patients with resected or controlled extrahepatic disease (25%) and those without extrahepatic disease (43%).

A more recent, similarly sized (n = 86) hepatic resection series produced a higher median survival (57 months) and a slightly higher 5-year survival (44%) (13). Similar to prior series, multivariate analysis demonstrated that estrogen-receptor-negative primary breast disease (p = .009) and preoperative progressive disease (p = .003) were associated with decreased overall survival. These two large surgical case series span several decades during which time there were significant advances in systemic and hormonal therapy. Therefore, in addition to standard limitations of retrospective analysis, interpretation of the surgical literature in this disease is limited by potential confounders from treatment pattern changes over time.

In summary, although the data are limited to case series, hepatic resection for metastatic breast cancer can be performed safely and may result in favorable median and 5-year survival rates for appropriately selected patients. However, hepatic resection has not been compared in a randomized trial with systemic chemotherapy alone or in combination with nonsurgical, liver-directed options.

NONSURGICAL, LIVER-DIRECTED, LOCALIZED TREATMENT OPTIONS

The data for nonsurgical, liver-directed, localized therapy are most thoroughly developed for primary hepatocellular cancer (HCC) and for metastatic colon cancer. However, there are emerging data for metastatic breast cancer. The lack of randomized, controlled clinical trials limits interpretation of survival benefit and comparative efficacy. In general, nonsurgical, liver-directed therapies can be done percutaneously, allowing for a shorter recovery time and facilitating the administration of systemic treatment.

Transarterial Chemoembolization and Intraarterial Chemotherapy

Tumors in the liver are often primarily supplied by the hepatic artery, in contrast to the nontumor liver parenchyma which receives blood supply from portal vein. Transarterial chemoembolization (TACE) takes advantage of this blood supply pattern by instilling cytotoxic agents mixed with iodized oil into the hepatic artery feeding the tumor and then embolizing this vessel (often with gelatin sponge particles) to cut off the tumor blood supply. Because of the differential blood supply, the nontumor liver parenchyma suffers relatively less harm. Attempts to further minimize hepatic damage and subsequent side effects, have led to development of related techniques: delivery of chemotherapy through the use drug-eluting beads, radioembolization in which radioactive particles are instilled instead of chemotherapy (intraarterial brachytherapy or selective internal radiation therapy [SIRT]) and "bland embolization," in which the only treatment is embolization (no chemotherapy or radiation).

Hepatic arterial infusion of chemotherapy (HAI) follows the same principles as TACE, but embolization is not performed. Chemotherapy may be distilled once during a single procedure, or a pump may be placed for longer-term, continuous infusion.

The technical success of TACE is demonstrated by the presence of hyperattenuating iodized oil within the tumor on unenhanced CT (20). Because the size of the liver tumor may not change after liver-directed therapy, the extent of necrosis (or lack of enhancement) observed on imaging may more accurately reflect treatment efficacy (21,22). A surrogate endpoint for response is the apparent diffusion coefficient (ADC), which measures the mobility of water in tissues: viable tumor cells restrict the mobility of water while necrotic tumor cells allow increased diffusion (20). In one study of TACE for patients with metastatic breast cancer (n = 14, prospective chart review), no tumors met the Response Evaluation Criteria in Solid Tumors (RECIST) criteria for complete response, but the ADC increased by a mean of 27% after treatment (20).

Overall treatment efficacy may be improved by combining TACE with other localized treatments such as radiofrequency ablation (23) and SBRT. However, the best sequencing of and the optimal interval between each therapy is unknown.

Selection Criteria for TACE

Although TACE and intraarterial chemotherapy techniques were developed to spare the nontumor liver, complications commonly stem from liver damage, especially if there is inadequate functional reserve or poor blood flow to the liver. Therefore, TACE selection criteria have a special focus on hepatic reserve. Commonly accepted contraindications to TACE for metastatic breast cancer are derived from the literature for other malignancies: (i) absence of hepatopetal blood flow (portal vein thrombosis), (ii) encephalopathy, and (iii) biliary obstruction (21). Relative contraindications are (i) serum bilirubin over 2 mg/dL, (ii) lactate dehydrogenase over 425 U/L, (iii) aspartate aminotransferase over 100 U/L, (iv) tumor burden involving more than 50 percent of the liver or both lobes of the liver, (v) cardiac or renal insufficiency, (vi) ascites, (vii) recent variceal bleed, and (viii) significant thrombocytopenia. Although there are limited prognostic data for metastatic breast cancer treated

with TACE, these contraindications are primarily related to technical issues and the patient's ability to tolerate tumor necrosis and injury to the nontumor liver.

Despite these selection criteria, "postchemoembolization syndrome" (fever, pain, nausea, and elevated liver function tests) is commonly seen after TACE in 60% to 80% of patients (21). These symptoms tend to be worst the first several days after the procedure and may persist for several weeks. For hepatocellular cancer, the disease in which TACE is most studied, a meta-analysis of 37 trials including about 3,000 patients demonstrated a 2.4% (range 0%–9.5%) 30-day mortality rate, primarily due to liver failure (21). This meta-analysis identified serious complications ranging from acute liver failure (7.5%), acute renal failure (1.8%), upper gastrointestinal bleeding (3%), to hepatic or splenic abscess (1.3%) (21). Other reported potentially serious complications from TACE are tumor rupture, encephalopathy, acute cholecystitis, acute pancreatitis, and arterial damage. Because of these side effects and complications, patients are commonly observed in the hospital postprocedure (21).

Outcome of TACE for Metastatic Breast Cancer

The largest study of TACE for metastatic breast cancer is a case series of 208 patients (24) for whom three TACE sessions were planned at least four weeks apart from November 1998 to February 2006. The majority of patients had liver only disease (n = 159), and chemoembolization was pursued in place of systemic therapy (24). In this series, patients who were adequately "downsized" by chemoembolization proceeded to laser-induced thermotherapy (LITT), a subgroup included in a subsequent report (24). With a maximal RECIST response 12 weeks after the first TACE session, post-TACE MRI imaging documented stable disease in 50%, progressive disease in 36.5%, and partial response in only 13% of patients. Most patients tolerated the procedure well, and the 3-year survival was 33% from the time of the first TACE procedure (24).

The same author also reported the results for 161 patients (out of 314 patients treated with TACE from November 2001 to November 2006) (25) who were subsequently treated with LITT (the extent of overlap between the patient groups in the two reports is not clear). For the selected group of patients downsized sufficiently for LITT, TACE produced a 27% reduction in tumor size. After combination therapy (TACE + LITT), 38.5% had a complete response, 5% had a partial response, and 12.4% had stable disease. However, 44% of the group had disease progression after initial stabilization that required additional TACE. Overall, the 3-year survival was similar to prior report that focused on TACE alone: 36.6% at 3 years and 13.7% at 5 years (25).

The most recent retrospective chart review reports the results of 44 patients who underwent TACE and systemic chemotherapy (SC) compared to 43 patients who underwent SC therapy alone (26). The criteria for treatment choice were not described, and patients received various chemotherapy regimens. Response rates (59.1% vs. 34.9%) and 3-year survival (47.6% vs. 7.4%) were higher for patients who received TACE compared to those who did not. Multivariate analysis results were similar to those seen in the surgical literature: estrogen receptor negative status of the primary tumor and short disease-free interval (less than 24 months) were associated with poor prognosis (26).

A prior retrospective chart review evaluated 48 metastatic breast cancer patients treated with TACE (n = 28) or systemic chemotherapy (n = 20) (again, criteria for treatment choice not described) (27). With no grade III or IV adverse events, TACE had a 35.7% response rate (30% 2-year survival), while systemic chemotherapy had a 7.1% response rate (11% 2-year survival). Recently, a study of 14 patients with 27 lesions evaluated with magnetic resonance (MR) imaging showed a median survival of 25 months and a 35% OS at 3 years (20). Finally, a 40-patient case series explored the safety of drug-eluting beads loaded with doxorubicin for patients with metastatic breast cancer to the liver (22). The median survival was 47 months, with a mild side effect profile, and response as per modified RECIST was 50% at 12 months (22).

Hepatic Artery Infusion

Although not widely employed, HAI is utilized in some centers for colorectal cancer liver metastases, and there are limited data in breast cancer (28,29). In the most recent HAI study for breast cancer metastatic to the liver (n = 10), 40% progressed during HAI therapy (29).

In summary, it is difficult to establish a survival benefit for TACE for breast cancer metastatic to the liver in the absence of randomized, controlled trials.

Radiofrequency Ablation

Radiofrequency ablation (RFA) is a minimally invasive technique that uses extreme heat to destroy cancer cells. An electrode is inserted into the tumor and high frequency alternating current is transmitted from the tip of the probe into the surrounding tissue. As the tissue molecules become excited, heat (over 60°C) is generated, and coagulative necrosis occurs (30). The amount of tissue destroyed is related to the impedance properties of the tissue and the distance of the tissue from the electrode (30). Tissue destruction may be modulated by the cooling effect of a heat sink such as blood vessels located adjacent to the tumor: heat is carried away, and the necessary temperature for coagulative necrosis may not be reached (30).

Sites treated with RFA frequently cavitate after the procedure, forming a distinctive scar band. The risk of complications increases with proximity to the porta hepatis. Rarely, hepatitis, infection, and injury to larger bile ducts and nearby bowels may occur. Patients with preexisting liver damage such as cirrhosis and those with larger tumors are more likely to experience complications. Although not typical, needle track seeding has been reported. Given the generally limited risks, RFA can be done as an outpatient procedure.

Selection Criteria for RFA

In addition to the general selection criteria for localized treatment of liver metastases, tumor size and the number of liver metastases are important selection criteria for other tumor types treated with RFA, both for achieving local control and for predicting a survival benefit. However, there are few prognostic data for metastatic breast cancer. In colorectal cancer, fewer lesions and smaller tumors are associated with improved survival. Similar size limitations are observed for hepatocellular cancer (HCC): RFA induced a complete response in 80% of HCC tumors 3 cm or less but was substantially less effective in HCC tumors larger than 3 cm (50% response) (31). Although it is unclear if these size limitations can be extrapolated to the metastatic breast cancer setting, it seems likely given physical limitations of RFA.

Outcome of RFA for Metastatic Breast Cancer

While RFA has been extensively studied for colorectal liver metastases (32), there is growing case series evidence for metastatic breast cancer. In the largest case series to date

(n = 52), follow-up imaging demonstrated complete necrosis in 97% of tumors that had a mean diameter of 2.5 cm (33). Consistent with the concept that metastatic breast cancer is a systemic disease, 53% of patients in this series developed new intrahepatic metastases, and the 5-year survival was 27% (33).

Similar recurrence results were seen in a case series of 24 breast cancer patients with 64 liver metastases treated with RFA and followed for a median of 19 months: 58% developed new metastases, the majority of which occurred in the liver (71%) (34). However, most patients with disease limited to the liver were disease-free at last follow-up. In contrast, a separate series demonstrated good survival for both those with and without extrahepatic metastases at the time of RFA: Six of 11 patients with extrahepatic disease were disease free after a median follow-up of 15 months (35). Several small series also report post-RFA survival: with a median follow-up of 16 months, one study reported 64% of patients were alive in a group of 14 patients with 16 tumors treated with RFA (36), while a second study of 12 patients reported a 30% 5-year survival (5).

In the largest series to date, the primary negative prognostic factor for survival was larger liver metastases (larger than 2.5 cm) (33). A separate series (n = 40) that evaluated hormone receptor status and *HER2* overexpression found only the presence of extrahepatic disease to be associated with poor survival after RFA (37).

In most reported cases for metastatic breast cancer, RFA was used in combination with systemic chemotherapy, and very few side effects (mild right upper quadrant discomfort and asymptomatic pleural effusion) were noted, but none required specific treatment (5,33,36–38). RFA has also been combined with surgical resection (4). Based on these data and the experience in other malignancies, RFA for metastatic breast cancer limited to the liver may be beneficial for select patients. The data for patients with concurrent extrahepatic disease are mixed.

Stereotactic Body Radiation Therapy

Stereotactic body radiation therapy (SBRT) approaches evolved from intracranial stereotactic radiosurgery (SRS) and stereotactic radiotherapy (SRT) to treat tumors outside the cranium and are therefore subject to physiologic movement. The term *stereotactic* describes the correlation of the tumor target position to fiducials with a reliable and readily known position (39). Unlike conventionally fractionated radiotherapy (CFRT), stereotactic radiation is completed with a limited number of high-dose fractions called oligofractionation (40).

While a large safety margin can be added to CFRT to compensate for tumor motion, the potent radiation dose in each fraction (10–20 gray [Gy]) of SBRT means that the tumor must be tracked to accommodate its motion without damaging normal tissue (39). Fiducials, often gold seeds, are placed such that they maintain the same relationship to the tumor despite physiologic movement and can be used to define the tumor target accurately. Fiducials define a coordinate system used in SBRT treatment and planning to achieve a conformal and compact dose distribution that treats effectively, controls for motion (4-D therapy), and minimizes normal tissue damage (41).

Patient Selection for SBRT

The most important feature for patient selection for SBRT is the predicted volume of viable liver left to function after therapy (rather than the number and size of tumors to be treated). As with surgical resection, it is essential that an adequate parenchymal remnant be preserved after SBRT along with its connecting hilar structures (i.e., vessels and ducts) so as not to isolate the remnant. With surgical resection performed according to the liver vascular anatomy, it is unlikely that a preserved remnant would be isolated. However, with SBRT's characteristic heterogeneous dosimetry, islands of liver tissue may be spared the threshold toxic dose. Nonetheless, such islands isolated from an intact vascular pedicle or unable to drain bile will eventually involute over weeks and months post treatment.

Based on the surgical literature, the critical liver volume (minimal liver remnant) is considered to be about 20% to 30% of the liver (around 500 to 700 ml) (42). Damaging more than this amount may lead to hepatic insufficiency or failure. The threshold dose beyond which the liver parenchyma no longer functions is fractionation dependent and not fully characterized. Several groups use 17 Gy for three fractions and 21 Gy for five fractions as the threshold dose (43). The dose damaging the vascular pedicle and bile ducts in a serial fashion is likely higher, in the range of 36 to 41 Gy. In some circumstances, a preplan is required to assess the critical volume and finally determine appropriateness of SBRT for liver-directed therapy.

For optimal SBRT treatment, tumors should be well demarcated on planning imaging. Tumors close to the central biliary structures are more prone to complication, but this is not an absolute contraindication. Patients with cirrhosis with hepatic insufficiency require a larger critical volume to be spared. Patients in frank liver failure, however, should not be treated with SBRT as even a mild radiation hepatitis could lead to death (44).

Outcome of SBRT for Metastatic Breast Cancer

As with all liver-directed therapies for breast cancer, there are no high level population cohort or randomized trials describing outcomes after SBRT for liver metastases. Furthermore, the majority of reports, even prospective trials, pool outcomes from a variety of primary sites, with breast cancer primaries typically constituting a minority. Despite these obvious shortcomings, the prospective trials and some retrospective reports demonstrate consistent treatment techniques and outcomes that may provide insight. Furthermore, while metastases from colon cancer have been shown to be more radioresistant, there is no such concern for breast cancer. While the impact on overall survival cannot be demonstrated from published reports, several series show that liver SBRT for breast cancer can durably control tumors and is tolerable in most patients.

Early retrospective reports of multiple tumor types in multiple areas of the body showed promise for SBRT and helped define selection criteria (44). Subsequently, four phase I dose escalation studies to find the ideal treatment dose were performed. Using a single fraction with dose escalated from 14 to 25 Gy, Herfarth et al. treated 37 patients with 60 lesions (4 primary liver tumors and 56 metastatic tumors, 14 of which were breast cancer) (46). No major complications were reported and the actuarial freedom from local failure rate at 18 months was 67% (46). However, an updated report with long-term follow-up showed higher rates of recurrence even at the highest dose level (47). A consortium of centers lead by the University of Colorado escalated a three-fraction regimen from 36 to 60 Gy attaining very high tumor control rates at the highest levels. The dose was escalated so long as the critical volume of 700 cc of normal liver could be spared the threshold dose of 15 Gy or less (40). The group from Princess Margaret Hospital escalated dose among 68 patients (12 with breast cancer)

to predefined limits to avoid radiation-induced liver disease (none observed at the highest dose levels within a bin, up to 60 Gy in six fractions). The median dose was lower than other reports (41.8 Gy in six fractions) as was the tumor control (71% at one year) (48). Finally, a study from the University of Texas Southwestern escalated a five-fraction regimen to a dose of 60 Gy. This study demonstrated a dose response relationship for local control with increasing dose potency (49).

Institutional retrospective and phase II prospective reports have confirmed the phase I findings. Rusthoven and coworkers built on the Colorado consortium phase I study with a multicenter phase II trial using the 60 Gy in three-fraction dose. This experience of 47 patients (63 lesions) included around 10% breast cancer patients. With median follow-up of 16 months, only three treated tumors progressed, producing a 2-year local control of 92% and median survival of 20.5 months (50) (all tumor types).

SBRT reports specific to breast cancer are also emerging. Thirty-nine patients with metastatic breast cancer (13 with liver metastases) were treated with SBRT for limited oligometastatic disease, resulting in a 6-year overall survival of 47% for the breast cancer cohort overall (51). Factors associated with a better outcome on univariate analysis for the overall breast cohort in an earlier report of the same patients population were: smaller tumor volume, bone-only disease, one metastatic lesions, stable/regressing lesions before SBRT (51).

Toxicity after SBRT

The most commonly discussed complication of liver radiotherapy is radiation-induced liver disease (RILD), which is a clinical syndrome of anicteric hepatomegaly, ascites, and elevated liver enzymes (particularly serum alkaline phosphatase) occurring 2 weeks to 4 months after completion of hepatic irradiation. RILD has most commonly been described in the context of large-volume liver irradiation to doses at or beyond the threshold. Clinically apparent RILD has rarely been described after SBRT, likely owing to the efforts to reduce the amount of nontumor tissue exposed to high and intermediate doses.

Early CT follow-up to assess response after SBRT can be hindered by a zone of *hypo*density seen on imaging that corresponds to normal tissue volume that received approximately 30 Gy (42,45). This phenomenon is of uncertain etiology, and there is no known clinical consequence (45). After a few months, the adjacent normal tissue may appear to have increasing *hyper*density (45).

Acute toxicity after SBRT includes fatigue and nausea consistent with acute radiation hepatitis. Depending on the position of the treated tumor, other potential SBRT complications include damage to the extrahepatic bile ducts, stomach, small bowel, kidney, large bowel, or lung (rare). Cytoprotectants (e.g., sucralfate) and acid blockers may help prevent and/or treat gastric or duodenal erosion (mucositis). Late toxicity such as bowel obstruction, gastric perforation, biliary sclerosis, and lung fibrosis have been occasionally observed.

Interstitial Laser Therapy

Localized tumor destruction can also be achieved through hyperthermic coagulative necrosis caused by laser light delivered through quartz diffusing laser fibers placed directly in the tumor (55). ILT has been used to treat tumors up to 5 cm and can be performed through a variety of modalities: percutaneously with local anesthesia in the outpatient setting, laparoscopically, or intraoperatively (55). The reported ILT serious complication rate (1.5%) is low, with four symptomatic pleural effusions, two liver abscesses, one bile duct injury, and no deaths occurring in a series of 452 patients (55). However, there were 41 (9%) asymptomatic pleural effusions and 20 (4%) asymptomatic subcapsular hematomas incidentally detected on imaging (55).

Accurate positioning of the laser can be ensured using real-time imaging; MR is preferred over CT and ultrasonography because of the heat sensitivity of the MR sequence and its ability to demonstrate the degree of necrosis by rapidly depicting temperature changes. Monitoring with MR imaging also minimizes destruction of healthy tissues and increases safety (55).

Patient Selection for ILT

Patient selection for ILT follows general guidelines for liver-directed therapy, and some suggest fewer than 5 lesions, with none measuring more than 40 mm in diameter (56).

Results of ILT for Metastatic Breast Cancer

The largest published experience with ILT for metastatic breast cancer included 232 patients with 578 liver metastases treated with ILT and systemic chemotherapy (1993 to 2002). Although 31% of patients had concurrent bone metastases, all patients had five or fewer hepatic metastases with no lesion larger than 5 cm in diameter (55). The rate of local liver recurrence 6 months after ILT was less than 5%, the median survival was 4.3 years, and the 5-year survival rate was 41% (calculated from the date of diagnosis of the target liver metastasis rather than the date of ILT treatment) (55). While ILT may be promising, data are limited for metastatic breast cancer to the liver.

OTHER LIVER-DIRECTED THERAPIES

Two radiation-based liver-directed therapies, brachytherapy (57,58), and radioembolization (59), are currently being developed for other cancers and the first reports in breast cancer are emerging.

MANAGEMENT SUMMARY

- Breast cancer patients with metastatic disease limited to the liver is uncommon and firm evidence regarding their management is scarce.
- For patients with liver metastases as the first site of metastases, thorough staging is indicated.
- In addition to surgical resection, there are a variety of nonsurgical liver-directed therapies that may offer local control with fewer side effects.
- The data for all liver-directed therapies in metastatic breast cancer is limited and there are no comparative randomized, controlled clinical trials.
- Case series evidence suggests that a variety of liver-directed therapies can be used successfully in carefully selected patients, with low morbidity and encouraging survival rates. Selected articles are listed in Table 81-1 for surgical approaches and Table 81-2 for nonsurgical approaches. A summary of the evidence is provided in Table 81-3.

- Careful selection is required to identify candidates for liver-directed therapy and, in many situations, systemic treatment is preferred (i.e., substantial extrahepatic metastases). A proposed algorithm for the management of a patient with metastases to the liver is given in Figure 81-1.
- Guidelines for patient selection are largely extrapolated from experience with liver-directed therapies for hepatocellular cancer and for colorectal cancer metastatic to the liver. Considerations for the selection of liver-directed therapy are given in Table 81-4.
- We advocate development of and enrollment in prospective clinical trials to address the unanswered question of comparative efficacy among liver-directed and systemic treatment options.

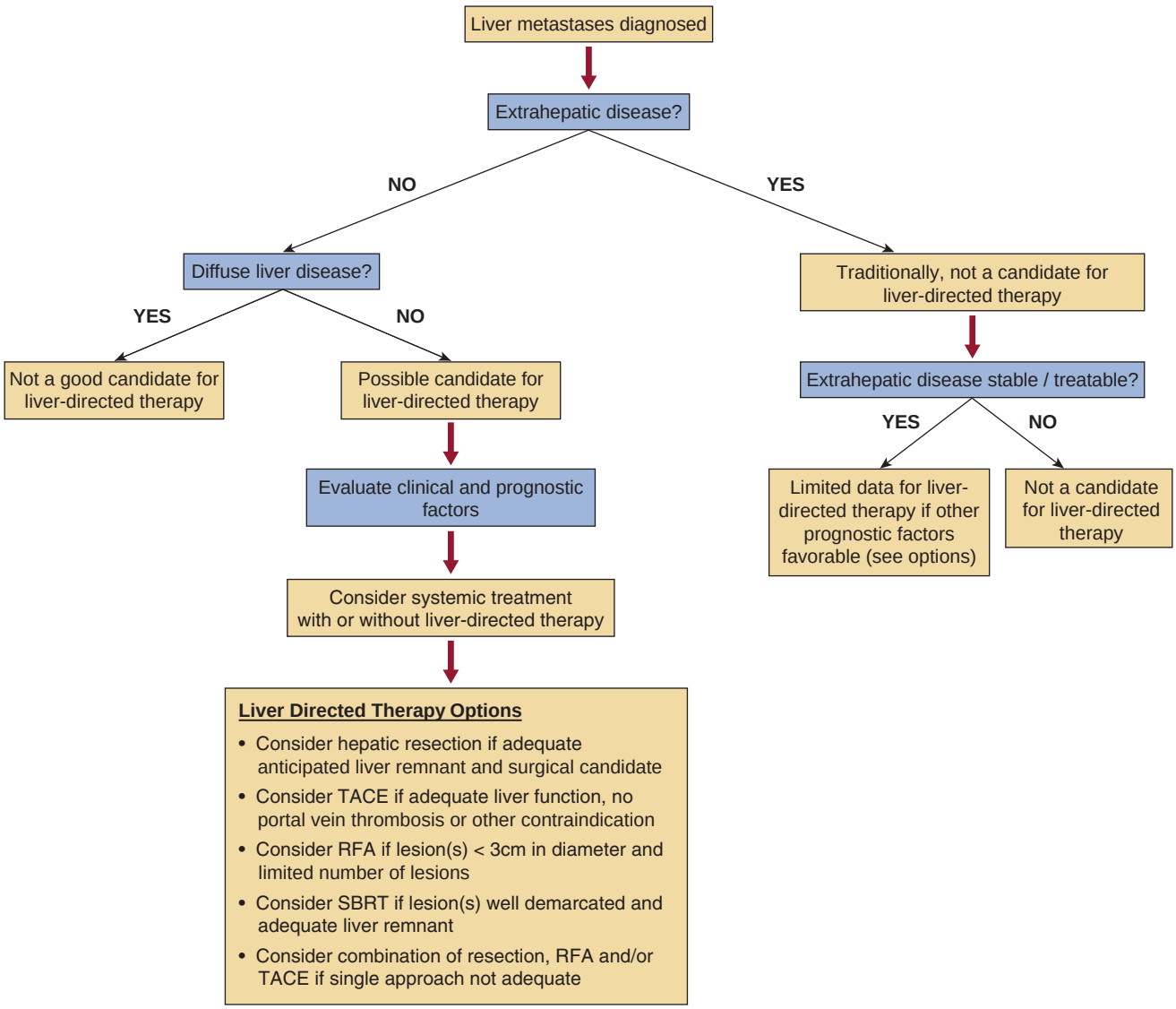

FIGURE 81-1 **Liver-directed treatment options for breast cancer metastatic to the liver.** The decision to proceed with a liver-directed approach for the treatment of breast cancer metastatic to the liver must be made after carefully balancing the risks and benefits of all options. Given the biology of the disease and the paucity of clinical trial data about liver-directed options, the authors believe that a bias toward systemic therapy is an appropriate starting point. In addition, the proposed algorithm should be individualized for each patient and modified as needed to take advantage of local expertise in specific treatment modalities. RFA, radiofrequency ablation; SBRT, stereotactic body radiotherapy; TACE, transarterial chemoembolization.

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CHAPTER 82

Medical Treatment for Bone Metastases

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CHAPTER CONTENTS

MEDICAL TREATMENT FOR BONE METASTASES

Skeletal metastases are a common event in breast cancer, responsible for profound patient morbidity and representing a significant public health burden. While the precise epidemiology of bone metastases in breast cancer is elusive, they affect over 7% of all women diagnosed with breast cancer in the United States (1). Bone is the *initial* site of metastasis for 47% of women with relapsed breast cancer (2) and the *only* site for 20% of women with metastases (3). The incidence may vary by subtype: among patients whose initial metastasis is to the bone, 82% will express either estrogen receptor (ER) or progesterone receptor (PR). Nonetheless, these events are common in all subtypes, noted in 69% of women who die from breast cancer (2). Importantly, the development of bone metastases is not a fatal event. Patients with skeletal metastases can have a prolonged survival, particularly when compared to patients with visceral involvement. One study reported a median survival of 24 months for patients with only skeletal metastases compared to 3 months for patients with liver metastases. As our treatment for advanced breast cancer evolves, we are likely to see further improvements in survival, increasing the chances for patients to develop bone metastases during their lifetimes. Because of the high incidence of bone metastases and the potential for extended survival, the cumulative morbidity of skeletal involvement in breast cancer is high and the potential for impaired mobility and loss of independence highlights their clinical relevance.

The morbidity from bone metastases has been difficult to objectively quantify. While helpful, the use of pain scores and analgesic logs is subject to various potential biases. As a result, the impact of bone metastases is often quantified by the incidence of skeletal-related events (SRE). SRE definitions vary by study but operationally represent a composite of pathologic fractures, spinal cord compression with vertebral compression fracture, hypercalcemia of malignancy, requirement for radiation to bone, and necessity for surgical intervention for pathologic fractures or cord compression (4). Unfortunately, SRE are common in breast cancer. In the absence of bone-targeted therapy, the rate of pathologic fracture for patients with bone metastases from breast cancer is 35% (5) and up to 70% of patients with bone metastases will have at least one SRE by 2 years (6). SRE are associated with decreased survival in breast cancer. Patients with a pathologic fracture have a 32% increased risk of death compared to those without a fracture (7). The clinical significance of SRE, however, extends far beyond survival. SRE have been associated with significant declines in physical and functional well-being as well as overall quality of life (8). The resulting economic impact of bone metastases in breast cancer is staggering, with an estimated national cost burden of nearly $4.5 billion annually (1).

Insight into the pathophysiology of bone metastasis has facilitated recent therapeutic advances. The tropism of breast cancer cells to bone has yet to be fully explained. Transcriptome analyses of breast cancer cells predisposed to metastasize to the bone have revealed a gene expression profile that mimics osteoblasts in a process called *osteomimetism*. These changes may facilitate survival of these cells in the bone microenvironment (9). Under normal physiologic conditions, osteoclast differentiation is directed by osteoblasts via signaling in the receptor activator of NF-κB (RANK) ligand pathway (10). The interactions between these molecules results in normal bone remodeling: a balance between bone formation and resorption. In the setting of bone metastases, normal homeostasis is disrupted. Osteoclast activation is felt to be an early event in the development of bone metastases in breast cancer, often associated with lytic bone lesions. Dysfunction of osteoblasts has been implicated in blastic bone metastases and is relevant in breast cancer, where mixed lesions are frequently encountered.

This dysfunction may be mediated by the RANK ligand pathway, an emerging target in the treatment of bone metastases. An increase in bone resorption can compromise the integrity of the affected bone, leaving it vulnerable to the development of SRE. This process can be mediated by several factors. One contributing factor is an increase in osteoclast precursors in the presence of tumor cells, a shift potentially mediated by tumor necrosis factor α (11). Another mechanism is activation of osteoclasts by breast cancer cells, which can upregulate RANK ligand and inhibit osteoprotegerin, which normally inhibits excessive osteoclast activation. Once activated, bone resorption can elicit a chemotactic response from tumor cells, cyclically propagating the process (12). Agents targeting this pathway, however, have provided inroads in stopping this cycle and preventing some of the morbidity associated with skeletal metastases.

Bisphosphonates are a class of medications commonly used in patients with bone metastases from breast cancer. Early-generation bisphosphonates such as clodronate do not contain nitrogen. These agents are metabolized to adenosine triphosphate (ATP) analogues that cannot be hydrolyzed, interrupting multiple cellular processes including bone remodeling (13). Nitrogen-containing bisphosphonates, including pamidronate, ibandronate, and zoledronic acid, accumulate in the bone microenvironment and are released during bone resorption. They are then internalized by osteoclasts where they affect their activity and survival. One target for nitrogen-containing bisphosphonates is farnesylpyrophosphate synthase (FPPS), an enzyme in the mevalonate pathway that is responsible for the prenylation of small guanosine triphosphatases (GTPases), which are critical for osteoclast survival (14). This indirect effect of nitrogen-containing bisphosphonates is augmented by a direct effect related to production of triphosphoricacid 1-adenosin-50-yl ester 3-(3-methylbut-3-enyl) ester (ApppI), an ATP analogue that induces osteoclast apoptosis (15). The effect of bisphosphonates may extend beyond the osteoclast. Preclinical studies have shown that zoledronic acid inhibits angiogenesis in several *in vitro* and *in vivo* models (16). In patients receiving zoledronic acid, there is an early and sustained reduction in circulating levels of vascular endothelial growth factor (VEGF), a cytokine involved in angiogenesis (17). Zoledronic acid also modulates migration and adhesion of endothelial cells by targeting integrins and sensitizing cells to tumor necrosis factor (TNF)–induced programmed cell death (18). In addition, nitrogen-containing bisphosphonates prevent adhesion of cancer cells to bone, which may interfere with tumor seeding and invasion (13). Nitrogen-containing bisphosphonates may also induce cell death by activating cytotoxic T-cells in the host, though the clinical role of this effect awaits further clarification (19).

Agents targeting the RANK ligand pathway have also demonstrated activity, primarily through inhibition of osteoclast function to suppress bone resorption (20). Denosumab is a humanized monoclonal antibody targeting RANK ligand that has recently garnered FDA approval in this setting (21). Similar to zoledronic acid, the activity of denosumab is mediated by several mechanisms, including a potentially similar antiangiogenic effect (22). Multiple randomized studies have shown a decrease in SRE with the use of bisphosphonates and denosumab, which are outlined next.

First-Generation Bisphosphonates

The initial use of bisphosphonates to alter bone metabolism extends back to the 1970s when etidronate, a first-generation bisphosphonate, was used in the treatment of Paget's disease of the bone (23). Subsequently, reports were published showing the benefit of etidronate in the treatment of both osteoporosis and hypercalcemia of malignancy (HCM). Another first-generation bisphosphonate, clodronate, was evaluated in small phase II studies followed by a randomized, double-blind, placebo-controlled trial comparing daily oral clodronate 1600 mg/day to placebo in patients with metastatic breast cancer with bone involvement (24). This study demonstrated a significant reduction in the development of HCM and vertebral fractures in patients receiving clodronate as well as a 33% reduction in all skeletal events. As a result of these trials, clodronate is approved outside of the United States for women with metastatic breast cancer and bone involvement. Despite this approval, the first-generation bisphosphonates are not optimal for long-term use. Etidronate adequately inhibits bone resorption, but also inhibits bone mineralization. Clodronate is poorly absorbed in the gastrointestinal tract and can cause local irritant toxicity, reducing the likelihood of long-term adherence.

Second-Generation Bisphosphonates

Further drug development led to the design of aminobisphosphonates, which are potent inhibitors of osteoclastic activity that do not alter bone mineralization. Examples of drugs in this class are pamidronate and alendronate. In light of the initial encouraging results of clodronate, multiple clinical trials were initiated with pamidronate for women with breast cancer metastatic to bone. Initial small studies sought to optimize the dose and schedule of intravenous pamidronate and had various endpoints including amelioration of bone pain and sclerosing of lytic bone metastases. Subsequently, two large placebo-controlled, randomized clinical trials (Aredia Protocols 18 and 19) were initiated in the early 1990s (25). Both of the trials' eligibility criteria included metastatic breast cancer and at least one predominantly lytic bone metastasis measuring ≥ 1 cm in its greatest dimension. Women enrolled in Protocol 18 received a stable endocrine regimen for their metastatic cancer, and those on Protocol 19 received cytotoxic chemotherapy. Patients were randomly assigned to receive either pamidronate 90 mg intravenously over 2 hours or an intravenous placebo, given every 3 to 4 weeks for 24 cycles. Patients were serially evaluated for any evidence of an SRE, defined here as pathologic fracture, spinal cord compression, or hypercalcemia. The primary efficacy endpoint was the skeletal morbidity rate, expressed as the number of events per year. Although the two trials were independently performed, their common time frame and eligibility criteria allowed the investigators to combine their efficacy data.

In this trial, 367 women were randomized to pamidronate and 384 women were assigned to placebo. The addition of pamidronate to systemic therapy for advanced breast cancer resulted in a significant improvement in multiple parameters. The skeletal morbidity rate was 2.4 events per year in the pamidronate group versus 3.7 in the placebo group ($p < .001$). Overall, skeletal events were seen in 51% and 64% of these same groups, respectively ($p < .001$). The median time to first skeletal event was 12.7 months with pamidronate and 7 months with placebo ($p < .001$), and the time to first fracture was 25.2 months and 12.8 months for these groups, respectively ($p < .003$). Although this was designed as a 24-month trial, only 31.3% of the pamidronate patients and 25.8% of the placebo patients completed 24 months of treatment. Despite the compelling skeletal benefits seen with pamidronate, there was no survival difference between the two arms. As a result of these and the previous smaller trials, the FDA-approved pamidronate for the treatment of women with bone metastases in July 1996.

Third-Generation Bisphosphonates

Following the development of pamidronate, more potent third-generation bisphosphonates entered testing. The potential benefits of increasing potency are to shorten the intravenous infusion times and allow for oral formulations with greater efficacy. Three of these potent heterocyclic, nitrogen-containing bisphosphonates began to enter clinical study: risedronate, ibandronate, and zoledronic acid (or zoledronate). Zoledronate is reported to be the most potent of these third-generation bisphosphonates with respect to bone resorption without affecting bone mineralization.

Ibandronate, in both the intravenous and oral form, has been compared to placebo in the setting of bone metastases. Ibandronate 50 mg orally when compared to placebo (26) significantly reduced the risk of an SRE in 564 randomized patients ($p < .001$). In a second trial of similar patients, ibandronate either 2 or 6 mg intravenously was compared to placebo (27). The 2-mg dose was ineffective, but the 6 mg dose significantly reduced the skeletal morbidity rate ($p < .03$). However, ibandronate is not currently approved in the United States for the ancillary treatment of skeletal metastases.

A large international, multicenter, randomized, double-blind clinical trial was performed comparing pamidronate with zoledronate in patients with bone metastases from not only breast cancer but also multiple myeloma (4). Patients participated as one of three strata: patients with multiple myeloma; patients with breast cancer receiving chemotherapy; and patients with breast cancer receiving hormonal therapy. Patients were randomized to receive pamidronate 90 mg over 2 hours in 250 mL of 0.9% sodium chloride or zoledronic acid either 4 mg or 8 mg administered in 50 mL of hydration over 5 minutes. Because of the observation of creatinine elevation in the zoledronic acid arms, two protocol adjustments were made during the conduct of the trial: the infusion duration was increased from 5 to 15 minutes with the volume of hydration increased to 100 mL; and the 8 mg zoledronic acid dose was reduced to 4 mg. Although the original trial was designed as a 13-month efficacy and safety trial, a 25-month extension phase was subsequently performed and reported. The primary efficacy endpoint of the trial was the percentage of patients in each treatment group who experienced at least one SRE during the 25-month study period. For this study, SRE were defined as pathologic fracture, spinal cord compression, radiation therapy to the bone, or surgery to the bone. Other endpoints included time to first SRE, skeletal morbidity rate, multiple event analysis, and overall survival.

This landmark trial included 1,130 women with metastatic breast cancer and 412 of these women entered the extension study. The proportion of patients who experienced at least 1 SRE in the 4 mg zoledronate and the pamidronate groups were similar (46% vs. 49%, respectively). The skeletal morbidity rate was reduced a nonsignificant 40% from 0.9 to 1.49 events per year, respectively, for the same two groups ($p = .125$). A multiple event analysis which measured the first and all subsequent SRE was found to be statistically superior for those receiving 4 mg of zoledronate versus pamidronate with a risk ratio = 0.799 ($p = .025$). Adverse events that were reported as drug-related were infections, arthralgias and myalgias, cytopenias, fever, eye disorders, electrolyte abnormalities, and injection site reactions and were similar among the initial three groups. With regard to renal toxicity, clear differences among the groups were seen prior to protocol amendments that increased the zoledronate infusion time from 5 to 15 minutes and increased the infusion volume. After this change, the reported increase in serum creatinine rate was seen in 10.7% of the 4 mg zoledronate patients and 9.3% of the pamidronate group. Based on the efficacy and safety results from both this trial and other trials comparing zoledronate to placebo, in February 2002 the FDA approved the use of zoledronic acid for patients with bone metastases not only from breast cancer but also from a wide variety of solid tumors. As a result of this approval, patients with breast cancer and bone metastases were routinely placed on either pamidronate or zoledronate delivered every 3 or 4 weeks for a minimum of 1 year accompanied by systemic therapy for the cancer.

Despite the emergence of intravenous bisphosphonates as a standard of care for the reduction of SRE, the dilemma continued as to whether the potency of oral ibandronate was adequate to match the efficacy of zoledronate. Barrett-Lee et al. recently presented preliminary data from a large phase III randomized trial comparing oral ibandronate to intravenous (IV) zoledronate in the treatment of breast cancer patients with bone metastases (28). Between 2006 and 2010, 1,405 newly diagnosed metastatic breast cancer patients with bone metastases were randomized to IV zoledronate (4 mg every 3 to 4 weeks) or oral ibandronate (50 mg/day) for up to 96 weeks. The primary statistical endpoint was noninferiority of oral ibandronate compared to zoledronic acid for the endpoint of the SRE rate (number of SRE/year). Secondary endpoints included time to first SRE, proportion of patients with SRE, pain scores, side-effect profiles, and survival. With a median follow-up of 18.4 months, ibandronate failed to meet the criteria for noninferiority to zoledronate for the primary statistical endpoint of SRE rate, but was similar in time to first SRE and survival. Renal adverse events were stated to be more frequent in the zoledronic acid group, although the specific incidence and severity were not presented. ONJ rate was low in both arms with no statistical difference. Although ibandronate is not approved in the United States for treatment of bone metastases, it is widely used in the United Kingdom and Europe for this indication. This is the first randomized trial comparing oral ibandronate with any other bisphosphonate therapy and will serve to educate both physicians and their patients regarding the optimal option for systemic therapy for bone metastases from breast cancer.

RANK-Ligand Inhibitors

Despite the significant reduction in SRE with intravenous bisphosphonates, not all bone morbidity is prevented. In addition, intravenous bisphosphonates carry the risk of inducing renal insufficiency as well as acute toxicities such as bone pain and fever. With the recognition that RANK-ligand is a mediator of osteoclast differentiation and survival, RANK-ligand inhibitors were thought to have potential in the treatment of bone metastases. Denosumab is a fully humanized monoclonal antibody that binds to and neutralizes RANK-ligand, thereby inhibiting osteoclast maturation and function.

Initially, Lipton et al. reported on a phase II randomized trial assessing the efficacy and safety of five different dose regimens of denosumab in 255 women with breast cancer and bone metastases that had not been previously treated with an IV bisphosphonate, and compared the efficacy to those treated with a bisphosphonate (29). The primary endpoint of the trial was the median percentage change in urinary N-telopeptide/creatinine ratio (uNTX/Cr) from baseline to week 13. It has been shown that the bone turnover marker uNTX/Cr is elevated in women with bone metastases from breast cancer. Elevated levels of uNTX/Cr are associated with an increased risk of skeletal complications. Presumably, a drug that more efficiently reduces these levels will be more effective in preventing skeletal-related

events. Patients were randomly assigned to receive denosumab subcutaneously every 4 weeks at a dose of 30, 120, or 180 mg; or denosumab every 12 weeks at a dose of 60 or 180 mg; or an open-label intravenous bisphosphonate every 4 weeks. Patients received 24 weeks of treatment and had a subsequent 32 weeks of follow-up. The study showed that the suppression of uNTX/Cr was greater with denosumab than intravenous bisphosphonates, though the degree of suppression was similar between all of the tested doses of denosumab. Based on data from this trial and pharmacokinetic and pharmacodynamic modeling, denosumab at a dose of 120 mg every 4 weeks was felt to be optimal.

Subsequently, a large phase III randomized, double-blind, double-dummy clinical trial was performed comparing denosumab 120 mg subcutaneously to zoledronic acid 4 mg intravenously every 4 weeks (21). Throughout the study, the dose of zoledronate was modified based on the creatinine. The primary statistical endpoint was the time to the first on-study SRE (noninferiority endpoint). Secondary endpoints included the time to the first on-study SRE (superiority endpoint), and the time to the first and subsequent on-study SRE (multiple event analysis).

Between April 2006 and December 2007, 2,049 patients with metastatic breast cancer and bone metastases were randomized. The trial revealed that denosumab significantly delayed the time to first on-study SRE by 18% when compared to zoledronic acid ($p < .001$ noninferiority; $p = .01$ superiority). The median time to the first SRE was 26.4 months for the zoledronic acid group, and had not been reached in the denosumab group. Denosumab also reduced the risk of developing multiple SRE by 23% and was associated with a lower mean skeletal morbidity rate of 0.45 events per patient per year versus 0.58 events with zoledronic acid. There were differences between the two groups in various adverse events. Acute-phase reactions and renal toxicity were more common in the zoledronic acid group and hypocalcemia was more common in the denosumab group. Although osteonecrosis of the jaw (ONJ) was numerically more common in the denosumab versus zoledronate group (2.0% vs. 1.4%), this was not statistically significant. As a result of these efficacy and safety data, in November 2010 the FDA gave approval to denosumab with the indication of treating bone metastases in patients with solid tumors, including breast cancer.

A tabulation of the larger phase III clinical trials as discussed above is summarized in Table 82-1. Although the trials had similar endpoints, no comparison should be made between the trials because of differing entry criteria and clinical factors for the women participating in the trial.

ASCO GUIDELINES

In 2011, the American Society of Clinical Oncology (ASCO) published a clinical practice guideline update on the role of bone-modifying agents (BMA) in metastatic breast cancer (30). The guidelines were based on a literature search using MEDLINE and the Cochrane Collaboration Library and evaluating studies published between 2003 and 2010. The primary outcomes evaluated were SRE and time to SRE. Secondary outcomes were adverse events and pain. The guideline group addressed seven specific clinical questions as follows:

1. Indications and timing for using BMA to reduce the risk of SRE
2. The role of BMA as treatment for extraskeletal metastases
3. The renal and ONJ safety concerns of BMA
4. The optimal duration of therapy
5. The best intervals between dosing
6. The role of BMA in controlling pain from bone metastases
7. The role of biochemical markers of bone turnover

The following are the guideline recommendations based on these questions:

1. BMA are recommended for patients with metastatic breast cancer with evidence of bone destruction. Choices for therapy are as follows: subcutaneous denosumab 120 mg every 4 weeks; IV pamidronate 90 mg over no less than 2 hours every 3 to 4 weeks; or IV zoledronic acid 4 mg over no less than 15 minutes every 3 to 4 weeks.
2. One BMA is not recommended over another.
3. If using a bisphosphonate, recommendations were made regarding dose adjustments for renal function and monitoring of the creatinine.
4. If using denosumab, no adjustments are needed for renal function, but for patients with poor renal function, close monitoring for hypocalcemia is recommended.
5. Patients should have a dental examination and routine preventative dentistry before initiating a BMA.
6. Biochemical markers to monitor BMA use are not recommended for routine care.

TABLE 82-1

Summary of Highlighted Phase III Randomized Trials

Phase III Trial	*Treatment*	*Patients*	*% with SRE*	*Skeletal Morbidity Rate (SRE/year)*	*Time to SRE (months)*	*Multiple Events Analysis (time to first and subsequent SRE)*
Lipton et al. (32)	Placebo	384	64%	3.7	7.0	NR
	Pamidronate	367	51%	2.4	12.7	
Rosen et al. (35)	Pamidronate	555	49%	1.49	NR	RR 0.799 ($p = .025$)
	Zoledronate	561	46%	0.9	NR	
Barrett-Lee et al. (36)	Ibandronate	699	67%	0.543	HR 0.11	NR
	Zoledronate	705	56%	0.444		
Stopeck et al. (38)	Zoledronate	1020	NR	0.58	26.4	RR 0.77 ($p = –.01$)
	Denosumab	1026	NR	0.45	Not reached	

NR, not reported.

SPECIAL CONSIDERATIONS

Duration of BMA Therapy

Women with metastatic breast cancer continue to see extension of their survival as a result of improvements in available systemic and supportive therapies. The majority of clinical trials evaluating the efficacy of BMA have durations of therapy ranging from 1 to 2 years. However, with improved survival of women with metastatic disease, especially those with only skeletal metastases, the optimal duration and schedule of the BMA has become a clinical challenge. Amodori et al. have presented the initial results of phase III prospective, randomized, open-label study (ZOOM) to assess the safety and efficacy of zoledronic acid given quarterly (4 mg every 12 weeks) versus monthly (4 mg every 4 weeks) in women who had received approximately 1 year of prior zoledronic acid for bone metastases (31). Between 2006 and 2010, 425 women were randomly assigned to one of these arms. The primary statistical endpoint for this noninferiority study was skeletal morbidity rate (SMR; skeletal events/year). Secondary endpoints included time to first SRE, bone pain, and bone marker (NTX) levels. The mean SMR was 0.26 in the quarterly arm and 0.22 in the monthly arm, indicating the efficacy of the quarterly arm was not inferior to the monthly arm. Adverse events were similar between the two arms with both renal insufficiency and ONJ infrequently reported. The authors pointed out study design limitations, such as an open-label design and different clinic visit frequencies between the arms, among others. Reference was made to an ongoing study (OPTIMIZE-2), which has a similar design and may be able to verify the results of the ZOOM trial. OPTIMIZE-2 is a phase III randomized, double-blind multicenter trial that has completed accrual comparing monthly versus every three monthly zoledronic acid for patients with metastatic breast cancer that were treated with between 9 and 12 doses of zoledronic acid over the prior year (Trial Identifier NCT00320710). No data have been reported from this trial.

Regardless of the schedule used after the first year, there are even less data studying duration of therapy. In this setting of inadequate data, several international breast cancer guideline groups have commented upon the use of BMA therapy beyond 2 years. The NCCN (32) has stated the following: "Current clinical trial results support the use of bisphosphonates for up to 2 years. Longer durations of bisphosphonate therapy may provide additional benefit, but this has not yet been tested in clinical trials. The optimal duration of treatment with denosumab is not known." The 2011 ASCO Clinical Practice Guidelines (30) suggest that with regard to duration of BMA use, the guidelines panel suggests that "once initiated, bone-modifying agents be continued until evidence of substantial decline in a patient's general performance status. The Panel stresses that clinical judgment must guide what constitutes a substantial decline." Although clinicians may decide to continue BMA beyond 2 years, it should be done while recognizing the lack of long-term adverse event data with respect to the risk of ONJ, the newly emerging atypical femur fractures, or chronic renal dysfunction.

Osteonecrosis of the Jaw (ONJ)

With the approval of pamidronate in 1996 and zoledronic acid in 2002, thousands of patients with either multiple myeloma or metastatic breast cancer were exposed to prolonged infusions of these agents. In 2003, a letter to the *Journal of Oral and Maxillofacial Surgery* was published describing what is now known as ONJ in 36 patients receiving either pamidronate or zoledronic acid (33). The majority of these cases were associated with tooth extraction, but some were spontaneous. This led to multiple case studies of ONJ in the literature. Clinical descriptions of ONJ were proposed and published by multiple societies including the American Academy of Oral and Maxillofacial Surgeons (AAOMS), the American Dental Association, and many others (34). The AAOMS has defined BMA-related ONJ as an area of exposed bone in the jaw persisting for over 8 weeks in patients without prior craniofacial radiation to the jaw. The pathogenesis of ONJ continues to be inadequately defined, and although the use of osteoclast inhibitors appear to increase the risk, the contributions of other factors such as the histology and location of the bone metastases, the use of concurrent chemotherapy and/or steroids, and underlying dental pathology are inadequately defined. Dental risk factors of ONJ have been described to include surgical procedures involving the jaw, ill-fitting dentures, periodontal disease, and dental abscesses. Preventative recommendations that have been published include a thorough dental examination and completion of dental procedures including extractions prior to the initiation of intravenous bisphosphonates or denosumab. Patients on BMA should be encouraged to maintain excellent oral hygiene and to continue regular dental visits as well. There are multiple specialty society recommendations regarding the treatment of documented ONJ, but most recommend consultation with an oral maxillofacial surgeon or dental oncologist with experience in managing patients with ONJ.

To better define the incidence, risk factors, and outcomes of ONJ, Saad et al. evaluated these endpoints in a combined analysis of three phase III trials in patients with metastatic cancer to the bone receiving either denosumab 120 mg subcutaneously or zoledronic acid 4 mg every 4 weeks (35). These three trials required on-study oral examinations at entry on the trial and every 6 months thereafter. An independent blinded committee of dental experts adjudicated all suspected episodes of ONJ. Of the 5,723 patients studied in the three trials, 276 were thought to potentially have ONJ, and 89 (1.6%) of the patients were subsequently adjudicated. Notably, 5447 patients had no reported oral events. The incidence rate of ONJ for the patients receiving zoledronic acid was 1.3% and for denosumab was 1.8% ($p = .13$). The median time from BMA initiation to ONJ was 14 months (range 4 to 30 months) with no differences between the two groups. Reported associated oral events included jaw pain in 80%, an associated tooth extraction in 61%, and a local infection in 48% of patients. The location of ONJ was limited to the mandible in 73%, maxilla in 22%, and both in 4% of patients. The authors conclude that with the current use of BMA, ONJ is an infrequent event and will not differ significantly between zoledronate and denosumab. Because investigators were actively surveilling patients for any dental events and educating their patients on appropriate preventative dentistry, a low incidence of ONJ may be anticipated for patients with bone metastases when following these simple standards.

Hypocalcemia

Although both pamidronate and zoledronate are approved for the treatment of hypercalcemia of malignancy, their use in patients who are normocalcemic may carry the potential risk of inducing hypocalcemia. In light of this risk, pamidronate and zoledronate therapeutic clinical trials required that patients be given both oral calcium and vitamin D supplements. Although it is likely that adherence to these supplements was not optimal, the incidence of hypocalcemia was infrequently reported. As more potent suppressors of

osteoclastic activity become available, the risk for clinically relevant hypocalcemia can increase. In the phase III trial comparing zoledronic acid with denosumab, oral calcium and vitamin D supplementation were required. Despite this, 3.4% of the patients receiving zoledronic acid and 5.5% of those on denosumab experienced hypocalcemia. Body et al. have recently summarized the incidence of hypocalcemia in the three pivotal phase III trials comparing denosumab with zoledronic acid in patients with bone metastases from multiple primary malignancies, including breast cancer (36). Of the 2836 patients who received zoledronic acid, 5.0% experienced hypocalcemia compared to 9.6% of the 2,841 patients who received denosumab. Grade 3 and 4 hypocalcemia were seen in 1.4% and 3.1% of patients, respectively, and 1.7% and 3.7% of patients required intravenous calcium. The incidence of hypocalcemia was twice as common in patients who reported taking no supplements. For those receiving denosumab, the risk of hypocalcemia was most common in the first 6 months, with the median time to hypocalcemia reported as 2.8 months. This comprehensive evaluation of hypocalcemia in a large number of patients confirms that hypocalcemia can be an expected adverse event of BMA. Calcium and vitamin D levels should be corrected prior to initiation of these therapies and the risks are highest in patients receiving denosumab.

FUTURE DIRECTIONS

Given the clinical relevance and ongoing morbidity of bone metastases in breast cancer, the optimal treatment strategy continues to evolve. The optimal agent and duration of therapy remains unclear, as discussed previously. The frequency of administration is also being debated. One study compared the standard treatment schedule of zoledronic acid to a marker-directed schedule based on uNTX levels, though the study was underpowered due to slow recruitment (37). Several novel classes of BMA are being developed that exploit distinct targets of bone metabolism. One molecule recently implicated in osteoclast function is Src. In preclinical models, an orally bioavailable Src-inhibitor, saracatinib, prevents bone resorption and migration of human osteoclast precursors (38). In early clinical studies, saracatinib significantly decreases uNTX/Cr levels, prompting ongoing studies examining its role in the adjunctive treatment of bone metastases from breast cancer (39). Dasatinib is a small molecule that inhibits several tyrosine kinases, including Src. This has led to a trial of dasatinib with zoledronic acid in patients with breast cancer metastatic to bone (Trial Identifier NCT00566618). Inhibition of mTOR (mammalian target of rapamycin) can also decrease osteoclast activity (40). This serves as the rationale for a phase II study (Trial Identifier NCT00466102) of the mTOR inhibitor everolimus in women with breast cancer and skeletal-only metastases. In addition, some investigators are exploring strategies to prevent bone metastases in women with breast cancer. As the mevalonic acid pathway is strongly implicated in bone metabolism, inhibitors of this pathway, such as statins, may alter the bone microenvironment in a way that prevents bone metastases. A retrospective study of 841 patients showed that statin use in women with breast cancer was associated with decreased rates of metastases specifically to bone but not to other distant sites, though prospective data are lacking (41).

Recently, there have been many powerful advances in the management of bone metastases in breast cancer. The unmet need for new treatment strategies has long been recognized given the clinical complications associated with skeletal metastases. A greater understanding of the physiology of bone metabolism has led to exciting discoveries. In the past decade alone, two agents, zoledronic acid and denosumab, have been approved in the United States for the adjunctive treatment of skeletal metastases in breast cancer patients and many other agents are undergoing preclinical and clinical evaluation. Much remains unclear but as we gain greater insight into the complex interactions between breast cancer and the bone microenvironment, our efforts to prevent the morbidity of bone metastases will be met with greater success.

MANAGEMENT SUMMARY

- Patients with bone metastases from breast cancer should be offered therapy with a bone-modifying agent in the absence of contraindications.
- BMA should be used as an adjunct to systemic therapy for the underlying malignancy.
- Appropriate bone-modifying agents include subcutaneous denosumab, IV pamidronate, and IV zoledronic acid.
- For patients receiving a bisphosphonate, creatinine clearance must be monitored and dose adjustments should be made as necessary.
- The use of calcium and vitamin D supplements should be explored in patients receiving bone-modifying agents, particularly with denosumab use.
- Routine dental care should be performed prior to initiation of a bone-modifying agent.
- Continuation of the bone-modifying agent for up to 2 years is certainly acceptable, although the optimal duration of therapy remains unclear.

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CHAPTER 83

Local Management of Bone Metastases

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CHAPTER CONTENTS

Historically, published information and clinical trials relating to the skeletal complications of malignancy combined data that included a variety of different primary sites. Many of the diagnostic and treatment strategies that were recommended for patients with metastatic bone disease as a whole are not applicable today for the unique group of patients with metastases secondary to breast cancer. It is only recently, and not widely, appreciated that skeletal metastases that result from breast primary differ dramatically from the other primary sites with respect to clinical presentation, prognosis, and treatment. Additionally, the introduction of bisphosphonates and more recently denosumab has dramatically changed the treatment strategy for patients with metastatic breast cancer to the skeleton, rendering much of the prior literature less useful. Only a few have published articles relating to the treatment of skeletal metastases focused on the cohort of patients with primary breast cancer rather than combining data with patients with skeletal metastases from any primary site. Table 83-1 presents web site resources for patients.

Although there has been an increasing appreciation for the differences in treatment among patients with metastatic bone disease from breast and other primary sites, the goals of treatment remain the same. They include relief of pain, restoration or maintenance of function, and avoiding hypercalcemia, metabolic derangements, bone marrow invasion, spinal cord compression, and pathological fracture.

More widespread use of sensitive imaging techniques such as magnetic resonance imaging (MRI) and positron emission tomography (PET) has created the ability to detect bone metastases at an earlier stage, often identifying asymptomatic disease. Although in general the number of patients coming to surgery for skeletal stabilization has decreased, carefully selected patients will reap major benefits from surgical intervention in terms of pain control and function.

INCIDENCE

It is estimated that there were 1.66 million new cases of cancer diagnosed in the United States in 2013. Half of those cancers will include breast, kidney, lung, thyroid, and prostate, which have a proclivity for skeletal metastases. This number far exceeds the estimated number of primary sarcomas of bone (3,010 per year), with many occurring in patients under the age of 40 years. Breast cancer is the most common cancer and the second leading cause of cancer-related morbidity among women in North America and Western Europe. In those patients who develop metastases, the skeleton is the most frequently involved site. Radiographic studies have demonstrated skeletal metastases in 70% to 80%, and autopsy studies as high as 85%, of patients who die of their disease. The most common sites of skeletal involvement include the spine and long bones (i.e., femur and humerus) (1). In part, due to the long survival of patients with breast cancer, bone metastases are common, and their potential impact on quality of life, morbidity, and mortality is significant. Certainly not all skeletal metastases will require treatment. Although the spine is the most common site of metastases from breast to bone, it is estimated that only one-third of spinal metastases will become symptomatic during the course of the patients' life. The treatment of a given skeletal lesion depends on a variety of factors including the clinical presentation. In a group of 115 cases of orthopaedic surgical management of breast cancer to bone, patients with solitary bone metastasis had a median 65-month survival, while those with visceral disease also had a median survival of 13 months (2).

TABLE 83-1

Relevant Patient Information Web sites

Entity	*Description*	*Web site*
American Cancer Society	General overview of bone metastasis for patients including symptoms, diagnosis, and treatments from the American Cancer Society	http://www.cancer.org/docroot/CRI/content/CRI_2_4_1X_What_Is_bone_metastasis_66.asp
Novartis	Commercial site with general information on symptoms, diagnosis, and imaging studies	http://www.us.novartisoncology.com/info/coping/bone_metastasis.jsp?usertrack.filter_applied=true&NovaId=3350119511325999391
American Academy of Orthopaedic Surgeons	Physician-authored site with general information on bone metastases for patients	http://www.orthoinfo.org/topic.cfm?topic=A00093
National Cancer Institute	Overview of metastatic cancer, including to bone	http://www.cancer.gov/cancertopics/factsheet/Sites-Types/metastatic
University of Michigan	General information on bone metastasis including symptoms, diagnosis, treatments, and glossary of terms	http://www.cancer.med.umich.edu/cancertreat/tissue_bone/bonegeneral.shtml

CLINICAL PRESENTATION

The clinical presentation of a patient with skeletal metastases will depend on a variety of factors. For the majority of patients with metastatic breast cancer, the primary is known before skeletal metastases become symptomatic. The clinical presentation of a patient with skeletal metastases from breast cancer may be initiated due to the onset of a symptomatic bone lesion (i.e., pain, radiculopathy, or pathological fracture) or the result of an imaging study that was performed as part of a staging evaluation (at the time of initial diagnosis or routine follow-up), or less commonly for unrelated reasons. The diagnostic workup and treatment for these conditions will depend greatly on whether the scenario takes place in the setting of a known history of breast cancer or not and whether the bone lesion is solitary or not. It is fundamentally important that in evaluating a patient with a destructive lesion of bone, a logical, thorough, and meticulous algorithm be followed in order to avoid major errors in diagnosis and treatment and minimize potential complications (3).

The majority of patients presenting with bone metastases report pain as an initial symptom, although there may be asymptomatic identification if the patient has a subsequent bone scan. In evaluating the treatment choices for patients with long bone (humerus, femur, tibia) metastasis it is particularly important to identify whether the pain is associated with weight bearing and relieved by rest, as this is one prognostic indicator of the likelihood of pathologic fracture (4). Careful assessment of the patient's analgesic use relative to pain reporting is important, as large doses of narcotics may obfuscate the severity of the symptoms and lead to undertreatment locally.

The various clinical presentations that a patient with suspected metastatic breast cancer to bone may present include the following:

1. New onset of skeletal pain *with* a known history of breast cancer (symptomatic)
2. New onset of skeletal pain *without* a known history of breast cancer (symptomatic)
3. Discovery of an asymptomatic lesion in a patient *with* a known history of breast cancer (as part of routine staging or follow-up or less likely an incidental finding)
4. Discovery of an asymptomatic lesion in a patient *without* a known history of breast (cancer as part of routine staging or follow-up or less likely an incidental finding)

DIAGNOSIS AND IMAGING OF BONE METASTASIS

Diagnostic Evaluation

Although it is true that for any patient over age 40 with a destructive bone lesion the most likely diagnosis is metastatic tumor or myeloma, the presumptive diagnosis of metastatic disease is strengthened if the patient has a history of breast cancer. However, all too often the assumption is made that a bone lesion is metastatic in a patient with a history of breast cancer and the assumption proves to be wrong. Conversely, a patient with a very remote history of breast cancer (20 years or more) and bone pain is not suspected of having potential metastases due to the lack of appreciation of the potential delayed presentation of skeletal metastases in breast cancer. As with any patient with a potentially malignant bone lesion, the patient with breast cancer requires a logical and systematic approach to evaluation in order to optimize outcomes, avoid unnecessary procedures and expenses, and expedite medical and emotional support.

The first step in evaluating a patient with a skeletal lesion requires a careful history and physical examination. The history should include the presence or absence of prior cancer diagnosis, the stage of disease, the histology, and accounting of any prior imaging studies and treatment to date. Although generally nonspecific, the presence or absence of pain, the character of pain, the onset, severity, duration, aggravating, and alleviating factors, and response to analgesics should be noted. These aspects of pain can be quantified using such tools as a 0 to 10 pain scale or the Brief Pain Index (5) pain related to skeletal metastases is usually described as a dull, aching pain that may be exacerbated with activity or weight-bearing when the lower extremities are involved. Night pain is more common in metastatic disease than in conditions such as arthritis, mechanical low back pain, or tendonitis.

A general history regarding risk factors for other cancers should also be elicited such as smoking, alcohol abuse, sun or toxin exposure, obesity, and family history.

Plain Radiographs

Plain films are the initial study to be obtained in the patient with suspected bone metastasis. Bone metastases from breast cancer may be lytic, blastic, or mixed. Use of bisphosphonates may result in a shift of the spectrum to a higher incidence of sclerotic metastases (6).

Typically lesions are poorly marginated, originate within the medullary space but cause some adjacent cortical destruction, with a characteristic "moth-eaten" appearance. Especially in the setting of pathologic fracture or insufficiency of bone, there may be adjacent periosteal reaction. Soft-tissue masses extending outside the bone may be present, particularly in deposits of long-standing.

Approximately 30% to 50% of the bone must be destroyed prior to the lesion being evident on the plain film. Generally surgical intervention is not considered in cases with less bone destruction. Although plain films are arguably the best modality for determining necessity of surgical intervention, they are not as sensitive as other modalities, particularly MRI, for determining the presence or absence of metastases.

Bone Scan

Bone scans remain relatively nonspecific as indicators of metastatic disease, with positive findings present on bone scans with unrelated causation, including arthritis, occult insufficiency fractures, and prior bone trauma. Additionally, bone scan, being a test of metabolic function, does not indicate the degree of structural damage, information important in determining which treatment modality might be most appropriate. Most skeletal metastases from breast cancer show increase radiotracer uptake at the site of involvement. Exceptions to this generalization include extremely aggressive lytic metastases (that would like be apparent on plain radiographs) and some estrogen-receptor-negative metastases, particularly those involving the cervical spine (7).

Computed Tomography Scanning

In patients with known metastatic breast cancer being followed with chest, abdomen, and pelvis computed tomography (CT) scanning, CT detected metastatic bone lesions in 43 of 44 (98%) patients with bone metastases. The remaining patient had a solitary, asymptomatic bony metastasis in shaft of femur. Bone scan was positive in all patients with bone metastases. There were 11 cases of false-positive findings on bone scan. These findings suggest that in patients with known metastases, CT scanning alone is likely sufficient to evaluate bone metastases and, in fact, bone scanning is more likely to lead to findings of false positivity (8).

Magnetic Resonance Imaging

MRI is the single best imaging modality to assess bone marrow. However, changes within the bone marrow due to skeletal metastases may be difficult to distinguish from marrow changes from nonneoplastic conditions. Benign conditions that may alter the appearance of the bone marrow on MRI include trauma, infection, radiation, the administration of growth factors (i.e., pegfilgrastim [Neulasta], filgrastim [Neupogen], granulocyte colony-stimulating factor), and osteoporosis.

With regard to decision making for intervention for symptomatic metastases, however, MRI is less useful. MRI signals are determined by paramagnetic qualities and on vascularity, depending on the sequences used, rather than structural factors. Cortical bone is relatively poorly imaged by MRI. In fact, MRI may artifactually indicate or overstate cortical erosions or bone destruction. Although MRI plays an important role in the assessment of etiology of local bone pain, it is of minimal utility in determining which patients may benefit from surgery.

Positron Emission Tomography, with or without Computed Tomography

PET scan and PET–CT are indicated for evaluating the response to treatment for patients with metastatic breast cancer. As a result, PET scans and PET–CT scans that have been performed for patients being followed with visceral metastases are discovering asymptomatic skeletal lesions. Both the PET scan and the CT scan portion of the PET are capable of discovering bone metastases prior to their becoming symptomatic. The sensitivity of PET and PET–CT compared with other imaging modalities such as the bone scan have not been well studied. Siggelkow et al. (9) in a study involving 57 patients with breast cancer found that PET scan had a relatively low positive predictive value of 74.5% and a relatively high predictive value of 98.3%. It is likely that the combination of the PET and CT will prove to be sensitive and specific when read by an experienced clinician.

EXTERNAL BEAM RADIATION THERAPY

Because bone metastases are so prevalent among women with metastatic breast cancer, treatment with external beam radiation in such patients is not uncommon. Although a number of systemic options are now available for treating diffuse bony metastatic disease, such as bisphosphonates and radionuclides, external beam radiation remains the least invasive and most effective established local therapy for the treatment of localized bony metastases. The most common reason for its use in this setting is pain control, but it can also be used to prevent progression of lesions that if left untreated could lead to fracture or spinal cord or cauda equina compression. Accordingly, the primary objective of such treatment should be to improve or maintain patients' quality of life and physical function for the duration of their lives with the least toxicity and inconvenience.

There are a surprising number of issues to consider when assessing whether such treatment has been successful. Not only is there the degree of pain relief but also the rapidity of its onset as well as its durability. One must also take into account potential acute (e.g., nausea and vomiting) and late toxicities (e.g., fracture or spinal cord damage), the possible need for retreatment, the potential to reduce dependence on narcotics thereby reducing any associated side effects, how well such treatment results in the ability of patients to maintain or improve their physical function, and the convenience of treatment. When surveyed, patients with bone metastases ranked from most to least important the duration of pain relief, likelihood of complications, degree of pain relief, mobility, dependence on narcotics, and last, the length of treatment (10).

When making decisions about whom to treat and how best to treat them, there are a number of issues to consider. One important factor is the natural history of the patient's disease. In the case of metastatic breast cancer, survival is typically longer than for the average patient with bone metastases, with median survival on the order of 2 to 3 years. Although physicians are not very good at estimating patients' life expectancies (11), it still needs to

be taken into account when deciding how best to manage these patients. The number of bony lesions and the presence of visceral metastases are also relevant, as are the extent of bone destruction and the presence of an associated soft-tissue mass. The site of the lesion can also influence the likelihood of toxicity (e.g., spine vs. extremity). Other issues to consider include the patients' performance status, any comorbidities, prior treatment with adjuvant or palliative radiation, and their ability and willingness to come for daily treatment. At the societal level, there are also the direct medical costs of treatment, the burden on family and friends, and the ability to access a nearby treatment facility in a timely fashion to consider.

When making decisions about where to treat, it is necessary to pay particular attention to patients' symptoms and any recent imaging studies, including plain x-ray images, CT scans, MRI scans, bone scans, or fluorodeoxyglucose (FDG)-PET scans. CT and MRI are especially helpful in defining the extent of any associated soft-tissue mass. Typically, the field arrangements used to treat patients with bone metastases are relatively straightforward and often consist of two opposed treatment fields or sometimes even a single rectangular field.

Conventional External Beam Radiation

Although there is general consensus regarding its efficacy, there is controversy about how best to deliver external beam radiation for the treatment of painful bone metastases. Numerous studies have reported overall response rates in the range of 60% to 70%, with complete response rates between 20% to 30% (12). The onset of pain relief usually occurs within 3 weeks of the completion of treatment, and the duration of pain relief is typically on the order of 3 to 5 months (13). The likelihood and severity of acute toxicity depends on the site and size of the field being treated, but is generally tolerable. The likelihood of patients developing significant late complications is also very low, with pathologic fracture and spinal cord compression rates in the range of only 2% to 3%.

When it comes to treatment with radiation, higher doses typically result in improved outcomes. However, this does not necessarily appear to be the case for palliative radiation for bony metastases. In a study completed over 20 years ago, the Radiation Therapy Oncology Group (RTOG) randomized 266 patients with solitary bone metastases to 40.5 Gy in 15 fractions or 20 Gy in 5 fractions and 750 patients with multiple bone metastases to 30 Gy in 10 fractions, 15 Gy in 5 fractions, 20 Gy in 5 fractions, or 25 Gy in 5 fractions and initially reported no differences in outcomes (14). Of note, in this trial pain was assessed by the treating physician, not the patient. Interestingly, these results did not lead to the use of short-course radiation. Instead, practice patterns in the United States over the past several decades have been heavily influenced by an unplanned reanalysis of these data in which patients with both solitary and multiple bone metastases were combined into a single group and the primary end point was redefined; it reported longer-course radiation (e.g., 30 Gy in 10 fractions) to be more effective (15).

Over the past decade, evidence has been mounting in patients with uncomplicated bony metastases, typically defined as lesions that have not been previously irradiated and have or will not soon result in fracture or spinal cord compression or require surgical intervention, that single-dose radiation treatment is just as effective as fractionated radiation therapy. In the Bone Pain Working Group trial 765 patients with painful bone metastases, 36% of whom had breast cancer, were randomized to 8 Gy in 1 fraction or either 20 Gy in 5 or 30 Gy in 10 fractions (16). They found no differences in terms of patient-reported time to improvement in pain, maximal pain relief, time to progression of pain, analgesics used, acute toxicity, pathologic fracture, or spinal cord compression. Patients treated with single fractions were retreated at a rate of 23% versus 10% for those receiving multiple fractions, although it was unclear whether this represented lower efficacy of single fractions or just a lower threshold to retreat patients after a single fraction.

The Dutch Bone Metastasis Study randomized 1,171 patients, 39% of whom had breast cancer, to either a single 8 Gy fraction or 24 Gy in 6 fractions and reported nearly identical results (17). Again, differences in patient-reported response rates, duration of response, use of pain medication, side effects, and quality of life were nonexistent between the two arms, while the retreatment rate was higher in the single-fraction group (25% vs. 7%). One difference in this study was that the rate of pathologic fractures was twice as high as in the single-fraction group; however, the absolute rates were still extremely low (4% vs. 2%). In a follow-up study, these investigators found that single-fraction patients who did not respond or who had progressive pain were much more likely to be retreated than multiple-fraction patients (35% vs. 8% and 22% vs. 10%, respectively), supporting the assertion that physicians are more willing to retreat patients with single fractions (18). They also reported that retreatment with radiation is highly effective in both patients without either an initial response (66% response rate after single fractions and 33% after multiple fractions) or progressive pain after an initial response (70% for single fractions and 57% after multiple fractions). Another issue especially relevant to patients with breast cancer, who, as noted above, often have prolonged survival, is whether single fractions provide pain relief that is as durable as fractionated radiation. To address this issue, the Dutch investigators looked specifically at 320 patients enrolled in their study who survived for greater than 52 weeks, 63% of whom had breast cancer (19). The mean duration of response and progression rates in this subgroup were similar between single- and multiple-fraction patients, 29 versus 30 weeks and 55% and 53%, respectively, again with high response rates following retreatment. Therefore, while the rates of progression among patients with prolonged survival are relatively high, these data suggest that it may be preferable to retreat those patients who progress rather than initially treating all patients with longer treatment courses. These investigators also examined cost and quality-of-life issues associated with single- versus multiple-fraction radiation using data from their trial and concluded that single fractions are less costly, associated with comparable quality-adjusted survival, and therefore are more cost-effective (20).

More recently the RTOG conducted another bone metastases trial limited to patients with either breast (50%) or prostate cancer and randomized 898 such patients to either a single 8 Gy fraction or 30 Gy in 10 fractions (21). Again the response rates were similar, while the retreatment rate was higher in the patients treated with single fractions (18% vs. 9%). Interestingly, the rate of acute toxicity was greater in the multiple-fraction arm than in the single-fraction arm (17% vs. 10%). Data from a Canadian trial confirmed this result and also found that the prophylactic use of antiemetics reduced the likelihood of nausea and vomiting when treating the lumbar or pelvic region (22).

In addition to the studies mentioned above, at least 12 other randomized trials have been performed examining this issue. The results of these trials have been summarized in several systematic reviews (12,23), and meta-analyses

(13,24), all of which fail to demonstrate a difference between single and multiple fractions. These data led Cancer Care Ontario to develop evidence-based guidelines on fractionation for palliation of bone metastases that recommended the use of single fractions for symptomatic uncomplicated bone metastases (25). More recently, the American Society for Radiation Oncology (ASTRO) developed a guideline that came to a similar conclusion (26). It is therefore interesting to note that when radiation oncologists are surveyed regarding the use of single fractions in this setting many are reluctant to use them (27,28) and these results have been confirmed by several studies of actual treatment records (29–32). When patients are surveyed, some have expressed a preference for single fractions, while others favor multiple fractions (27).

To date, treatment of so-called complicated bone metastases has been less well studied. As noted above, significant experience now exists regarding the efficacy of retreating bone metastases with radiation. However, the optimal retreatment regimen has not yet been identified but is currently the subject of a large international randomized trial comparing retreatment with single versus multiple fractions (33). As discussed elsewhere in this chapter, patients with bone metastases that have or are about to cause a pathologic fracture often undergo surgical stabilization. Although the data supporting its use in this setting are limited, multiple-fraction radiation is typically employed postoperatively (34).

Another related issue that is also not well studied concerns bone remineralization. In the only randomized study to investigate remineralization, Koswig and Budach (35) reported significantly more remineralization 6 months following 30 Gy in 10 fractions than 8 Gy in a single fraction (173% vs. 120% mean increase in bone density, respectively) and suggested that multiple fractions be considered when this is felt to be an important issue. Radiotherapy is also frequently used to treat bone metastases that are causing actual or impending spinal cord or cauda equina compression. In all these settings, it is still generally accepted that patients be treated with conventional fractionated radiation (e.g., 30 Gy in 10 fractions).

Stereotactic Body Radiation Therapy

Advances in the delivery of external beam radiation have recently led to interest in treating spine metastases more aggressively with radiation using an approach known as stereotactic body radiation therapy. Based on the same principles as stereotactic radiosurgery, stereotactic body radiation therapy generally refers to the use of very precise, highly conformal radiation therapy delivered to an extracranial site in one to five treatments. To achieve these goals patients typically need to be reproducibly immobilized, imaged at least immediately prior to, and sometimes during, treatment to confirm proper patient positioning, and treated with multiple, often noncoplanar and unopposed, static beams or dynamic arcs to achieve highly conformal treatment plans that spare adjacent critical normal tissues. Although initially developed for treating lung lesions, this approach is also starting to be used to treat spine metastases in patients who have previously received dose-limiting treatment to the spinal cord or in those who are felt to have such a good prognosis that more aggressive treatment may be considered.

Preliminary results from several centers in breast cancer patients have been encouraging with response rates upward of 90%, response duration of 13 months, little to no long-term toxicity, and retreatment rates between 0% to 15% (36,37). Investigators from MD Anderson recently reported results from their phase I and II prospective single arm study with comparable results (38). In addition, the RTOG is conducting a phase II and III trial comparing a single 16 Gy treatment delivered with SBRT to a single 8 Gy fraction delivered with conventional treatment techniques for treatment of painful spine metastases. The study is ongoing but has reported preliminary data from the phase II component that such treatment is feasible and tolerable in a multi-institutional setting (39).

Hemibody Radiation Therapy

At the other end of the spectrum, hemibody irradiation has been used in the past to treat diffuse bony disease and is effective in that setting with response rates of 70% to 90% (40,41). However, because of newer systemic options (e.g., bisphosphonates and radionuclides, see Chapter 82) as well as concerns regarding acute toxicity, mostly gastrointestinal, and the ability to deliver subsequent myelosuppressive chemotherapy, its use has generally declined.

SURGICAL MANAGEMENT

A large proportion of patients with metastatic breast cancer will require some type of intervention for symptomatic disease to bone. Wedin et al. (42) looked at a population of patients in Sweden with metastatic breast cancer to bone, and of 641 patients with breast carcinoma presenting with symptomatic skeletal metastasis during 1989 to 1994, 107 (17%) subsequently underwent surgery. Metastases were located in long bones (77 patients), spine (14 patients), and pelvis (6 patients). The median survival postoperatively was 6 months. It is likely that the rate of operation in this population is diminishing. In another study of patients presenting with bone metastases, Cazzaniga et al. (43) reported on a series of 459 patients presenting with metastatic breast cancer, and in their 28-month follow-up, new skeletal-related events were observed in 122 patients (26.6%).

Patients can be expected to have a relatively lengthy survival on average after surgical intervention, and surgical efforts should be directed at reasonably durable reconstructions. Durr et al. (44), looking at a group of patients undergoing orthopaedic surgery for fractures or impending fractures secondary to metastatic breast cancer, noted survival rates of 59% after 1 year, 36% after 2 years, 13% after 5 years, and 7% after 10 years.

The evaluation of the outcomes of surgical intervention in patients with bone metastases has been markedly hampered by the variability in presentation of patients with regard to site and disease status and the variability in treatment approaches. No prospective randomized data are available to compare outcomes of surgical interventions with different techniques, or even comparing surgical intervention to nonsurgical care. The participation of a multidisciplinary team can help address issues of integration of imaging findings, prognosis, coordination with other forms of care, and examination of potential surgical benefit versus morbidity (45).

The health care costs of skeletal-related events in the metastatic breast cancer population are significant. Delea et al. (46) evaluated a group of 617 patients with breast cancer and metastatic disease to bone, about half of whom had had one or more skeletal-related events. After matching cases based on propensity scores, there were 201 patients each in the skeletal-related events and no skeletal-related events groups, with mean follow-up of 13.8 and 11.0 months, respectively. In the skeletal-related events group, costs of

treatment of skeletal-related events were $13,940 (95% confidence interval [CI], $11,240–$16,856) per patient. Total medical care costs were $48,173 (95% CI, $19,068–$77,684) greater in skeletal-related events versus no skeletal-related events patients (p = .001). Along the same lines, Zhou et al. (47) evaluated a group of women with breast cancer who presented with fractures, and for older women with early-stage breast carcinoma, the direct costs for bone fracture were estimated at $45,579, and 57% of those costs came from treating the bone fracture (32% came from inpatient hospital costs, and 25% came from noninpatient hospital costs), 25% came from other excess treatment costs, and 18% came from excess long-term care costs.

There are special considerations in the management of pathologic fractures secondary to malignancy compared to conventional fracture management in normal, traumatized bone. Typically fixation is more difficult in the involved bone, not only at the site of the metastatic deposit but also in adjacent bone, which is often osteoporotic in the metastatic breast cancer population. In contrast to traumatic fractures, fracture healing in the metastatic setting is relatively poor due to multiple factors, including local tumor regrowth, effects of chemotherapy and radiation therapy, and overall catabolic state of the patient. Additionally, the prolonged time for immobilization and protected limb function is unacceptable in the palliative setting of a patient with limited lifespan in whom prompt restoration of function is paramount. Because of this, excision of bone and prosthetic reconstruction is more frequently utilized, as well as load-sharing intramedullary devices (rather than load-bearing plate and screw constructs, which also require screw fixation in bone). Prosthetic replacement may be preferable in some situations where long bones are fractured adjacent to a joint in such a way that fixation in the small, periarticular segment cannot be achieved. Definitive fixation with prosthetic implants allows for immediate weightbearing and may be associated with a lower reoperation rate than with use of intramedullary fixation (48). In general, functional outcomes are better in the lower extremities than in the humerus with this approach (49).

Preoperative Assessment and Counseling

In considering patients for possible surgical intervention, multiple levels of assessment must take place in order to ensure an intervention that provides effective palliation, has an acceptable complication risk, and is consonant with the patient's wishes.

It is difficult to document when or if surgical intervention for bone metastasis may be associated with prolonged survival. For the most part, goals of surgical intervention in long bones is with the goal of providing pain relief and improving function. However, this is not always apparent to the patient and family, and in order to ensure that expectations of all parties are aligned, detailed preoperative counseling regarding the palliative nature of the intervention is necessary. In most cases of intervention, a nonsurgical alternative can be provided for consideration, which typically includes altered or protected weightbearing (sometimes wheelchair status) and an increase in narcotic use.

The identification of the bone metastasis and its contribution to the pain and disability the patient is experiencing is critical and typically can be achieved only by a careful history and musculoskeletal examination. It is important not to assume that the metastasis is *de facto* the source the pain, but rather to exclude other potential causes of pain including arthrosis of adjacent joints, tendinopathies, bursitis, and other bone, joint, and soft-tissue maladies.

The risks of surgery should be carefully itemized, including the possibility of life-threatening complications or a possible clinical deterioration, leading to failure to leave the hospital, as high as 10% in some series. Infection, particularly in arthroplasty, can be catastrophic, requiring long-term suppressive antibiotics at best, and necessitating multiple reoperations and even amputation, at worst.

Anticipated prognosis must be carefully weighed against surgical recovery and surgical risks. Typically, patients should have a minimum expected 6-week longevity in order to benefit from long bone stabilization with intramedullary devices, and about 3 months in order to benefit from arthroplasty.

The patient must be sufficiently robust to withstand surgery. If a patient is nonambulatory, the reasons for this and the duration should be carefully assessed preoperatively before considering surgery to restore lower limb long bone function. If general fatigue and disability are limiting factors rather than the skeletal issues, or if the patient has been nonambulatory for a considerable period of time, the prognosis for restoration of ambulation may be quite poor.

Chemotherapy effects must be considered. Platelets normally should be above 50,000 in order to withstand surgical blood loss and may need to be higher (100 K) for pelvic or open spine cases. Neutrophils must be over 1 K in order to adequately guard against infection. If the patient is on myelosuppressive therapy, this should be discontinued in such a time frame that a nadir below this level will not be anticipated.

Site-Specific Surgical Considerations

Pelvis

Reconstruction of the fractured or severely involved pelvis secondary to bone metastases remains one of the more challenging aspects of orthopaedic oncology. Successful surgical restoration involves effective transfer of loads normally three times body weight from the femur to the sacrum, bypassing or reconstructing damaged or missing bone.

A number of reconstructive options have been described, including the use of Steinmann pins threaded through remaining intact pelvis combined with cement and protrusion rings to create sufficient integrity for hip replacement (50,51). Another option is to excise the affected area of the pelvis entirely and replace it with a saddle prosthesis that spans the gap between femoral shaft and upper ileum. A minimum of 2.5 cm of intact ileum is necessary to stabilize the pelvis, and complications of this procedure include dislocation of the saddle element off the pelvis. All reconstructions for the pelvis entail relatively lengthy operative times and the potential for significant blood loss. In selected highly symptomatic patients with limited ambulatory goals, girdlestone resection can be contemplated for palliation and improved sitting.

In selected patients with lytic lesions of the acetabulum refractory to radiation who may be poor surgical candidates, percutaneous cementoplasty can be considered. In this procedure, liquid polymethylmethacrylate (PMMA) is injected percutaneously into the lytic defect with the intent of providing some structural support without an extensive surgical procedure to completely reconstruct the acetabulum. This can provide pain relief and immediate improvement in structural support (52,53). This technique is primarily suited to periacetabular lesions.

Radiofrequency ablation has been reported in combination with cementoplasty in a small series of bone metastatic patients with 100% initial pain relief (54), but more research is needed to evaluate this combined modality approach (55).

Femur

Proximal Femur (Neck and Peritrochanteric): In contrast to pathologic fractures arising from osteoporosis of the femoral neck in elderly patients, pathologic fractures of the femoral neck, even nondisplaced fractures, should be considered for hemiarthroplasty. Fixation with screws along the femoral neck, while effective in nondisplaced osteoporotic fractures, is fraught with the complications of persistent pain, nonhealing, and need for additional surgery. In contrast, replacement of the proximal femur (femoral neck) with hemiarthroplasty results in predictable pain relief and early functional recovery (Figs. 83-1 and 83-2) (56). Use of a long-stemmed prosthesis can guard against subsequent fractures distal to the implant. Resurfacing of the acetabulum is usually unnecessary unless there is coexistent, symptomatic arthritis. In proximal femur fractures, arthroplasty may yield more durable results than intramedullary nailing (57,58).

With regard to femoral shaft fractures, or impending shaft fractures, treatment has been described with a number of intramedullary implants (59). Although in past decades surgical treatment algorithms for long bone metastases focused on open procedures and cement augmentation, newer fixation options allow for excellent fixation proximally and distally, with implants inserted proximally or distally to the fracture site with smaller incisions and less necessity for augmentation locally with bone cement. With the opportunity to bypass the fractured site there is in general a lower blood loss and speedier recovery. In a series of 182 surgical interventions for metastatic disease of the femur, treatment of 97 impending pathologic fractures yielded better results than treatment of 85 completed pathologic fractures with less average blood loss (438 ml vs. 636 ml), shorter hospital stay (7 vs. 11 days), greater likelihood of discharge to home as opposed to an extended care facility (79% vs. 56%), and greater likelihood of resuming support-free ambulation (35% vs. 12%). Prophylactic intramedullary nailing of the femur, rather than intramedullary nailing of completed fractures, results in shorter hospital stays, lower perioperative complication rates, and better functional outcomes (60).

Femoral nailing of pathologic fractures or impending fractures can be associated with hypoxia and pulmonary complications thought to be related to tumor and fat embolism. Acute oxygen desaturation and hypotension occurred in 11 of 45 patients in a small series of patients in whom this was rigorously studied (61). In prophylactic intramedullary nailing of the femur, venting (creation of small distal "vent" in the bone) may decrease intramedullary pressures and the risk of fat and tumor embolization (62).

Lesions of the distal femur, including the condyles and of the proximal, periarticular tibia, are relatively less common. Lesions refractory to external beam therapy or those that have fractured can be treated with segmental replacement or resurfacing arthroplasty. Due to the high rate of wound healing complications following radiation and the disastrous results of infection, liberal use of soft-tissue flaps, generally the gastrocnemius, should be considered for reconstructions

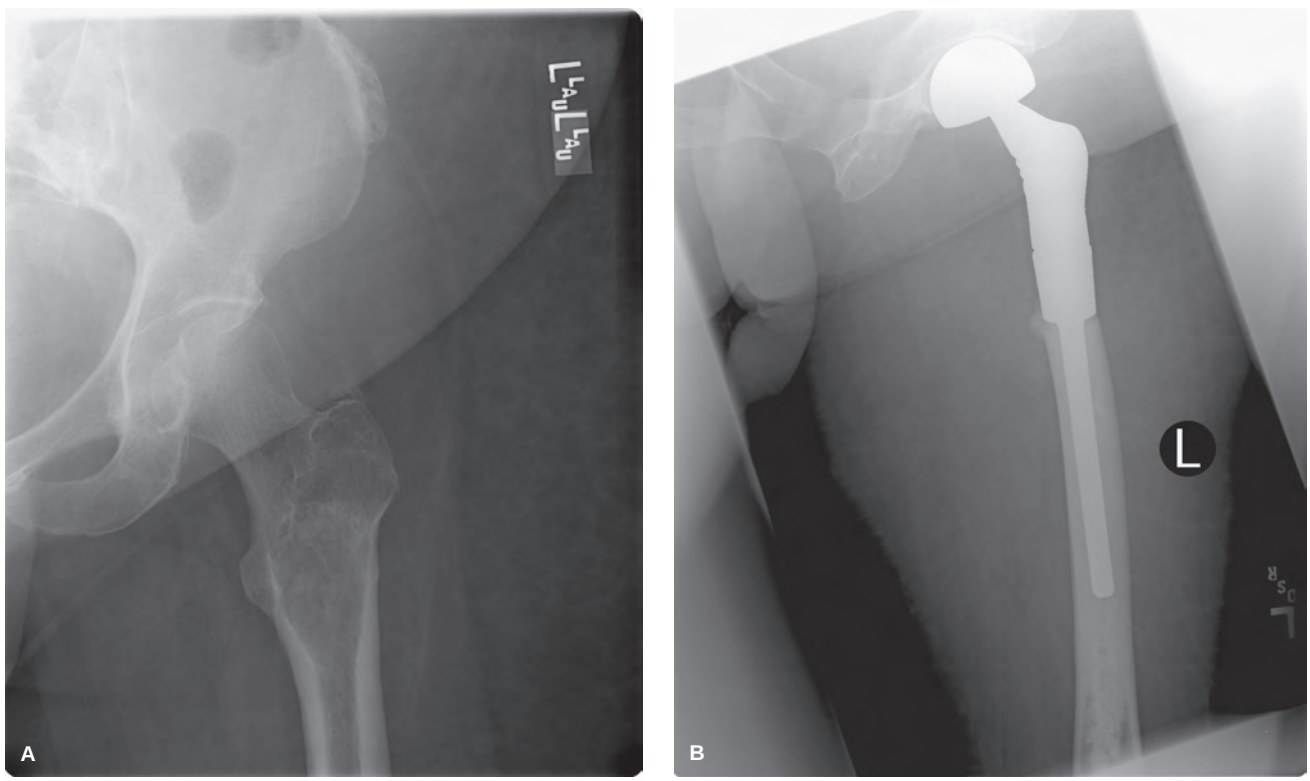

FIGURE 83-1 **(A)** Anteroposterior proximal femur in 60-year-old woman with metastatic breast caner. Plain film shows disease in proximal femur extending into femoral neck and head. Patient had prior external beam therapy and presentation with 3-week history of debilitating groin pain and inability to walk. **(B)** Postoperative plain film shows long-stemmed hemiarthroplasty. Patient was able to return to ambulatory status prior to succumbing to disease 1 year later.

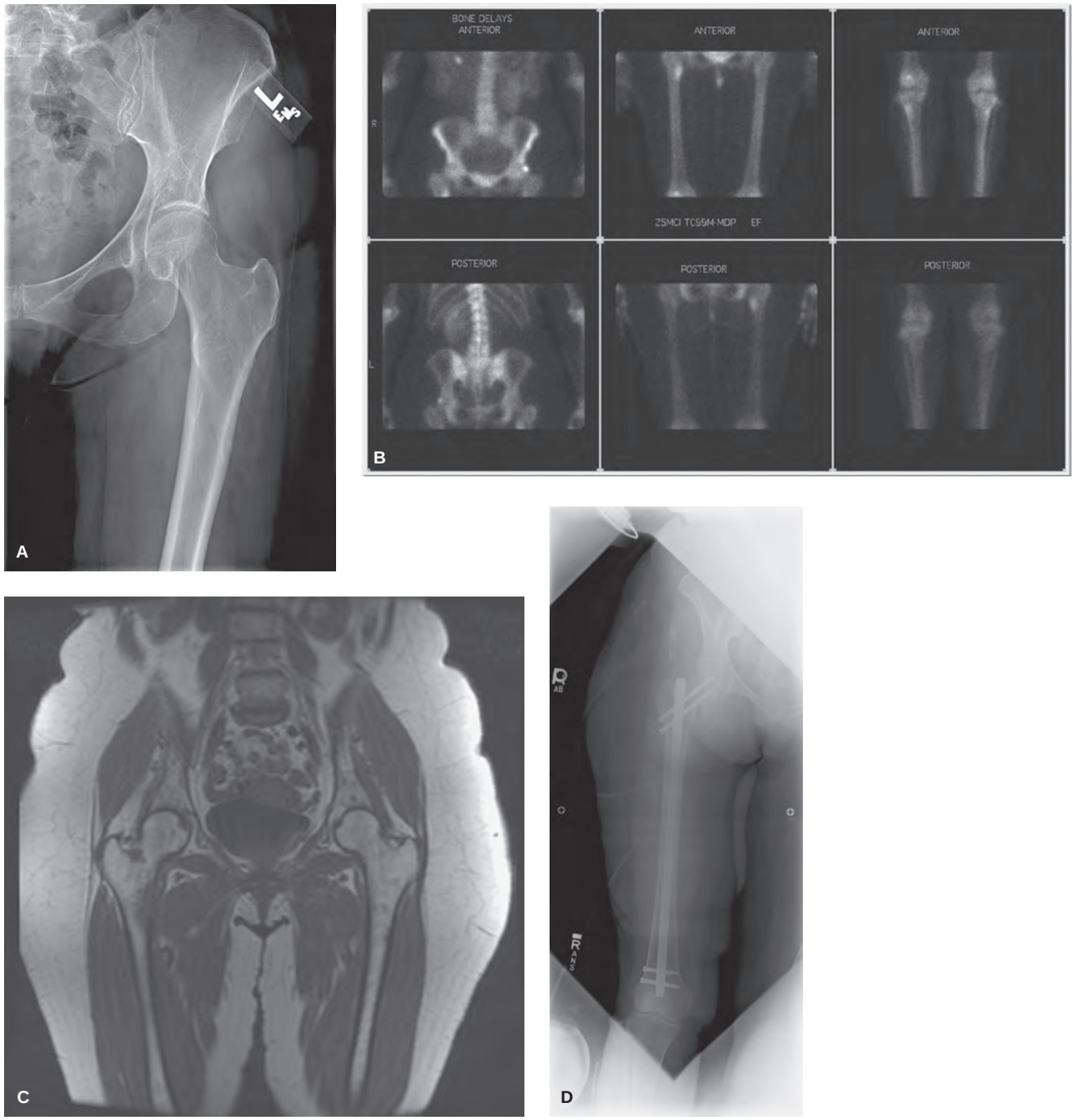

FIGURE 83-2 **(A)** Anteroposterior proximal femur in 56-year-old woman with 2-month history of increasing weightbearing pain in the femur and a history of breast cancer treated 1 year previously. Lytic destructive disease present extending from trochanter to proximal shaft. **(B)** Tc-94m methylene-diphosphonate (MDP) scan shows uptake in proximal right femur subtrochanteric region. **(C)** Coronal T1-weighted magnetic resonance image shows marrow replacement of proximal shaft of femur as well as other lesions in ilium. **(D)** Anteroposterior femur plain radiograph following intermedullary nailing of the femur. Percutaneous biopsy prior to nail placement confirmed metastatic breast cancer. Patient resumed ambulation without pain.

in this location. Patients with symptomatic metastatic disease to the femur who can undergo palliative intervention should be treated. Survival rate is higher for patients with metastatic breast cancer to femur than for other tissue types with a relatively low complication rate (63).

Humerus

The humerus is more typically involved later in the disease process in bone metastasis. Considerations include the potential for considerable disability, particularly if the dominant extremity is involved, in activities of daily living, and the potential to lose the ability to live independently.

Disease in the proximal humerus typically is extensive and requires excision of the involved bone rather than stabilization (64). Involvement of the attachments of the rotator cuff to the humerus leads to difficulty in reconstructing this defect with a conventional shoulder replacement, and segmental replacing systems should be considered. Regaining of full functional range of motion of the shoulder is rarely a possibility due to muscle insertion loss; however, regaining a stable, painless shoulder will allow the patient to use the elbow, wrist, and hand more successfully and free the opposite limb from a "tending" function.

From the proximal one-sixth of the humerus to the distal fourth of the humerus, stabilization of destructive lesions can be carried out using an intramedullary nail. These devices are inserted through small incisions in the shoulder area typically with relatively short operative times and minimal blood loss (65). The limb can be used for light activities within days.

In the distal fourth of the humerus, due to the unique anatomical considerations compounded with the adjacent elbow joint, interlocked nails are not an option. Approaches to the distal humerus include open curettage and plating and segmental replacement of the distal humerus with elbow joint replacement. Although generally done under tourniquet to reduce blood loss, these interventions have longer operative times and higher complication rates than locked nailing.

Spine

The vertebral column is the most common of all sites of bone metastases to the spine, with the spine metastases present in the majority of patient succumbing to metastatic disease from breast cancer. Manifestations of spinal involvement include pain, vertebral collapse, and neurological compromise from either tumor or extruded fracture fragments.

Pain is the most common presenting symptom from spinal metastases. While bony involvement may be treated with radiation therapy, the symptoms arising from vertebral collapse are likely to be refractory to radiation treatment and more responsive to measures to reintroduce more normal height to the vertebrae. Often patients are able to localize the offending levels, which is very helpful in targeting treatment in the patient with diffuse spine involvement. Vertebral compressions fractures can cause pain, spinal deformity (kyphosis, due to forward collapse, or scoliosis due to rotatory or sagittal plane bending), loss of height, or pulmonary or visceral compromise due to volume restrictions. Nerves exiting the spinal column may experience compression due to loss of height. Spinal cord compression can occur from either direct epidural extension of tumor, from collapsed fracture fragments forced into the spinal canal, or from tenting of the spinal cord due to deformity, most commonly kyphosis. Careful examination of the patient to ascertain the cause of pain and presence or absence of myelopathy is essential in the initial evaluation and management of the patient with spinal metastasis.

Surgical intervention potential for spinal metastatic disease has changed greatly in the past decade. Newer surgical approaches allow for improved access to all spinal levels. Improved instrumentation systems that allow for better fixation in compromised bone and more intraoperative flexibility are now available. Vertebral body replacing systems have allowed for greater opportunity to remove diseased segments with safe, structural supports (66).

Surgical intervention can be considered even in patients with multiple levels of disease or with relatively advance stage cancers. Sciubba et al. (67) reported on a series of 87 patients undergoing 125 spinal surgeries to evaluate prognostic variables. Presence of visceral metastases, multiplicity of bony lesions, presence of estrogen receptors (ER), and segment of spine (cervical, thoracic, lumbar, sacral) in which metastases arose were compared with patient survival. Those with ER positivity had a longer median survival after surgery compared to those with ER negativity. Patients with cervical location of metastasis had a shorter median survival compared with those having metastases in other areas of the spine. The presence of visceral metastases or a multiplicity of bony lesions did not have prognostic value.

Preoperative functional status likely has an impact on the effectiveness of spinal decompression procedures, and early surgical intervention should be considered in patients with spinal metastases and neurological findings. North et al. (68) evaluated results in 61 open spinal procedures for spine metastases. Preoperatively, 53 of 61 (87%) patients in the study population suffered neurological symptoms (e.g., weakness) and 52 (85%) were ambulatory. Postoperatively, 59 (97%) were ambulatory. Most patients who survived 6 months (81%) remained ambulatory, as did 66% of those alive at 1.6 years. The median postoperative survival was 10 months. The risk factors for loss of ambulation were preoperative loss of ambulatory ability, recurrent or persistent disease after primary radiotherapy of the operative site, a procedure other than corpectomy, and tumor type other than breast cancer. Prognostic factors for reduced survival were surgical intervention extending over two or more spinal segments, recurrent or persistent disease after primary radiotherapy involving the operative site, diagnosis other than breast cancer, and a cervical spinal procedure.

Percutaneous structural options for the symptomatic treatment of painful collapse of spinal vertebrae without neurological abnormalities include vertebroplasty and kyphoplasty. Percutaneous vertebroplasty is a radiographically image-guided procedure in which the surgeon or radiologist injects liquid PMMA into the collapsed vertebrae under image intensification with the intention of improving pain by increasing the structural integrity of the affected bone. Vertebroplasty was initially used for benign vascular tumors, but its use has spread to osteoporotic fractures as well as vertebral collapse secondary to metastatic or myelomatous bone tumors. Complications from vertebroplasty largely result from inadvertent extrusion of the PMMA into undesirable and unplanned areas outside the vertebral body, inducing posterior leakage with the potential disastrous consequence of cord trauma.

Kyphoplasty was introduced to essentially perform vertebroplasty in a more controlled fashion. In kyphoplasty, a small balloon or "bone tamp" is introduced under fluoroscopic guidance into the vertebral body through a percutaneous transpedicular approach and then inflated to create a

"space" into which the PMMA can then be injected. It offers the advantage of significantly greater height restoration (69) and a lower rate of cement extrusion and leakage outside the vertebral body (70). The inflatable tamp compresses adjacent compromised bone and potentially occludes alternative pathways for the cement to extrude while creating a space for the cement to occupy. Due to the increased procedural time and instrumentation, kyphoplasty is associated with higher expense and increased exposure to radiographic contrast agents. Randomized trials comparing vertebroplasty and kyphoplasty, or, indeed, either of these procedures compared to nonoperative management, have yet to be performed. However, reports of kyphoplasty have indicated that it is associated with safe, reliable pain relief, restoration of vertebral height, and even when cement is extruded it is generally without neurologic complication (71–73). Combinations of radiofrequency ablation with percutaneous bone stabilization may prove helpful in the spine and elsewhere (74).

MANAGEMENT SUMMARY

- Asymptomatic breast cancer metastases may occur, particularly in the setting of widespread metastases to bone, and can be managed medically.
- Pain that is controlled by analgesics and not weight-bearing in nature or associated with spinal compression may be improved with the initiation of bisphosphonates or the beginning of new systemic therapy; bone metastases in these situations may be observed and followed radiographically to assess whether systemic treatment may be sufficient. Progression in pain or radiographic findings would indicate the potential indication for radiation or surgery or both.
- External beam radiotherapy usually improves pain due to bone metastases.
- Patients with uncomplicated painful bone metastases should ideally be treated with a single 8 Gy fraction.
- Multiple-fraction radiation should still be used for patients at significant risk for pathologic fracture, following surgical stabilization and for patients with spinal cord or cauda equina compression.
- Prophylactic surgery for stabilization should be considered in medically appropriate candidates with weight-bearing pain in the long bones, particularly the femur.
- Spinal decompression surgery should be strongly considered for patients with spinal involvement and neurologic compromise.
- Patients with frank long bone or pelvic fractures should be considered for stabilization of fractures or joint-replacing surgery.
- Percutaneous kyphoplasty can be considered for patients with symptomatic vertebral collapse secondary to bone metastatic involvement without neurologic involvement.
- Radiofrequency ablation is a relatively new technique available at selected centers and may be considered in selected patients with failed radiation therapy who do not have lesions requiring surgical stabilization.

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SECTION XIII

Breast Cancer in Special Populations

CHAPTER 84

Breast Cancer in Older Women

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CHAPTER CONTENTS

BACKGROUND: EPIDEMIOLOGY AND BIOLOGY

Disparities in breast cancer outcome in older women, where older is typically defined as age over 65 years, has drawn attention to the disease in this group which comprises almost one-half of all new cases. High incidence is due to the fact that age is a major risk factor for breast cancer; U.S. cancer statistics from 2004 to 2008 show that breast cancer occurred in 1 of 15 women aged 70 years and older and 1 of 28 women aged 60 to 69 years, compared to 1 of 27 women aged 40 to 49, and 1 of 203 women younger than 39 years (1). We also know that although breast-cancer-specific survival has improved over recent decades, improvements have occurred preferentially in women diagnosed at ages younger than 70 years (2). If the U.S. Census Bureau predictions hold true, by 2060 the number of older women age 65 to 84 years will nearly double and those 85 and older will nearly quadruple (Fig. 84-1A), resulting in a substantial increase in the number of breast cancer diagnoses in older women. Research thus far has only begun to determine how much of the disparity in age-related breast cancer mortality can be reduced. Epidemiologic studies have compared survival rates of older women with breast cancer to age-matched older women without breast cancer and to younger women with breast cancer. Compared to controls without breast cancer, matched for age, comorbidity, prior mammography use, and sociodemographic factors in a linked Surveillance, Epidemiology and End Results (SEER)-Medicare dataset, women with early-stage breast cancer (stage 0-I) who received standard treatment had similar mortality, while women diagnosed with stage II or greater disease had significantly greater mortality (adjusted hazard ratio for death, 1.5, 95% CI, 1.5–1.6) (3). Compared to younger women with breast cancer, survival disparities also appear to be most pronounced with higher stage, higher risk disease. In the Finnish Cancer Registry, survival rates were similar in older and younger women with node-negative disease, whereas with node-positive disease the 10-year relative survival was best for women 41 to 45 years (49%) and poorest in women over 75 years (35%) (4). Mortality trends seen between 1990 and 2003 in the Surveillance, Epidemiology, and End Results (SEER) program show that there was a decrease in mortality in younger and older women with estrogen receptor-positive disease, but, in estrogen receptor-negative disease, mortality decreased in women younger than 70 years and stayed stable in women age 70 and older (2). The detection of early-stage disease in older women, therefore, is important. For women with higher stage, higher risk tumors, the causes of differential outcomes by age is a topic of active research.

Studies of patterns of care in older breast cancer patients show that they are at risk for "less than standard" management, even after controlling for factors such as comorbidity, cognitive status, social support, and functional status. In addition, lack of receipt of standard, guideline concordant care increases the risk of poor outcomes. In a study using a SEER-Medicare linked dataset from 1992 to 2003, older women with early stage cancer who received standard treatment were significantly less likely to die within 5 years than were

FIGURE 84-1 Population projections for women in the United States (in thousands). (From U.S. Census Bureau, Population Projections, Last Revised: 2012-12-14T16:41:27.218-05:00.)

women who did not receive standard therapy (16% vs. 39% for stage I disease, respectively, and 33% vs. 64% for stage II disease, respectively) (3). This is true even for women over age 80 years, where 5-year breast cancer survival is 90% for standard breast conserving surgery with systemic therapy, compared to 46% with no treatment, 51% with tamoxifen alone, and 82% with mastectomy alone (5). The rate of guideline concordant care and associated lower survival reported in population studies is confounded by patient, tumor, physician, and other factors. Admittedly, delivery of standard care depends on the risk-benefit ratio, which is sometimes difficult to assess in older, possibly frail, women. The use of potentially toxic adjuvant therapies in older women is not well supported by the literature because they have traditionally been excluded from randomized clinical trials. Furthermore, as a group, older women are perceived as having more indolent breast cancers that require less aggressive therapy.

In older women, the rate of local recurrence of ductal carcinoma in situ (DCIS) is lower than in younger women. Pathologic features of DCIS, however, do not appear more indolent in older women (6). Some authors attributed the lower local recurrence rate to immunohistochemical and genetic differences; HER-2/neu is less often overexpressed in DCIS in older patients, whereas ER, PR, bcl-2, cyclin D1, Ki-67, and p53 expression is similar (7).

With invasive breast cancers, the incidence of biologically aggressive phenotypes is less common in older women. Infiltrating ductal cancer is the most common histologic type. The more indolent histologic types, although still rare, are seen more commonly in older than in younger women. Mucinous carcinomas represent only 1% of breast cancers in premenopausal women, but 4% to 5 % in women aged 75 to 85 years and approximately 6% in women more than 85 years old (8). Papillary cancers are very rare in all age groups: 0.3% of cancers in premenopausal women and less than 1% in older women. The vast majority of breast cancers in older women are hormone receptor-positive, HER2-negative, so-called luminal A and B tumors. Markers of lower cell proliferation are common, including lower thymidine-3H labeling index, diploidy, lower histologic grade, normal p53 expression, and less overamplification of epidermal growth factor receptor (EGF-1) and c-erb-b2 (HER-2/neu) (8). Despite the apparent less aggressive phenotype, a large report, spanning 60 years and including 2,136 elderly women treated with surgery and without adjuvant systemic therapy, showed no difference in the rate of distant metastases between women over age 70 years compared to women age 40 to 70 years (9). Some attribute this to the fact that very low estrogen levels in older women affect the expression of progesterone receptors, which are less frequently positive, and androgen receptors, increasing the metastatic potential of the cancer. More aggressive tumors, such as ER/PR negative and HER2 positive cancers, however, do occur in even the oldest old patients and pose a higher recurrence and mortality risk regardless of age. In women age 70 and older with stage I–II breast cancer, for instance, tumors expressing HER2 carried 10 times the risk of recurrence at 5 years (30 vs. 3%) and lower cancer-specific survival rates (86% vs. 98%) compared to HER2 negative tumors (10).

LIFE EXPECTANCY—THE COMPLICATED INTERDEPENDENCE OF AGE, COMORBIDITY, AND FUNCTIONAL STATUS

As age increases, life expectancy decreases (Table 84-1), but even at age 80, the average woman's life expectancy is 9.6 years. Most patients and clinicians realize that the range of expected life expectancy varies more as we get older due

TABLE 84-1

Average Remaining Lifetime Expectancy for Women at Various Ages

Age (y)	*Life Expectancy, Women (y)*
60	25.3
65	20.9
70	16.7
75	12.9
80	9.6
85	6.8
90	4.7
95	3.2
100	2.3

Table shows average number of years of life remaining life at the given age. Calculated using the longevity calculator of the official Web Site of the U.S. Social Security Administration (http://www.ssa.gov/cgi-bin/longevity.cgi).

to other existing illnesses (comorbidities), the presence of frailty and disability, and other factors. Geriatricians use the Comprehensive Geriatric Assessment (CGA) to assess domains of functional status, comorbidity, medication use, cognition, social support, and nutritional status. The CGA can detect treatable geriatric syndromes in cancer patients, but it is time-consuming and rarely used in medical oncology practice. Instead, its components, screening tools, and abbreviated versions are in development. There are also tools to estimate survival, using information available clinically or excerpted from a geriatric assessment, that may assist in complicated treatment decisions in older patients. Some of these tools are available online, at ePrognosis (http://www.eprognosis.org). Several groups of experts, including the International Society of Geriatric Oncology (SIOG) and the National Comprehensive Cancer Network, recommend some form of comprehensive geriatric assessment be performed in older patients with cancer (11,12).

Functional status is a strong and significant indicator of mortality risk. In oncology, the Eastern Cooperative Oncology Group (ECOG) and Karnofsky (KPS) Performance Status are typically used to measure functional status. These measures correlate well with cancer-related mortality, but they do not correlate as well with functional status assessed in the CGA, and may underestimate the degree of functional impairment in older patients (13). In a CGA, functional status refers to one's ability to perform daily tasks, which allow one to care for oneself—activities of daily living (ADL)—and other tasks that allow one to live independently—instrumental activities of daily living (IADL). ADL and IADL are also strong predictors of survival. In addition, self-rated health is an independent risk factor for cancer-related and overall mortality (14). Compared to those rating themselves as "healthy," the relative risk of cancer-related mortality for patients rating themselves as "moderately healthy" or "not healthy" was 4.2 (95% confidence interval [CI], 1.9–9.4), and the relative risk of mortality from other causes was 3.0 (95% CI, 1.2–7.8)—even after adjusting for the presence of major chronic diseases, age, medication use, smoking, alcohol consumption, physical activity, body mass index, systolic blood pressure, serum cholesterol concentration, education, marital status, and a family history of chronic diseases. Dementia, an important geriatric syndrome, and progressive functional decline are determinants of life expectancy as well (15). Related issues of poor social support and limited access to transportation may lead to delays in diagnosis with resulting increase in the likelihood of inadequate treatment of cancer in patients aged 65 and older.

The presence of comorbidity increases with increasing age and complicates management of breast cancer because as comorbidity increases, both overall mortality (16,17) and breast-cancer-specific mortality increase. Comorbid conditions that impose functional limitations and that are expected to progress, such as diabetes with end-organ damage, steroid- or oxygen dependent chronic obstructive pulmonary disease, or a known terminal illness, definitely limit survival (18). With aging, heart and cerebrovascular diseases become increasingly more important as causes of death (Fig. 84-2). In addition, there is an interaction between comorbidity and stage of disease, such that the effect of comorbidity on survival varies by breast cancer stage (18); among patients with three or more comorbid conditions, prognosis is poor regardless of stage.

In conclusion, not only age but also geriatric indices, including functional status and comorbidity, are important in predicting overall survival, breast-cancer-related survival, and treatment tolerance. Consideration of these and other factors will ultimately help us optimize treatment strategies for older women with breast cancer.

PREVENTION

Like younger women, older women should be encouraged to maintain a healthy life style that includes exercise and weight control. Overall, available data suggest that few older women are likely to be good candidates for pharmacologic strategies of breast cancer prevention; the risk/benefit ratio is rarely favorable. (See Chapter 21 for a detailed review of breast cancer prevention strategies.)

SCREENING

Breast cancer screening, also discussed in Chapter 11, involves serial mammography, clinical breast examination, breast self-examination, and in some high-risk situations, although not typically in older patients, breast MRI. For older postmenopausal women, the higher probability of developing breast cancer as compared to younger women translates to a greater likelihood that a newly detected breast mass or mammographic abnormality is likely to be a breast cancer. In one study comparing mammographic results of women aged 50 to 64 years (n = 21,226) to women aged of 65 years and older (n = 10,914), Faulk and colleagues found that mammography had a higher positive predictive value, a higher yield of positive biopsies, and a greater cancer detection rate per 1,000 studies in older women (19). Finding an early cancer in an older woman, however, may not lengthen or improve her life and raises concern of overdiagnosis. The current questions about screening older women are, therefore: (i) Do older women who are screened live longer than those who are not screened (due to finding cancers at a more curable stage)? (ii) Do older women who are screened have a higher quality of life than women who are not screened (due to finding cancers earlier when they require less aggressive treatment)? (iii) Do older women require screening less frequently than yearly (due to slower-growing cancers)? (iv) Is there an age at which screening mammography should cease?

The answers to the first of these two questions are not directly available. Large randomized trials show that routine annual or biannual mammography in women aged 50

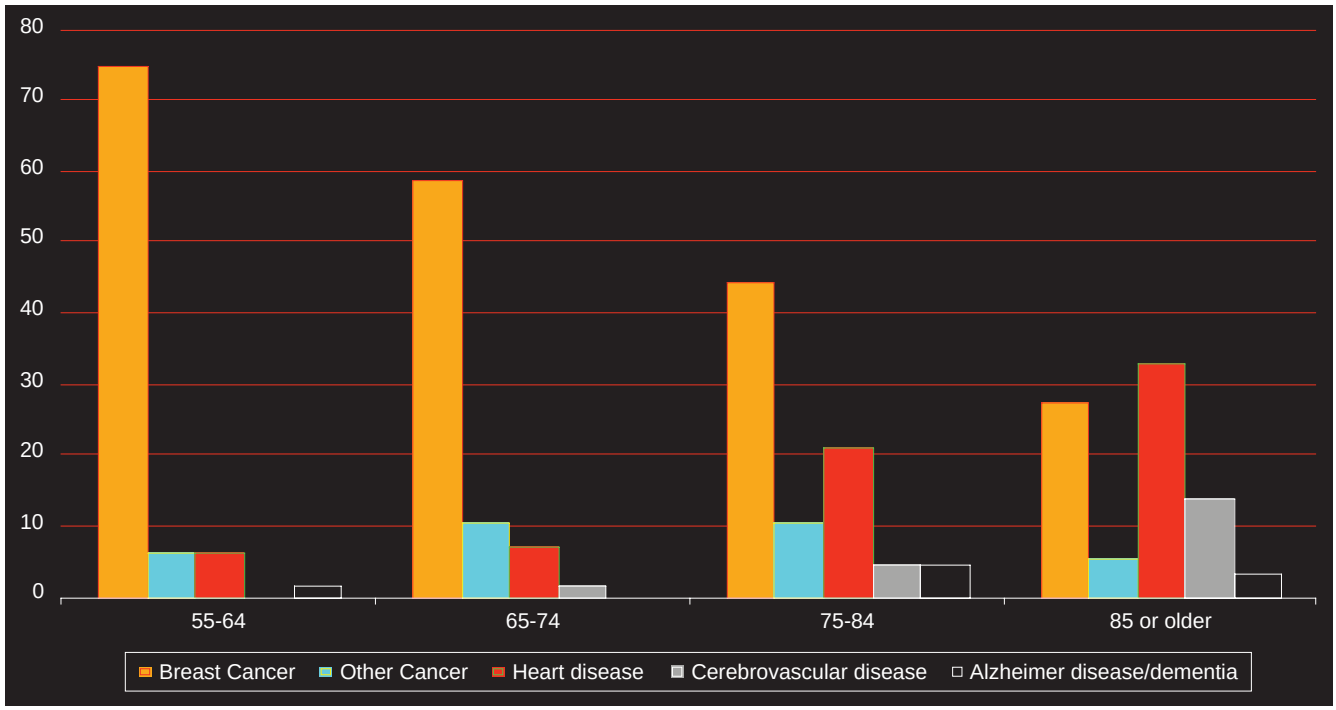


FIGURE 84-2 Cause of death within age-groups (percent). (Data from Yancik R, Wesley MN, Ries LAG, et al. Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. *Jama* 2001;285:885–892, with permission.)

to 75 years is associated with a reduction in breast cancer–related mortality of 25% to 30% within 5 to 6 years of initiation (20). As only two of these trials included women older than 75 years, the optimal upper age limit for mammographic screening is still a matter of debate (21). The U.S. Preventive Services Task Force recommends biennial screening mammography be performed in women between the age of 50 and 74 years, but concludes that the evidence is insufficient to assess the additional benefits and harms of screening mammography in women age 75 and older (22). Population-based studies suggest that cancers detected by screening mammogram in older women may result in lower stage cancer at diagnosis, but there is no demonstrable survival benefit. The frequency of screening mammography in women older than age 75 is an area of debate. The fact that breast cancers in older women tend to have features suggesting slower growth suggests that less than annual screening is reasonable. Prospective data to support screening mammography in older women do not exist.

An upper age limit for screening mammography does not exist. Most experts deem that screening is justifiable as long as the benefits outweigh the risks. One study claimed that, since high bone mineral density (BMD) was associated with increased risk of breast cancer, that women should first be screened with BMD and, if high, should have screening mammogram (23). After age 80, when life expectancy is most likely less than 10 years, screening mammogram can probably be discontinued. In fact, the risks of screening women over age 80 may outweigh the benefits. In a cohort study of 2011 women age 80 and older, for instance, there was no difference in breast cancer rates, stage, or death between screened and unscreened women, but among the 1,034 women screened, 11% had false-positive mammograms that led to 19 benign breast biopsies (24). The use of a framework or decision aid for guiding decision-making about screening that is based on life expectancy, risk of dying of cancer, and procedure-related complications has also been suggested (25,26).

In 1991, Medicare made screening mammography every 2 years a covered benefit and, in 1999, annual screening was made a covered benefit. During the first years of Medicare coverage, most older women were unaware that screening was a Medicare benefit, which led the Health Care Financing Administration to publicize mammography coverage. Self-reported 2-year mammography screening rates for women more than 65 years old increased from 43% in 1990 to 64% in 1998. Even with screening mammography as a covered benefit and after several national informational campaigns, 60% of a sample of 1,000 older female Medicare beneficiaries in Michigan between 1993 and 1997 either had not undergone a mammogram or had undergone only one (27). Attention to factors associated with lower mammography use improves screening rates. The physician's recommendation is probably the most important stimulus for obtaining screening mammography in older women. On-site mobile mammography, personalized mailings, and emphasis on the reassurance that mammography brings recipients are also helpful in improving screening rates.

The American Geriatrics Society Clinical Practice Committee published guidelines for breast cancer screening in older women (see Table 84-2) (28). The committee recommended annual or biennial mammography until age 75 years and then biennially or every 3 years thereafter in women with a life expectancy of 4 or more years. Overall, while it is less clear that mammography saves lives in women over age 75, it definitely finds cancers at an earlier stage, thus allowing less aggressive treatment and perhaps a better quality of life and survival. Longer intervals between mammograms are likely adequate and careful clinician breast exam may be beneficial. Mammography for women with a life-expectancy

TABLE 84-2

Breast Cancer Screening Recommendations for Older Women

Technique	*Recommendation*
Mammography	Annual or biennial mammography until age 75 and biennial or every 3 y thereafter, with no upper age limit for women with an estimated life expectancy of 4 or more years.
Clinical breast examination	Annual
Breast self-examination	Monthly

Modified from American Geriatrics Society Clinical Practice Committee. AGS position statement: breast cancer screening in older women. *J Am Geriatr Soc* 2000;48:842–844, with permission.

of at least 5 years and intact mental function and mobility makes good medical sense.

TREATMENT OF THE PRIMARY LESION IN THE OLDER PATIENT

After the publication of the NSABP Protocol B-06 in 1985, it became accepted that women with invasive breast cancer should be offered the choice between modified radical mastectomy and breast conservation (lumpectomy, axillary dissection, and breast irradiation). Since that time, breast conservation has become the more common surgical approach, and axillary dissection has been replaced by sentinel node biopsy, with the addition of axillary dissection reserved for the highest risk cases (see Chapters 41 and 42).

Older women should be offered the option of breast preservation, because body image and the loss of a breast are important issues regardless of age. In addition, breast preservation is a much less morbid procedure, mostly done as an outpatient procedure, and is thus preferable to mastectomy in the older individual with comorbidities. There should be a low threshold for the use of preoperative endocrine therapy to increase the rate of lumpectomy or decrease the extent of surgery as discussed elsewhere in this chapter (adjuvant therapy). In fact, women aged 70 and older are more likely to prefer breast conservation than mastectomy. Individualization of treatment is appropriate, and decisions should be made based on patient preference, overall health, tumor stage, and biology.

Today, most older patients can receive effective surgical treatment with minimal mortality risk and morbidity. Operative mortality rates for breast surgery are very low, at 1% to 2%. The main factor influencing surgical morbidity is not age but the presence of comorbidity and frailty. There may be at least a short-term decrease in cognitive function after general anesthesia in elderly patients, and even a slight decrease in cognition in an older frail patient may mean the difference between independence and consignment to assisted or total care. Attention should be paid to functional status and comorbid illnesses in making decisions about surgical management.

MANAGEMENT OF THE AXILLA IN OLDER PATIENTS

In the management of invasive breast cancer, sentinel node biopsy is preferred in the patient with clinically node-negative disease. Axillary dissection may also be omitted in women who have breast conserving surgery and pathologically involved nodes, as long as surgical margins are negative, the tumor is less than 5 cm, there are fewer than three involved nodes and the nodes are not matted, there is no extranodal extension of tumor, and in the absence of neoadjuvant endocrine or chemotherapy; these recommendations are based on the eligibility criteria for the Z11 trial (see Chapters 37 and 38). In the elderly woman with clinically benign preoperative nodal exam, however, axillary evaluation may not always be necessary.

Axillary lymph node dissection may lead to arm morbidity and other complications, especially in the elderly. In a longitudinal cohort study of 571 patients with stage I and II breast carcinoma who were 67 years of age and older, the risk of arm dysfunction during the 2 years after initial treatment was more than four times higher for women who underwent axillary dissection compared with women without axillary dissection (83% vs. 17%; $p = .0001$) (29). In a study that randomized women age 60 and older to axillary clearance or not, however, after the first postoperative visit (at which point the physician and patient assessment of quality of life related to arm symptoms was worse for women who had the axillary dissection), disruptions in quality of life disappeared within 6 to 12 months and there was no long-term difference in arm movement or pain (30). Thus, despite the potential morbidity, for elderly women with clinically positive axillary lymph nodes who can tolerate surgery and do not meet the Z11 criteria noted above, axillary dissection represents the best treatment. Alternative treatments, such as irradiation and tamoxifen (if the tumor is ER- or PR-positive) may play a role in controlling disease for a short time in patients too ill to have surgical treatment.

For older women with clinically negative nodes and a hormone receptor-positive tumor, in whom chemotherapy is unlikely to be used, axillary evaluation by sentinel node biopsy may be superfluous and add morbidity without benefit. A retrospective study of patients treated with lumpectomy plus tamoxifen, but without irradiation or axillary dissection, for instance, found low rates of recurrence in the ipsilateral axilla at 5 and 10 years; axillary relapse rates were 4.3% and 5.9%, respectively (31). Axillary recurrence was also low among older women who did not have axillary surgery in the Cancer and Leukemia Group B (CALGB 9343) trial (32). This trial, done in conjunction with RTOG and ECOG, included women age 70 and older with small (≤2 cm), clinically or pathologically node-negative, ER-positive or PR-positive primary breast cancers treated by lumpectomy plus tamoxifen who were then randomized to receive breast irradiation or not. Axillary surgery was not a requirement for study entry. In the radiation arm none of the 200 women who did not undergo axillary dissection had an axillary recurrence, whereas 2.9% (6 of 204) who did not undergo axillary clearance or have breast radiation had axillary recurrence. Finally, the International Breast Cancer Study Group (IBCSG) trial 10-93 randomized women age 60 and older with clinically node-negative, operable breast cancer, in whom adjuvant tamoxifen was indicated, to axillary clearance or not (30). Of participants in this trial, 80% had hormone receptor-positive breast cancer. At a median follow-up of 6.6 years, axillary recurrence (~2% overall), disease-free survival (67% vs. 66%. HR 1.06; $p = .69$), and overall survival

(75% vs. 73%, HR 1.05; $p = .77$) were not significantly affected by axillary surgery. Even in the absence of axillary evaluation or treatment, therefore, axillary recurrence is rare in older women with small, ER-positive tumors treated with tamoxifen, radiation, or both.

In summary, for older women with ER-positive or PR-positive cancers that are 2 cm or less who undergo breast conservation therapy, for whom chemotherapy is unlikely to be beneficial regardless of node status, axillary evaluation, even with sentinel node biopsy, has little utility. For tumors greater than 2 cm, or ER-negative and PR-negative tumors, sentinel node biopsy has utility for determining who might best benefit from adjuvant chemotherapy or axillary treatment. For the node-positive patient who does not meet the Z11 criteria, axillary dissection remains the standard for those who can tolerate the procedure.

BREAST RADIATION AFTER LUMPECTOMY

Older women tolerate breast irradiation as well as younger women, but consigning an older person to 4 to 6 weeks of radiation therapy may be exhausting and be detrimental to her quality of life. Thus, the schedule and duration of adjuvant breast radiation may be obstacles for older patients. One approach to this problem has been the development of radiation therapy schedules that are more tolerable for older patients. Two retrospective analyses examined the use of once-weekly radiation schedules. Rostom et al. reported the use of once-weekly irradiation for 84 older patients with breast cancer (stages I to IV) (33). Treatment was well tolerated. Reactive fibrosis, skin thickening, or both occurred in 25 patients; symptomatic pneumonitis was reported in 4 patients; and brachial plexopathy occurred in 1 patient. Among patients with stage I and II tumors, local tumor control and cosmetic results were encouraging. Maher et al. (34) evaluated a regimen that included once-weekly radiation therapy for a total of seven fractions and concurrent tamoxifen in a group of older women with a mean age of 81 years (range, 64 to 91 years). At a median follow-up of 36 months, the overall survival rate was 87%, the disease-specific survival rate was 88%, and the local recurrence rate was 14%. With the high dose per fraction, 39% of patients experienced moderate fibrosis at the primary site. No rib fractures, radiation pneumonitis, or brachial plexopathy were seen.

Another approach to decreasing the inconvenience of radiation therapy is accelerated partial breast irradiation (APBI) using external beam radiation or intracavitary balloon brachytherapy, and which treats only the affected area of the breast and requires about 1 week for completion (35). This usually requires two treatments per day, obviating some of the convenience gain hoped for in the elderly. APBI is discussed in great detail elsewhere in this text (see Chapter 35), but there are some data specific to the elderly. Smith et al. (36), using the National Medicare Data set for women age 67 or older, identified that brachytherapy produced significantly greater morbidity than whole breast radiation (WBRT) at 5 years (fat necrosis 8.26% vs. 4.05% and breast pain 14.55% vs. 11.92%). They also found a significant difference in ultimate mastectomy rates in favor of WBRT (3.95% APBI vs. 2.53% WBRT), although we would be hard pressed to call this difference clinically relevant. However, another report by Khan et al. found no difference in local recurrence, cosmesis or toxicity when comparing women over 70 versus women 70 or younger treated with brachytherapy (37). Finally, targeted intraoperative radiotherapy (IORT) offers the option of radiation given as a single dose intraoperatively, markedly decreasing inconvenience for the patient. Initial reports suggest a low rate of in breast recurrence (38).

While shorter courses of radiation seem feasible and likely effective in older women, the question remains whether older women need radiation after breast preservation at all. Standard local treatment for breast cancer has similar disease-free and overall survival benefits in older and younger women, but older women have more deaths from illnesses other than breast cancer (11% vs. 2%; $p = .0006$) (39,40). In CALGB 9343, only 3% of all study patients died of breast cancer while 47% died of other causes and survival was the same with or without radiation (32).

Of note is the lower risk of ipsilateral breast tumor recurrence (IBTR) in older women, with or without radiation. A regimen of breast-conserving surgery and breast irradiation was found to yield a 10-year rate of local treatment failure of 4% in older women compared with 13% in women younger than 65 years (39). Similar findings were seen in the Milan trial 3 without breast irradiation, where women treated with quadrantectomy younger than 45 years had an IBTR rate of 17.5% versus 3.8% for women older than 55 years (41).

An alternative approach has been to use tamoxifen alone after lumpectomy as a means of obviating the need for radiation therapy in women with hormone receptor-positive tumors. A retrospective study of patients treated with lumpectomy plus tamoxifen, but without radiation, demonstrated ipsilateral breast cancer recurrence rates of 5.4% and 8.7%, and incidences of distant metastases of 6.2% and 13.4%, 5 and 10 years after initial surgery, respectively (31). In a controlled clinical trial comparing quadrantectomy versus quadrantectomy plus radiotherapy in postmenopausal women older than 55 years with breast cancers smaller than 2.5 cm, a low local relapse rate (3.8%) was found for patients who had quadrantectomy alone at a median follow-up of 39 months (41). Two other small studies addressing the same issue, however, showed higher locoregional recurrence rates (about 10%) in women older than 70 years who were treated with local excision and tamoxifen alone, without adjuvant radiation (42,43).

This question has been more completely studied in CALGB 9343 (32), which randomly assigned 636 women 70 years of age or older with clinical stage I (T1N0M0), ER-positive breast carcinoma treated by lumpectomy plus tamoxifen and radiation (317 women) or tamoxifen alone (319 women). The only significant difference in outcome between the two groups was in the incidence of locoregional recurrence. Freedom from in breast recurrence at 10 years was 98% in the group randomized to tamoxifen plus radiation and 91% in the group randomized to tamoxifen alone. The difference in freedom from ultimate mastectomy at 10 years (98% with irradiation and 96% without) did not reach statistical significance. No significant differences were seen between the two groups with regard to distant metastases, all-cause mortality, or breast cancer-specific mortality. Decreasing IBTR by 7% at 10 years did not have an impact on ultimate breast conservation, distant metastases, or death from other causes. It should be noted that this trial accepted minimal margins (no ink on tumor) and that with more modern attention to margins and use of aromatase inhibitors, the difference in IBTR might be even less.

Thus, while lesser and lesser courses of radiation are possible, it is unclear that the inconvenience, morbidity, and expense can be justified. In women age 70 and older with small ER-positive tumors, the approach of endocrine therapy alone is compelling, and the National Cancer Center Network (NCCN) changed its guidelines in 2004 to make irradiation optional in women age 70 and above (44). Despite this, there was little change in the use of radiation in this older group

by 2007, 3 years after the initial publication of 9343 (45). But there is hope, because at NCCN hospitals, the rate of irradiation in women age 70 and above who meet the 9343 criteria has decreased in women age 70 to 74 (94% in 2000 to 88% in 2009) and women age 80 and above (80% in 2000 to 38% in 2009) (44). Further progress is needed. For older women with small (≤2 cm), ER-positive cancers, lumpectomy, selective axillary surgery, endocrine therapy, and no radiation appears to be a very reasonable approach to management.

Wide excision of the primary tumor alone in older women has resulted in local control rates ranging from 71% to 97% (41). In general, these results are inferior to those of other treatments, such as lumpectomy and breast radiation or lumpectomy plus endocrine therapy, but wide excision alone may be considered for patients with progressive localized breast cancer that is ER- and PR-negative and who have significant comorbidity, to minimize and potentially prevent complications of locally advanced breast cancer.

ENDOCRINE THERAPY ALONE AS PRIMARY TREATMENT

The use of tamoxifen alone as initial treatment for localized breast cancer was first studied in women who were not candidates for surgery or who refused surgical treatment; this approach is still appropriate in these settings. Subsequent randomized trials including a 2003 Cochrane analysis of 1,571 patients 70 and older fit for surgery and entered on seven randomized trials comparing tamoxifen to surgery showed that although primary endocrine therapy with tamoxifen was not as effective as surgery in preventing local recurrence, tamoxifen had no adverse effect on survival (46). The HRs for progression-free survival showed the benefit of surgery over endocrine therapy alone (0.55 and 95% CI, 0.39–0.77) and the time to tumor progression ranged from 18 to 24 months for all patients treated with tamoxifen as initial therapy. The Cochrane analysis, however, included trials that did not assess hormone receptor status and the time to tumor progression for patients on tamoxifen represents a worst-case scenario. Response durations of 10 to 50 months, however, remain the limiting factor to this approach for most patients, although in one series tumor regression can persisted up to 5 years in one-third of patients (47). For overall survival, the Cochrane analysis hazard ratio for surgery alone versus primary endocrine therapy was 0.98 (95% CI, 0.74–1.30) and for surgery plus endocrine therapy versus primary endocrine therapy was 0.86 (95% CI, 0.73–1.00). These survival data should not be surprising because tamoxifen is an extremely effective adjuvant therapy in hormone receptor-positive patients and likely compensates for the better local control gained with surgery.

In women with hormone receptor-positive breast cancer, response rates to neoadjuvant endocrine therapy are high and responses are usually evident within the first few months of starting therapy. However, further reduction in tumor size is frequent with longer durations of therapy. This latter observation is especially important for older women who present with advanced locoregional tumors not amenable to initial surgery. It is also likely that other factors known to predict the benefits of adjuvant endocrine therapy are likely to predict the likelihood of a response to neoadjuvant endocrine therapy, including lower tumor grade, a greater percentage of tumor cells displaying estrogen and progesterone receptors, and a lower proliferative index. A low 21-gene recurrence score obtained from a core biopsy may also be predictive of a response to neoadjuvant endocrine therapy (48).

In both the adjuvant and metastatic settings, aromatase inhibitors have proven superior to tamoxifen and this appears also to be true in the neoadjuvant setting. In a prospective randomized trial of 327 postmenopausal women with inoperable hormone receptor-positive tumors, complete and partial responses assessed by breast examination were 55% and 36%, and breast conserving surgery possible in 45% and 35% of patients treated with letrozole or tamoxifen, respectively (49). In another trial of 250 postmenopausal women with hormone receptor-positive primary breast cancer ineligible for breast-conserving surgery, tumor regression was noted in 60% and 41%, and breast-conserving surgery was successful in 48% and 36% of women randomized to letrozole or tamoxifen, respectively (50). These trials support the use of preoperative endocrine therapy, especially AIs, to improve a woman's chance for breast conservation after presenting with advanced locoregional disease. There is often concern that neoadjuvant endocrine therapy may be less effective than chemotherapy in causing tumor reduction. In one of the few randomized trials addressing this, neoadjuvant anastrozole or exemestane for three months was equally as effective as four cycles of paclitaxel and doxorubicin in causing tumor reduction and making patients candidates for breast conservation (51). Median time to clinical tumor response was similar (7 to 8 weeks); breast conservation rates were similar, pathologic complete response was seen in 6% of patients with endocrine therapy and 3% with chemotherapy, and disease progression while on treatment was 9% in both groups. As expected, toxicity was greater in the chemotherapy group.

In summary, primary endocrine therapy is not an ideal management approach for older women with hormone receptor-positive breast cancer who are fit for surgery, but it does offer those not able to undergo surgery or who refuse surgery the chance of disease control. The majority of older women with estimated survivals of greater than 5 years are likely to have tumor progression with endocrine therapy alone and should be encouraged to undergo surgery. Primary use of endocrine agents is only indicated for patients who refuse surgery or who have life expectancies limited to several years. For older patients who present with advanced locoregional hormone receptor-positive disease not amenable to surgery, neoadjuvant endocrine therapy should be considered; it is likely to be as effective as chemotherapy for reducing tumor size an making such patients candidates for surgery.

ADJUVANT THERAPY—GENERAL PRINCIPLES

As in younger women, the goal of adjuvant therapy in elders is to increase the chance for cure, and adjuvant therapy decisions should be based on risk of recurrence, estimated survival, and the potential benefits and toxicities of treatment. Adjuvant endocrine therapy is usually well tolerated. The decision to recommend chemotherapy is complicated by the fact that many older women have shortened survival due to existing comorbidity and are wary of the potential toxicities of treatment. The patient's life expectancy is a key factor in the adjuvant treatment decision because there is little role for adjuvant therapy in patients with life expectancies of 5 years or less. Life expectancy based on U.S. census data is factored into the treatment estimates provided by Adjuvant! (www.adjuvantonline.com) and can be estimated by other helpful tools (see reference (52) and www.eprognosis.org).

About 75% of elders with breast cancer have hormone receptor-positive and HER2-negative tumors and adjuvant endocrine therapy, regardless of nodal status, will offer them the greatest benefit. Although endocrine therapy can result

TABLE 84-3

Recommendations for Adjuvant Therapy in Women Older than 70 Years

Risk Category	*Definition*	*Treatment*
Node Negative and HER2 negative		
Minimal or low	<1 cm, ER and/or PR positive, grade I	No treatment or hormonal therapy
Moderate	>1 cm and <2 cm, ER and/or PR positive, grade I or II	- Hormonal therapy ± chemotherapy - If ER/PR positive and eligible for and willing to take chemotherapy, GEP is indicated to determine if chemotherapy is necessary.
High	>2 cm or grade II or III (any ER/PR)	- Hormonal therapy ± chemotherapy - If ER/PR negative, chemotherapy is indicated - If ER and/or PR positive and eligible for and willing to take chemotherapy, GEP is indicated to determine if chemotherapy is necessary
Node Positive and HER2 negative		
ER positive and/or PR positive	Any	- Hormonal therapy + chemotherapy - If minimal node involvement (1-3 nodes) and eligible for and willing to take chemotherapy, GEP is indicated to determine if chemotherapy is necessary
ER and PR negative	Any	Chemotherapy
HER2 positive	≥1 cm, any ER/PR	Consider chemotherapy and trastuzumab Hormonal therapy, if ER or PR positive

ER, estrogen receptor; PR, progesterone receptor. GEP, genetic expression profiling.

in toxicity, it is usually mild and not likely to affect function. The major decision is whether to offer chemotherapy, which can be associated with major toxicity. In one study of older patients with serious illness, 74% and 88% patients stated they would "rather die" than accept a treatment that caused loss of independence or cognitive function, respectively (53). Thus the decision to offer adjuvant treatment in older patients must strongly factor in the potential role of toxicity on functional status and quality of life. Our general recommendations for adjuvant therapy in women older than 70 years are outlined in Table 84-3 and are discussed below. Consensus recommendations and reviews for adjuvant therapy in elders have recently been published (54,55).

SELECTING ADJUVANT CHEMOTHERAPY

Adjuvant Endocrine Therapy for Hormone Receptor-Positive and HER2-Negative Tumors

The 2005 updated meta-analysis of adjuvant therapy trials by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) clearly shows the benefit of tamoxifen therapy and chemotherapy in improving relapse-free and overall survival in postmenopausal women with early-stage, hormone receptor–positive breast cancer (56). For such women 70 years and older 5 years of tamoxifen significantly decreased the annual risk of recurrence by 54% (standard deviation [SD] 13) and the annual risk of death by 34% (SD 13). Of note, these proportional reductions in breast cancer relapse and mortality were independent of nodal status, grade, tumor diameter, and chemotherapy use. A more recent 2011 EBCTCG analysis confirmed the benefits of 5 years of tamoxifen in women 70 years and older but noted a 0.6% combined risk of mortality from venous thromboembolism and endometrial cancer in women 55 years and older (57). This small but important risk should be factored in when considering tamoxifen in older women at low risk for recurrence.

Adjuvant endocrine therapy is discussed in Chapter 43. Although AIs may be a safer long-term choice for extended adjuvant therapy in elders, an extended duration of tamoxifen therapy may be an option for some older patients who cannot tolerate AIs, have a high risk of recurrence, and life expectancy of at least 5 years from completion of their endocrine therapy. The American Society of Clinical Oncology (ASCO) guidelines currently recommend that AIs be used as adjuvant therapy in postmenopausal women although no recommendations concerning the use of specific agents or schedules were made (58).

Unlike tamoxifen, AIs are not associated with endometrial cancer or thromboembolism but do increase the risk of fracture. In one study specifically looking at outcomes by age, women older than 70 years treated with letrozole did not have an increase in side effects when compared to placebo (59). As in younger postmenopausal women, the most common symptomatic toxicities of AIs are arthralgia and myalgia, which in some patients can be severe and lead to discontinuation of treatment. Older women who have osteoporosis at the time of endocrine therapy initiation may be best managed by starting with tamoxifen, which may improve bone density, and then switched to AIs 2 to 3 years later. Another option for women with severe osteopenia (T-score less than –2.0) or osteoporosis would be to start AIs and also to concurrently administer bisphosphonates or denosumab (60). In addition to preventing further bone loss, bisphosphonates may decrease risk of recurrence although this remains controversial.

Under-use of adjuvant endocrine therapy may put older patients with breast cancer at higher risk of disease recurrence and death. However, older women with hormone receptor-positive breast cancer with estimated survivals of 5 years or less who are frail or who have well-differentiated tumors ≤ 1cm are unlikely to benefit. A major issue in older patients taking endocrine therapy is compliance with treatment recommendations and a careful discussion of risks and benefits with patients and families is mandatory. In one study, women older than 80 years were half as likely as younger women to report a discussion about tamoxifen with their doctor (61). Also, from 15% to about 50% of older women discontinue tamoxifen before 5 years (62). Factors related to stopping tamoxifen early include toxicity, being older than 75 years, having increased comorbidity, and of major concern, having breast-conserving surgery without breast radiation. Compliance with aromatase inhibitor use is also a major issue with as many as half of patients discontinuing treatment by 4.5 years (63). Health-care providers must query older patients about compliance at every visit and continuously encourage patients to take their medications.

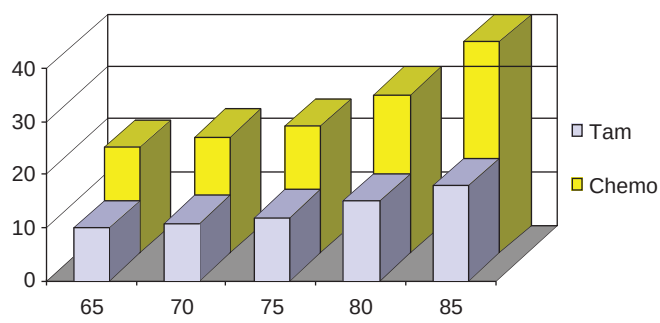
Chemotherapy in Older Women with Hormone Receptor-Positive, HER2-Negative Breast Cancer

For hormone receptor-positive, HER2-negative cancers, endocrine therapy is the mainstay of adjuvant treatment, but the major treatment decision is whether to recommend chemotherapy. The EBCTCG meta-analysis clearly showed that in women with hormone receptor–positive tumors, the combination of tamoxifen and chemotherapy was significantly better than the use of either modality alone (56). The proportional reductions in recurrence and death were 22% (SD 4%) versus 12% (SD 4%) for chemotherapy versus no adjuvant chemotherapy; 19% (SD 3%) versus 11% (SD 4%) for chemotherapy and tamoxifen versus tamoxifen alone; and 52% versus 47% for chemotherapy and tamoxifen versus chemotherapy alone. Of note, the EBCTCG meta-analysis included only about 1,000 women age 70 years or older entered in randomized trials comparing polychemotherapy with no chemotherapy. This sample size was insufficient to clearly define the benefits of chemotherapy in this oldest age cohort. However, the proportional benefits of chemotherapy for patients aged 70 years and older are likely to be similar to the benefits in postmenopausal women 50 to 69 years old. For patients aged 50 to 69 years, about 6 months of anthracycline-based chemotherapy reduced the annual breast cancer death rate by about 20%, irrespective of endocrine treatment.

The CALGB analyzed data from four randomized trials of adjuvant chemotherapy in 6,489 women with node-positive breast cancer, including three trials that included anthracyclines (64). These four trials compared different doses, schedules, and chemotherapeutic agents; patients receiving more treatment (higher doses of therapy or anthracyclines in addition to CMF regimens, or taxanes in addition to doxorubicin and cyclophosphamide) had superior relapse-free and overall survival compared with patients receiving less treatment. Similar to younger patients, those 65 years and older fared significantly better with more chemotherapy compared with less chemotherapy (31% risk reduction in relapse for those receiving more treatment; 95% CI for risk reduction, 9% to 47%). However, about 1% of older patients died of treatment-related toxicities (64). A recent meta-analysis of the EBCTCG evaluated the benefits of different polychemotherapy regimens for early breast cancer among 100,000 women in 123 randomized trials (65). This supported observations from prior trials that adding four cycles of a taxane to an anthracycline-based regimen leads to a significant reduction in breast cancer mortality (RR 0.86, SE 0.04, two-sided significance [$2p$] = 0.0005). Of note, there was no significant improvement in survival when longer or dose enhanced anthracycline-based regimens were compared to anthracycline regimens followed by taxanes (RR 0.94, SE 0.06, $2p$ = 0.33). In this meta-analysis proportional risk reductions were little affected by age, ER status, nodal status, tumor diameter, tumor grade, or tamoxifen use. However as in prior EBCTCG analyses involving chemotherapy, not enough patients 70 years were accrued and these data are not generalizable to older women.

Few older women with node-negative, hormone receptor-positive cancers will derive a meaningful survival benefit from chemotherapy. In addition, the natural history of hormone receptor-positive breast cancer in women treated with endocrine therapy indicates that the majority of relapses and the vast majority of cancer deaths occur after 5 years (56). Some older women with hormone receptor-positive cancer undoubtedly will benefit from chemotherapy, and those with estimated survivals exceeding 10 years should be considered for a gene-based assay (OncotypeDx and others) because some may have high 10-year risks of metastases and breast cancer death with endocrine therapy alone and may derive major benefit from chemotherapy (see Chapter 45). For women with one to three lymph nodes and low or low-intermediate recurrence scores, endocrine therapy alone may suffice, and a clinical trial randomizing women with hormone receptor-positive tumors and 1 to 3 positive lymph nodes (who will receive endocrine therapy) to chemotherapy or not is now in progress to confirm these observations (RxPONDER; NCT01272037). For all older women with node-positive tumors, the use of the web-based program Adjuvant! (www.adjuvantonline.com) can help in the chemotherapy decision process because benefits of treatment are based on estimated life expectancy and comorbidity. Although helpful, the potential benefits of newer more effective but toxic treatments provided by the program have not been validated independently and may overestimate treatment value.

Other estimates of the value of adjuvant chemotherapy in older women with hormone receptor-positive breast cancer may be helpful. Extermann and associates studied the threshold risk of relapse at which adjuvant tamoxifen and chemotherapy offered benefit to women up to age 85 years, including those with and without comorbidity (66) (Fig. 84-3). Using data from the 1992 overview analysis (67), these investigators examined the threshold risk of recurrence



Extermann et al, JCO 2000 12:1709

FIGURE 84-3 Ten-year risk of breast cancer relapse needed to improve mortality by 1% in patients with estrogen receptor–positive tumors.

for a 1% benefit in 5-year or 10-year relapse-free survival in older women with ER-positive tumors and for tamoxifen therapy, standard chemotherapy, or both. For tamoxifen, the threshold risks of relapse were 11% and 20% for a 1% benefit in 10-year survival for healthy and sick women at age 65 years while for age 85 years, the risks were 28% and 35% for a 1% benefit in 5-year survival for healthy and sick women, respectively (no 10-year survival benefit was seen in this age group). For chemotherapy, the threshold risk of relapse was 19% for a healthy 65-year-old patient and 62% for a sick 85-year-old patient. Although newer chemotherapy regimens are likely to lower the thresholds for treatment, the changes in these thresholds are likely to be very modest. This analysis further supports the view that chemotherapy benefits are likely to be very small in patients 75 years and older whose tumors are ER or PR receptor-positive.

The EBCTCG meta-analysis showed that six cycles of CMF and four cycles of standard AC were equivalent (RR 0.98, SE 0.05, $2p = 0.67$), but that anthracycline-based regimens with substantially higher cumulative dosage than standard AC (e.g., six cycles of CAF or CEF) were superior to standard CMF or four cycles of AC (65). Recent data suggests that four cycles of the non-anthracycline containing regimen docetaxel and cyclophosphamide (TC) are superior to four cycles of AC and result in superior disease-free and overall survival (68). At a median of 7 years follow-up, the difference in DFS and OS between TC and AC was significant with hazard ratios of 0.74 (95% CI, 0.56–0.98) and 0.69 (95% CI, 0.50–0.97), respectively, and the patients 65 and older did as well as their younger cohorts. The favorable hazard ratios for TC compared AC appear similar to the benefits seen for more intensive chemotherapy regimens in the EBCTCG analysis (65). The effect of the TC regimen on function has been retrospectively evaluated in 110 patients 70 years and older, many of whom had geriatric assessment (69); the regimen was reasonably well tolerated and 91% of patients received 4 or more cycles and 11% had dose modifications. This regimen currently represents a reasonable chemotherapy choice for many older women with hormone receptor-positive, HER2-negative breast cancer and avoids the use of anthracyclines.

Two instruments are available to predict chemotherapy toxicity in older patients. One, developed by the Cancer and Aging Research Group (CARG) (70), found 11 characteristics and clinical factors predictive of toxicity that were used to develop a score: a score of 3 was assigned for GI/GU cancer-type, delivery of standard-dose chemotherapy, hemoglobin less than 10 g/dL in women (<11 g/dL in men), creatinine clearance <34 mL/min, and 1 or more falls in the last 6 months; a score of 2 was assigned for age ≥73 years, use of poly-chemotherapy regimen, hearing impairment, and limited ability to walk 1 block; and a score of 1 was assigned if assistance was required in taking medications or for decreased social activity. Among 500 patients age 65 and older with stage I-IV cancer, at least one grade 3-5 toxicity occurred in 53% and there was 2% treatment related mortality. In the 1-19 point scale, higher scores indicated higher risk of grade 3-5 toxicity. Risk of grade 3-5 toxicity was 25% to 32% for scores of 1–5, 50% to 54% for 6–9, and 77% to 89% for 10–19. This model was better able to predict toxicity than the KPS (70). A second tool, the Chemotherapy Risk Assessment Scale for High-age patients (CRASH) score, uses both geriatric assessment tools and information classically used in clinical oncology practice to determine risk of hematologic and non-hematologic toxicity from chemotherapy (71). This tool, available online at www.moffitt.org/saoptools, is composed of two sub-scores, one predicting the risk of grade 4 hematologic toxicity and one predicting the risk of grade 3–4 non-hematologic toxicity.

Chemotherapy in Older Women with Hormone Receptor-Negative, HER2-Negative Breast Cancer

About 15% of older women present with hormone receptor-negative and HER2-negative (triple-negative) breast cancer. In this setting chemotherapy is of great value in node-positive and high-risk node-negative disease. Triple-negative breast cancer has a similar natural history in older and younger women (72), and a 2008 EBCTCG meta-analysis of women with estrogen-receptor-poor breast cancer showed a significant benefit for polychemotherapy in both women less than 50 years and those 50 to 69 years (73). The 10-year risks of recurrence and dying of breast cancer for those treated with polychemotherapy versus no chemotherapy (about six cycles of CMF or CAF) were 33% versus 45% and 24% versus 32% for those less than 50 years, and 42% versus 52%, and 36% versus 42% for those 50 to 69 years, respectively. Tamoxifen was of no benefit in these patients, and although there was no information on HER2 status, the vast majority of these patients are likely to have triple-negative tumors. The majority of these patients relapse within 5 years of diagnosis and, except for frail patients and those with a short life expectancy, the major decision is whether to use anthracycline or non-anthracycline chemotherapy. More aggressive treatment regimens using taxanes or longer durations for anthracycline-based therapy have resulted in better outcomes for patients on clinical trials and should be considered in healthy elders. Calculating treatment benefits from newer regimens using Adjuvant! (www.adjuvantonline.com) can be helpful in making treatment decisions, although there is not yet clinical validation of the benefits of these newer treatment regimens in older women.

Chemotherapy in Older Women with HER2-Positive Breast Cancer

For patients with HER2-positive tumors, the major consideration for therapy (in addition to endocrine therapy for those with hormone receptor-positive tumors) is the use of chemotherapy and trastuzumab. Older patients with small HER2-positive, node-negative, hormone receptor-positive tumors (T1a and T1b) are not likely to derive major benefit from chemotherapy and trastuzumab, while elders with hormone receptor-negative, HER2-positive tumors are likely to derive the greatest benefit from such treatment. Calculating the benefits of trastuzumab and chemotherapy in elders is challenging and at present Adjuvant! (www.adjuvantonline.com) does not provide for a simple assessment of treatment benefits. The Predict+ program (http://www.predict.nhs.uk/predict.shtml) has been validated in patients with HER2-positive tumors, incorporates age into treatment benefit estimates, and can of great help in determining the benefits of trastuzumab and chemotherapy in older patients (74). The use of trastuzumab or other anti-HER2-directed therapy without chemotherapy in lower risk, HER2-positive patients has not been studied and trials are being planned.

There is a greater risk of cardiac toxicity with trastuzumab in older patients and treatment requires careful monitoring. After 7 years of follow-up of National Surgical Adjuvant Breast and Bowel Project B-31, a randomized trial comparing anthracycline-containing chemotherapy with or without trastuzumab, 4.0% of 944 patients in the trastuzumab arm had a cardiac events compared to 1.3% of 743 patients who received chemotherapy alone. The majority of patients with cardiac toxicity recover after stopping trastuzumab, and only two cardiac events occurred more than 2 years after trastuzumab initiation (75). The authors have developed a

cardiac risk model from this trial that includes patient age that may be of major interest to clinicians caring for elders. In addition, data from another practice-changing randomized trial comparing chemotherapy with and without trastuzumab suggests that the non-anthracyline regimen of docetaxel and carboplatin combined with trastuzumab ("TCH") is as effective as anthracycline/trastuzumab regimens but less cardiotoxic (76). The TCH regimen should be considered for older patients with HER2-positive tumors. The use of beta blockers and ACE inhibitors can help reverse cardiac toxicity associated with trastuzumab (77); older patients with cardiac risk factors who are candidates for trastuzumab may benefit from cardiology consultation prior to initiation of treatment and may be considered for prophylactic use of these agents.

TREATMENT OF METASTATIC DISEASE

Selecting Therapy

Metastatic breast remains incurable. The goal of treatment in older women, like in younger women, should be to control symptoms, maintain function, and maximize quality of life. All women, regardless of age, should be managed using the principles outlined in Chapters 70–72. At least 75% of elders have metastases from a hormone receptor-positive primary lesion. These patients should be treated with endocrine therapy until there is clear evidence that the tumor is resistant to treatment. Endocrine agents should be used sequentially, and patients who have responded or had at least several months of stabilization to a specific agent may be rechallenged with the same agent, provided at least 6 months have lapsed since prior use. Once metastases are clearly refractory to endocrine therapy, older patients will be candidates for chemotherapy. For older patients with metastases but with good organ function, metastases that are not rapidly progressing, and with moderate or absent symptoms, treatment with single agent sequential chemotherapy is the best strategy. There is no compelling evidence that there is an optimal sequence of either endocrine therapies or chemotherapeutic agents and, for chemotherapy, we recommend starting treatment with the least toxic agents. Combination chemotherapy is associated with convincingly superior response rates and time to progression compared to single agents but is more toxic and does not lead to convincing improvement in survival. It should be considered for patients with rapidly progressive tumors where even modest progression would be life threatening. For patients with tumors that are HER2 positive, anti-HER2 directed therapy can substantially improve response to treatment and the duration of the response (see Chapter 72).

Older patients with lytic bone metastasis should be treated with bone resorption inhibitory drugs (bisphosphonates or denosumab). Since these agents are not associated with improved survival, there is no compelling reason to administer these drugs to asymptomatic or minimally symptomatic patients with blastic lesions only. Bisphosphonates and denosumab are effective at preventing skeletal-related events (SREs), bone pain, and hypercalcemia. This topic is discussed in detail elsewhere in this textbook (see Chapter 82). For patients with multiple painful bony metastases, treatment with radioactive pharmaceuticals such as strontium-89 and samarium-153 may result in major palliation with modest toxicity.

Endocrine Therapy

For patients with metastases that are detected while on adjuvant tamoxifen or whose cancer recurs greater than a year after stopping adjuvant aromatase inhibitors, initial endocrine treatment should be with an aromatase inhibitor. Large randomized trials have consistently shown that aromatase inhibitors (AI) are equally or more effective than tamoxifen in the metastatic setting (see Chapter 70). Although there is an increased risk for osteoporosis and fracture with long term AI use, in the metastatic setting osteoporosis is less problematic than in the adjuvant setting due to shortened life expectancy and the likelihood that many of these patients will have bone metastases and are also being treated with bisphosphonates or denosumab. Of note, a recent trial comparing anastrozole alone versus anastrozole and fulvestrant as initial therapy in 694 postmenopausal patients (median age of 65 years) with metastatic breast cancer showed both a significant improvement for the combination for both progression-free (15.0 months vs. 13.5 months, HR 0.80; p = .007) and overall survival (47.7 months vs. 41.3 months, HR 0.81; p =.05) (78). The major benefit was seen in the approximately 60% of patients who had no prior tamoxifen (PFS of 17.0 months for the combination vs. 12.6 months for anastrozole alone). A similar trial in 514 women showed no difference for the combination (79). The reasons for these differences are uncertain, and it is also uncertain if sequential use of an AI versus tamoxifen would be as effective because fewer than 41% of the patients on the Mehta trial (78) crossed over to fulvestrant after progression on anastrozole. At present the combination would appear to be a reasonable choice for the small percentage of older women who present with large volume and/or functionally impairing metastatic disease who have not had prior endocrine therapy. For the majority of older patients who develop metastases while on an AI, tamoxifen remains the treatment of choice.

About 30% to 60% of elders treated with first-line endocrine therapy have an objective response by RECIST criteria that can result in a dramatic improvement in symptoms and generally lasts for 9 to 12 months. Another 20% to 30% of patients have stable disease with no change in tumor size for at least 24 weeks. As in younger patients, higher response rates and long durations of response to endocrine therapy are more frequently seen in patients with longer disease-free intervals, those with only bone or soft tissue metastases, or a lesser number of metastatic sites. After tumor progression on initial treatment, subsequent response rates and durations of response are about half that for initial therapy. Optimal use of endocrine therapy is achieved by using agents sequentially until metastases progress. Those with metastases resistant to both tamoxifen and an AI can be treated with a different AI or fulvestrant, a selective estrogen receptor down regulator ("SERD"). Patients with very slow growing tumors refractory to these agents can be further treated with progestins (megestrol acetate and others), estradiol, and even glucocorticoids. Using endocrine therapy until metastases are convincingly refractory to such treatment allows for a delay in chemotherapy and maintenance of the highest quality of life.

A list of endocrine therapies and their potential toxicities are found in Table 84-3. A recent phase III trial (BOLERO-2) in 724 patients (median age 62 years) who had recurrence or progression of metastases on non-steroidal AIs (anastrozole or letrozole) compared the AI exemestane either alone or in combination with the mTOR inhibitor, everolimus (80). Median PFS was 6.9 months for the combination compared to 2.8 months with exemestane alone (HR 0.43; p <.001), but the combination was quite toxic and associated with increased stomatitis, fatigue, asthenia, diarrhea, cough, pyrexia, and hyperglycemia; 19% of those taking the combination withdrew from study, but quality of life was similar among both arms. Objective response rates were low in both groups—about 1%

for exemestane and 10% for the combination; mature survival data are not yet available. Of note, of 118 patients 70 years and older in the everolimus group, grade 3/4 toxicity was substantial with fatigue in 10%, anemia 10%, hyperglycemia 9%, stomatitis 8%, dyspnea 7%, pneumonitis 5%, neutropenia 3%, and hypertension 3% (81). These results are of interest, and consideration of this combination in older patients who meet the eligibility criteria for this trial is reasonable, although such patients should be carefully monitored for toxicity and should be advised of the high costs of everolimus.

Chemotherapy

The response rates and toxicity profiles of the standard chemotherapy regimens for metastatic breast cancer in older women who are functional and in reasonably good general health are similar to younger women. Chemotherapy for metastatic disease is discussed in detail in Chapter 71. The pharmacology of chemotherapeutic agents in older patients should be considered when selecting treatment because of the organ decline associated with increased age. The severity and duration of myelosuppression are modestly increased in older patients treated with chemotherapy, but this has not resulted in major differences in mortality related to neutropenia, sepsis, or bleeding. Nausea and vomiting may be less frequent in older patients, and psychosocial adjustment to chemotherapy appears better for older than for younger women. Models to help predict chemotherapy related toxicity have been discussed above (70,71). In older patients especially, sequential treatment with single agents is the strategy of choice. Only in the uncommon circumstance where urgent reduction in tumor burden is needed should combination chemotherapy be the initial choice.

There are many options for first-line chemotherapy. Capecitabine represents an excellent treatment choice for the older patient because it can be given orally and is rarely associated with myelosuppression or nausea and vomiting; it does not cause neuropathy. Starting at a lower dose and increasing the dose on subsequent cycles can avoid or minimize the hand-foot syndrome and diarrhea that can be dose limiting (82). Weekly paclitaxel has also been studied as first-line chemotherapy in elders and is highly effective but associated with a 15% occurrence of serious toxicities (83). Closely monitoring taxane-treated older patients for neuropathy is essential because even grade 1 or 2 neuropathy can adversely affect function. After tumor progression on the first chemotherapy regimen, response rates to subsequent "salvage" chemotherapy regimens are generally poor. Eribulin has been shown to be effective in elders with metastases (84), but it is also associated with neuropathy. Vinorelbine has also been evaluated in older patients; it had similar pharmacokinetics and a favorable toxicity profile when older patients were compared to younger women (85). Liposome-encapsulated doxorubicin is being tested in older patients because it is less cardiotoxic than other anthracyclines and easy to administer (86). Although a large number of biologic agents are currently in phase II and III trials, none except for those directed against HER2 tumors (see below) are FDA approved as monotherapy or in combination with chemotherapy.

Anti-HER2 Therapy

About 10% to 15% of elders have HER2-positive tumors. In the metastatic as in the adjuvant setting, the addition of trastuzumab to first-line chemotherapy has improved survival compared to chemotherapy alone (see Chapter 72). Elderly patients can tolerate trastuzumab well but require close monitoring for potential cardiac toxicity that increases with increasing age, especially in those with a history of cardiac disease or diabetes (87). Trastuzumab used as monotherapy can also be very effective and, except for cardiac risk, is associated with only minimal toxicity. Lapatinib, another anti-HER2-directed small molecule, can also increase response rates and duration of response when added to chemotherapy in trastuzumab-treated patients; its rate-limiting toxicity is diarrhea. In addition, when added to endocrine therapy with aromatase inhibitors, it is associated with increased response and progression free survival (see Chapter 72). It is uncertain however whether the combination of endocrine therapy and lapatinib is superior to endocrine therapy alone followed by lapatinib. The combination of lapatinib and trastuzumab has been shown to be extremely effective and well tolerated in patients with metastases refractory to trastuzumab. Other new anti-HER2 therapies, including pertuzumab and ado-trastuzumab-emtansine, have great potential but as yet there are no detailed data as to the tolerance of these agents in older women.

MANAGEMENT SUMMARY

Older age is a major determinant of life expectancy but is not an adequate independent predictor of treatment tolerance, disease outcome, or survival. It is essential to consider functional status, disability, and comorbidity in formulating an optimal management plan. In addition to careful screening for comorbid illness and its severity, we recommend making use of (i) available screening tools for geriatric syndromes, (ii) survival predictors, such as ePrognosis, and (iii) tools that determine risk of treatment toxicity, such as that created by CARG and the CRASH score. The composite of these proven tools in geriatrics, together with knowledge of breast cancer stage and biology, will aid older patients and their physicians in weighing the risks and benefits of surgical, radiation, and systemic therapies.

Screening

- Yearly clinical breast examination and monthly breast self-examination is recommended for all women.
- Yearly mammography is recommended up to age 75 years.
- Mammography every 2 or 3 years is recommended for women over age 75 years who have minimal limiting comorbid conditions.
- Compliance with mammography is best if it is recommended by the primary physician.
- In women with multiple comorbidities, the benefit of screening mammography should be weighed against estimated life expectancy.

Local Definitive Therapy

- No single approach for managing the primary lesion fits all older women. For older women with severe comorbidity and hormone receptor-positive tumors, treatment with endocrine therapy (tamoxifen or aromatase inhibitor) alone is reasonable. Otherwise, selection criteria for BCT and mastectomy do not differ on the basis of age.

- Preoperative endocrine therapy with tamoxifen or aromatase inhibitors may be tried in an effort to make breast-conserving therapy possible in patients with hormone receptor-positive tumors not initially amenable to breast conserving surgery.
- Sentinel node biopsy is appropriate for clinically node-negative tumors in women who plan to have a mastectomy, those with larger or hormone receptor negative tumors, or those where the outcome will impact use of chemotherapy.
- For women with small (T1), hormone receptor-positive tumors who undergo lumpectomy and where chemotherapy would not be seriously considered, sentinel node biopsy has little value.
- For women with hormone receptor-negative cancers, or T2 or greater hormone receptor-positive tumors, who will undergo lumpectomy, breast irradiation is recommended.
- Patients with clinically positive nodes who do not meet the criteria for the Z11 trial should undergo axillary node dissection (if patients are sufficiently healthy to undergo surgery), followed by breast radiation.
- For the patient with a T1, node-negative, hormone receptor-positive cancer, the use of endocrine therapy, with or without radiation (full course or abbreviated), should be discussed. Some patients are too frail for surgery when they present for treatment, and their tumors are ER and PR negative. Individualized treatment and frank discussions with these patients and their families are essential.

Systemic Adjuvant Therapy

- Adjuvant endocrine therapy should be considered in all older women with hormone receptor–positive tumors. Only older women with a very low risk of distant metastases (<10%) or severe comorbid illness should not be offered tamoxifen or an aromatase inhibitor.
- Adjuvant chemotherapy should be considered for older women whose risk of systemic breast cancer recurrence is sufficiently high and who are in good general health (estimated survival of at least 5 years).
- Chemotherapy is most beneficial in older women who have ER/PR negative or HER2-positive tumors. For older women with hormone receptor–positive tumors, however, there may be only a small added value to chemotherapy, even in patients with positive lymph nodes; the added value of chemotherapy in these patients should be estimated from available models (i.e., www.adjuvantonline.com) and new genetic tests may be helpful in selecting treatment (OncotypeDx and others).
- Trastuzumab and chemotherapy should be considered for older women with HER2-positive tumors.

Treatment of Metastatic Disease

- Endocrine therapy is the standard front-line treatment for almost all women with hormone receptor–positive metastatic breast cancer.
- There is no optimal sequence of endocrine therapy. Aromatase inhibitors tamoxifen and fulvestrant are the mainstays of treatment. Megestrol acetate, estrogens, or corticosteroids may be considered in selected patients.
- Patients who have responded to endocrine therapy can be rechallenged with the same agent or a similar agent (i.e., a steroidal aromatase inhibitor in a patient whose disease has progressed during treatment with a nonsteroidal inhibitor).
- Chemotherapy should generally be reserved for women with symptomatic disease who have progression of metastases during endocrine therapy.
- The sequential use of single chemotherapeutic agents is the preferred strategy.

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CHAPTER 85

Breast Cancer in Younger Women

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CHAPTER CONTENTS

OVERVIEW

Breast cancer rarely occurs in young women. Of the hundreds of thousands of breast cancers diagnosed worldwide, fewer than 0.1% occur in women under age 20 years; 1.9% between ages 20 and 34; and 10.6% between ages 35 and 44 (1,2). Although fewer than 7% of women diagnosed with breast cancer are younger than age 40, more than 13,000 young women are diagnosed annually with invasive or noninvasive breast cancer in the United States alone, with thousands more diagnosed worldwide (3). Incidence rates in young women appear to be fairly stable over the past several decades in young women in the Western world, despite increases in mammography and reproductive and lifestyle trends (4). A suggestion is that rates are increasing among young women, particularly in less-developed countries, but this may be owing to improvements in awareness, diagnosis, and reporting (5,6).

Despite the relative rarity of breast cancer in young women, it is the leading cause of cancer-related deaths in women under age 40, and survival rates for young women with breast cancer are lower than for their older counterparts. The 5-year relative survival rate for women with breast cancer diagnosed before age 40 is 84% compared with 90% for women diagnosed at age 40 or older (3). The preponderance of evidence to date suggests that young age is an independent risk factor for disease recurrence and death, despite young women having conventionally received more intensive treatment than older women (7,8). Delays in diagnosis and the lack of effective screening in younger women may contribute to the poorer prognosis because they are more likely to present with larger tumors and more involved lymph nodes (9,10). However, survival differences also likely reflect biological differences in the type of breast cancer identified in young women. Young women are more likely to develop more aggressive subtypes of breast cancer with unfavorable prognostic features, and are less responsive to conventional therapy compared with disease arising in older premenopausal or postmenopausal women (11,12). Specifically, tumors in young women are more likely to be high-grade, hormone receptor (HR)–negative, and have high proliferation fraction and more lymphovascular invasion. Accumulating evidence suggests that young women are also more likely to develop more aggressive tumor molecular subtypes including greater proportion of triple negative and ERBB2 (formerly HER-2/neu) overexpressing tumors (13,14) (Fig. 85-1). Furthermore, studies suggest that the prognostic effect of age may vary by tumor phenotype, although additional research is clearly warranted (15,16).

Recent studies have sought to determine whether breast cancer arising in young women may represent a distinct biologic entity with unique patterns of gene expression and deregulated signaling pathways that may affect prognosis (17–19). However, at the present time, it is uncertain whether young age will remain an independent prognostic factor as we continue to elucidate further the distinct molecular biologic features of breast cancers arising in both young and older women.

Also, evidence suggests that biologic subtypes of breast cancer vary by race as a function of age (14,20). In a large, population-based study of breast cancer subtypes within age and racial subsets, the basal-like breast cancer subtype (ER–, PR–, ERBB2–, cytokeratin 5/6 positive, and/or ERBB1+) was more prevalent among premenopausal black women (39%) compared with postmenopausal black women (14%) and

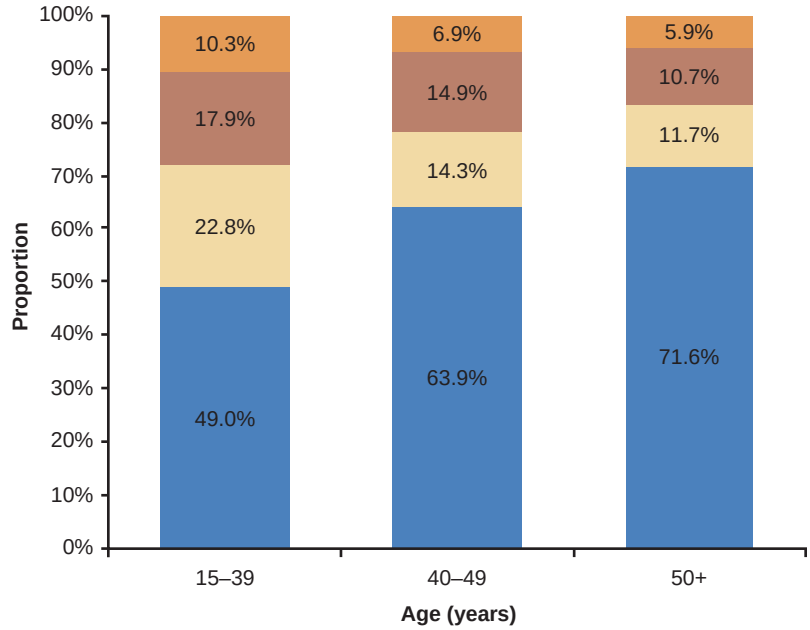

FIGURE 85-1 Proportion of breast cancer subtypes among California women by age group, 2005–2009. Hormone receptor (HR)–positive and ERBB2 negative (blue), HR+/ERBB2+ (red), HR–/ERBB2+ (green), and triple-negative (purple). (From Keegan TH, et al. Occurrence of breast cancer subtypes in adolescent and young adult women. *Breast Cancer Res* 2012;14:R55.)

nonblack women (16%) of any age ($p < .001$), whereas the better prognosis luminal A subtype (ER+ and/or PR+, ERBB2–) was less prevalent (36% vs. 59% and 54%, respectively). This higher prevalence of basal-like breast tumors and lower prevalence of luminal A tumors likely contributes to the poorer prognoses of young black women with breast cancer (20) (see Chapter 31, Prognostic and Predictive Factors: Molecular).

In addition to being at higher risk of dying from breast cancer, despite conventionally receiving more aggressive therapy, young women face a variety of problems unique to, or accentuated by, their young age. They are more likely to be diagnosed at a life stage when role functioning in the home and work can be threatened or disrupted by the diagnosis and treatment of breast cancer. Issues such as attractiveness and fertility may be of substantial importance. Young women are more likely to have young children for whom they are responsible, or desire to have biologic children following treatment. They also have an increased risk of harboring a genetic risk factor for breast cancer, and often suffer from a relative lack of information regarding treatment and survivorship issues compared with older patients. These concerns may contribute to the greater psychosocial distress seen in younger women at both diagnosis and in follow-up (21).

Research to date on breast cancer in young women is limited by generally small sample sizes and heterogeneous cut-offs used to differentiate between young and old. Although, age is a continuum and any cut-off is somewhat arbitrary. Many investigators have chosen up to age 35 or 40 to define breast cancer in younger women, recognizing that previous work focusing on premenopausal women is composed primarily of women in their 40s, owing to the higher incidence of the disease in older premenopausal women.

RISK FACTORS FOR EARLY-ONSET BREAST CANCER AND GENETICS ISSUES

Aside from female gender, increasing age is the strongest risk factor for developing breast cancer. Consequently, younger women are at much lower risk even when compared with older premenopausal women. An average woman has a 1 in approximately 1,800 risk of developing breast cancer in her 20s, 1 in 230 in her 30s, and 1 in 70 in her 40s (3). Family history is the primary risk factor for developing breast cancer at a young age, particularly when breast cancer has occurred in a first-degree relative at a young age. Although 5% to 10% of breast cancers are attributable to germline mutations such as *BRCA1* and *BRCA2* on chromosomes 17 and 13, respectively, another 15% to 20% of breast cancers are associated with the presence of gene polymorphisms and environmental factors (e.g., radiation; see later). By virtue of her age alone, a young woman diagnosed with breast cancer has a greater probability of carrying a *BRCA* mutation. In an unselected group of women under age 40 having surgery for early breast cancer, 9% harbored a deleterious *BRCA1* or *BRCA2* mutation (22). Other factors, including a personal or family history of ovarian cancer, bilateral breast cancer, or Ashkenazi Jewish ancestry, may increase that risk. The meaning of an unknown variant of the *BRCA1* or *BRCA2* genes may also vary by race (23). Young women with breast cancer should consider genetic counseling and testing for *BRCA1* and *BRCA2*, particularly if they have a family history of breast or ovarian cancer. Please see Chapters 17 and 18 for more details.

Some rare genetic disorders may predispose younger women to develop breast cancer. These include Cowden disease (*PTEN* gene mutation on chromosome 10 and associated with hamartomas, as well as with breast or thyroid cancer at a young age), and Li-Fraumeni syndrome (mutation of *TP53* gene on chromosome 17, with increased incidence of soft tissue and bone sarcomas, brain tumors, adrenocortical tumors, and breast cancers) (24) (see Chapter 17 for more detail). Young women exposed to ionizing radiation during childhood and the teenage years, such as survivors of pediatric Hodgkin disease treated with mantle field irradiation, are also at high risk of developing breast cancer (25). Despite preconceptions, most cases of breast cancers occurring in young women appear to be spontaneous and not clearly related to either carcinogens in the environment or family cancer syndromes (26). However, environmental and hormonal risk factors for breast cancer are not well characterized for younger women, but appear to be somewhat different than for older women. Although breastfeeding appears to be protective against breast cancer at any age,

pregnancy appears to have a dual effect on the risk of breast cancer. Large epidemiologic studies indicate that earlier age at first live birth has a long-term protective effect on the lifetime risk of breast cancer, yet it transiently increases the risk immediately following childbirth for 3 to 15 years postpartum (27–29). The excess transient early risk of breast cancer is most pronounced among women who are older at the time of their first delivery. Thus, pregnancy has a protective effect for postmenopausal breast cancer and is a risk factor for premenopausal breast cancer, particularly for older premenopausal women. The biologic mechanism for this is not well elucidated. Also contrary to what has been demonstrated in older women, weight gain and higher body mass index appear to be protective against the development of breast cancer at a younger age (30–32).

BREAST DIAGNOSTIC ISSUES FOR YOUNG WOMEN

Most lesions arising in the breasts of young premenopausal women will be benign (see Chapter 10, Benign Breast Disease). Mammography is often of limited value in this population because of high breast tissue density, and targeted ultrasound or magnetic resonance imaging can provide additional discriminatory information in the workup of a breast abnormality (33,34). Breast cancers may be more extensive in younger patients, although it is not clear whether they are at higher risk of multicentricity or bilateral disease, in the absence of a hereditary predisposition, and no evidence indicates that multifocality affects survival in this population (35,36).

TREATMENT ISSUES

Many clinical trials have divided patient populations based on menopausal status, or age greater or less than 50. Virtually no published clinical trials have focused on treatment issues for the youngest women. Trials reporting results of treatments for premenopausal women largely reflect outcomes for patients in their 40s. Thus, findings from studies that consider average results for premenopausal women may not be directly applicable to very young patients.

Local Therapy Issues

Partly owing to inadequate screening options for young women, breast cancer in young patients tends to be diagnosed at a more advanced stage, with more stage 2 and 3 disease diagnosed than in older women (9,12). Consequently, young women may more likely need or benefit from preoperative systemic therapy than older women, although available data in this area are limited (37). Despite the large benefit that young women obtain from an irradiation boost to the tumor bed, most studies continue to indicate that young age is a risk factor for local recurrence, for both invasive and noninvasive disease (38–40) (Fig. 85-2). No evidence suggests, however, that mastectomy in young women improves survival compared with breast conservation, likely because these women are also at increased risk of systemic recurrence (41,42). In a population-based Danish cohort of 9,285 premenopausal women with breast cancer, the incidence of local recurrence was 15.4% after breast-conserving therapy among the 719 women under age 35 compared with 3.0% in women ages 45 to 49, although no difference was found in the risk of death between the two age groups (42). Thus, young age alone is not a contraindication to breast conservation. Nonetheless, an increasing number of young women are opting not only for mastectomy, but for contralateral prophylactic mastectomy (43). Reasons for this trend are not completely clear, nor is there evidence that such aggressive surgical measures will improve outcomes. For some young women, local therapy decisions may be influenced by the presence or absence of a known genetic risk for new primary breast cancer (i.e., a *BRCA1* or *BRCA2* mutation). Thus, prompt genetic counseling and testing for young women at risk for harboring a deleterious genetic mutation should be considered, especially for women for whom the results would have an impact on local therapy decisions. Bilateral prophylactic mastectomy and oophorectomy are increasingly considered for young women with known *BRCA1* or *BRCA2* mutations, despite the current lack of clear benefits of such risk-reducing strategies in breast cancer survivors (44,45).

At present, no relevant data are available on the late effects of radiation therapy plus modern systemic therapy (including anthracyclines, taxanes, and trastuzumab) on cardiac functioning in young women. Moreover, other effects of radiation therapy in patients with very long life expectancy must be taken into account (46).

Attention to margin status may be particularly important for young women undergoing breast conservation treatment. In one evaluation including 37 women younger than age 35 with lymph node–negative breast cancer having breast-conserving therapy, local recurrence rates were 50.0% for women with positive margins compared with 20.8% for those with negative margins (47). In a more recent publication, women age 40 or younger with invasive disease had 10-year local recurrence-free survival of 84.4% with negative margins versus 34.6% with positive margins, whereas women over age 40 had local recurrence-free survival of 94.7% if margins were negative compared with 92.6% if margins were positive (48). These findings translated to a 10-year distant disease-free survival (DFS) of 72.0% for younger women with negative margins compared with 39.7% (relative risk [RR] = 3.4) for the younger age group with positive margins, whereas for older women, no significant difference was seen in DFS among those with negative compared to positive margins. There is also evidence that young women may benefit additionally from postmastectomy breast irradiation in the setting of one to three positive axillary lymph nodes (49). Despite the clear benefits, recent population-based data suggest that very young women may be less likely to receive adjuvant breast irradiation after breast-conserving surgery (50). Further research is needed to understand these trends.

Systemic Therapy Issues

Adjuvant treatment recommendations are based on tumor and patient characteristics predicting the risk of systemic recurrence and potential responsiveness to therapy, as well as the patient's preferences and values. Increasingly, treatments are tailored, regardless of age, to the phenotypic subtype of the tumor as assessed by conventional factors, such as grade, proliferation rate, estrogen and progesterone receptors, and ERBB2 expression. More recent application of genetic signature technology has provided additional predictive information regarding the degree of risk and responsiveness to therapy (see Chapter 31). However, most of the data on adjuvant treatment response was obtained during an era when details related to endocrine responsiveness were either incomplete or imprecise. Even today, endocrine responsiveness evaluation requires improved reporting of steroid hormone receptors and a better understanding of the role of ERBB2 overexpression and amplification (51). Currently it is recommended that the estimation of

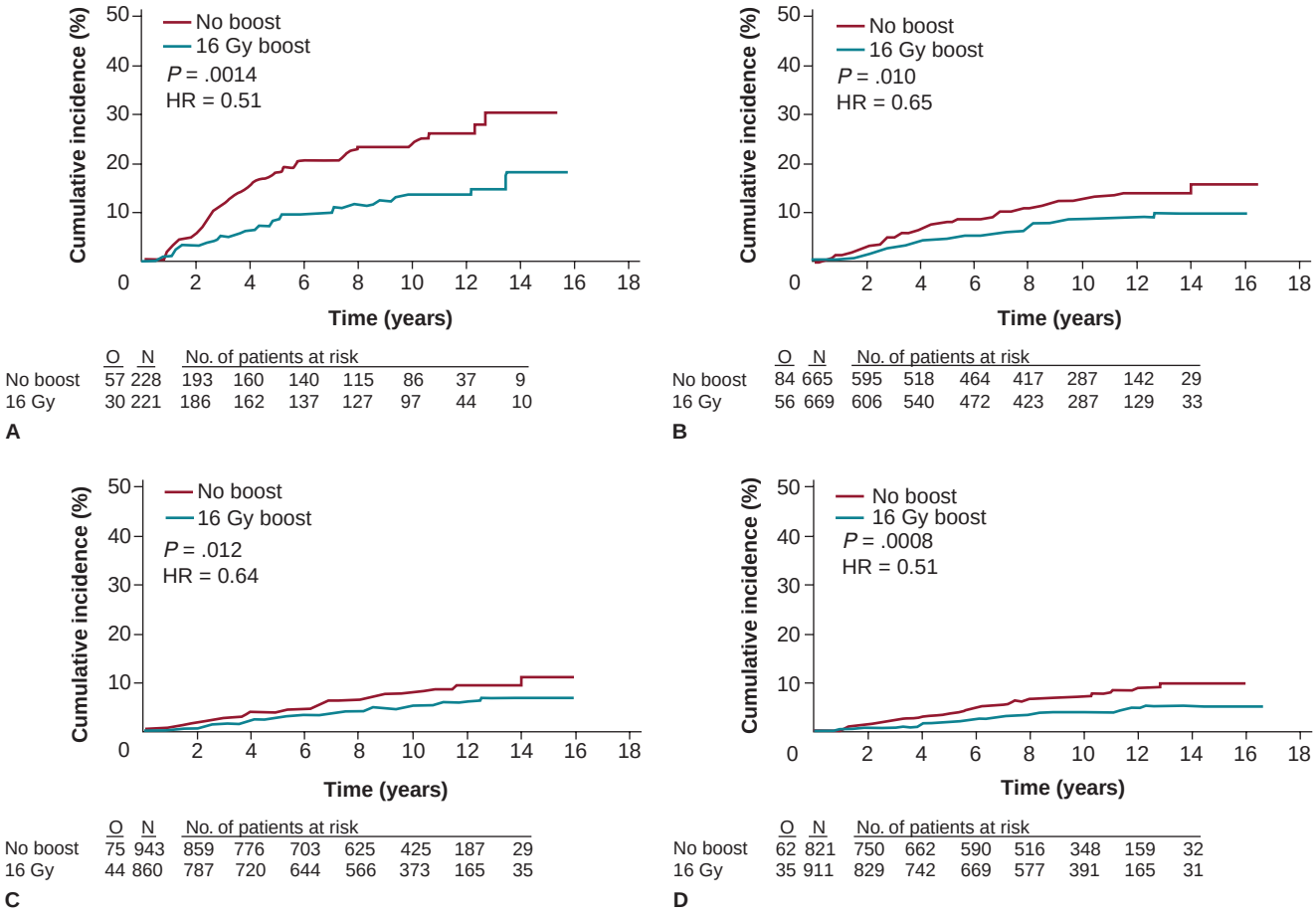

FIGURE 85-2 **Cumulative incidence of ipsilateral breast cancer recurrence according to age.** Age **(A)** ≤40, **(B)** 41 to 50, **(C)** 51 to 60, and **(D)** >60 years. (From Bartelink H, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881-10882 trial. *J Clin Oncol* 2007;25:3259–3265, with permission.)

endocrine responsiveness should be the first consideration in tailoring adjuvant therapies for patients with breast cancer, regardless of age (52). Adjuvant chemotherapy has historically been used extensively in premenopausal patients because of its overwhelming beneficial effects on outcome (53). The incremental benefits of newer cytotoxic drugs and regimens, including the addition of the taxanes, dose density, and trastuzumab, appear to be present across age groups, although data for very young women are limited (54–58).

Adjuvant Systemic Therapy in Patients with Hormone Receptor–Negative Disease

For premenopausal women with hormone receptor (HR)–negative disease, adjuvant chemotherapy is a very important component of successful treatment. Only one trial, however, has prospectively tested the use of chemotherapy in women with HR-negative, node-negative disease (National Surgical Adjuvant Breast and Bowel Project [NSABP] B13) (59). Table 85-1 displays the relative risk of relapse for the chemotherapy-treated group compared with the surgery-alone group. No difference was found between the risk for very young patients compared with the older premenopausal patients, with a 38% reduction in the risk of recurrence from the use of chemotherapy. Novel biologic (e.g., anti-ERBB2-directed therapies, parp inhibitors) and chemotherapeutic regimens (e.g., platinum agents) that have shown promise in women with early and advanced disease may also be particularly relevant in the treatment of young women with breast cancer, given this population is more likely to develop more aggressive breast cancer subtypes and that they are more likely to harbor a BRCA1 or BRCA2 germline mutation.

Adjuvant Systemic Therapy in Patients with Hormone Receptor–Positive Disease: Chemotherapy and Endocrine Therapy

Controversy exists about the optimal management of young women with HR-positive breast cancer. Since the 1990s, adjuvant tamoxifen has been the mainstay of endocrine therapy for premenopausal women when the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) overview, a large meta-analysis consisting of dozens of randomized trials, revealed a beneficial effect in women under age 50 similar to the benefit seen for older women (60). The first adjuvant systemic therapy for premenopausal women with breast cancer was ovarian ablation, but its use was almost abandoned in the mid-1970s when the benefits of adjuvant cytotoxic chemotherapy became clear. When the results of all trials of ovarian ablation were summarized by the EBCTCG meta-analysis, the beneficial effect of ovarian ablation appeared to be large in the absence of chemotherapy, whereas no

TABLE 85-1

Relative Risk of Relapse Comparing Patients in the Chemotherapy Group (Methotrexate → Fluorouricil) versus the No Adjuvant Therapy Group: Results from the National Surgical Adjuvant Breast and Bowel Project Trial B-13 for Estrogen Receptor–Negative, Node-Negative Cases

Age Group	*Patients (N)*	*Events (N)*	*Relative Risk*	*95% Confidence Interval*	*p-Value*
<35	69	28	0.62	(0.29, 1.30)	.21
35–49	371	107	0.62	(0.42, 0.91)	.01

From Goldhirsch A, Gelber RD, Yothers G, et al. Adjuvant therapy for very young women with breast cancer: need for tailored treatments. *J Natl Cancer Inst Monogr* 2001;30:44–51, with permission.

apparent advantage was seen when ovarian ablation was added to cytotoxic chemotherapy (61). More than 80% of the women in this chemotherapy-alone group experienced ovarian function suppression with the cytotoxic treatment, however, and the cohort was also a mixture of women with ER-positive and ER-negative disease (62). The International Breast Cancer Study Group (IBCSG) evaluated treatment outcome for very young women compared with older premenopausal women who received adjuvant chemotherapy alone. Very young premenopausal women (<35 years of age) with HR-positive tumors had a worse outcome compared with older premenopausal women, and compared with both older and younger women with HR-negative disease (63). This led to the hypothesis that the effects of cytotoxic chemotherapy on ovarian function, and the timing and duration of treatment-related amenorrhea, differ between older and younger premenopausal women. Very young women are much less likely to experience ovarian dysfunction with chemotherapy resulting in a poorer prognosis, particularly in the absence of additional endocrine therapy (64–67) (see Chapter 90, Reproductive Issues in Breast Cancer Survivors). To confirm the interaction between age and ER status in premenopausal women treated with chemotherapy alone, the IBCSG, NSABP, Eastern Cooperative Oncology Group (ECOG), and Southwest Oncology Group (SWOG) conducted a pooled analysis of 9,864 patients. Table 85-2 summarizes the results from all four cooperative groups. In each analysis, the relative risk of an event, estimated from a Cox proportional hazards regression model stratified by study and treatment group, was substantially higher for young patients with ER-positive tumors compared with the reference population of older patients with ER-positive tumors. This phenomenon was not observed for patients with ER-negative tumors. In recent years, it has become clear that in patients with HR-positive disease, the beneficial effects of cytotoxic agents are probably a result of a complex mixture of cytotoxic and endocrine effects of chemotherapy. IBCSG Trial VIII compared sequential chemotherapy followed by the gonadotropin-releasing hormone agonist goserelin with each modality alone in 1,063 pre- and perimenopausal

TABLE 85-2

Relative Risk of Relapse[a] and Corresponding 5-Year Disease-Free Survival[b] for Premenopausal Women in Chemotherapy Alone Groups in Trials Conducted by the International Breast Cancer Study Group (IBCSG), the National Surgical Adjuvant Breast and Bowel Project (NSABP), the Eastern Cooperative Oncology Group (ECOG), and the Southwest Oncology Group (SWOG)[c]

		ER-positive		*ER-negative*		
Group	Total Patients (N)	<35	≥35[b]	<35	≥35[b]	Interaction *p*-Value
		Relative Risk of Relapse (Number of Events/Number of Patients)				
IBCSG	2,233	1.84 (72/96)	1.00 (737/1353)	1.13 (50/88)	1.02 (370/696)	.009
NSABP	5,849	1.72 (254/402)	1.00 (1210/2716)	1.27 (214/441)	1.12 (1045/2290)	.0001
ECOG	1,112	1.54 (42/71)	1.00 (274/602)	1.40 (40/73)	1.26 (195/366)	.17
SWOG	670	2.67 (11/29)	1.00 (48/293)	0.81 (7/55)	1.13 (52/293)	.012

[a]Includes breast cancer relapses, second primary breast tumors, and deaths without relapse for IBCSG (also includes nonbreast second primaries), ECOG, and SWOG; includes only breast cancer relapses (other events are censored) for NSABP.
[b]Premenopausal ≥35 years of age for IBCSG, ECOG, and SWOG; 35 to 49 years for NSABP. Chemotherapy regimens of the various trials included in the collaboration: IBCSG: classic CMF (cyclophosphamide, methotrexate, fluorouracil) for 12, 9, 6, or 3 courses; NSABP: melphalan + fluorouracil ± methotrexate ×12; melphalan + fluorouracil + doxorubicin ×12; AC (doxorubicin + cyclophosphamide) ×4 ± CMF (given intravenously on day 1, 8 q 28 days) ×6; classic CMF ×6; AC "intensified dose" ×4; AC "intensified dose" with growth factors ×4; ECOG: classic CMF ×12 or 6 courses; CAF ×6 courses; intensive "16-week regimen"; SWOG: classic CMF ×6 courses; CAF ×6 courses.
[c]Cohorts defined by age and estrogen receptor status are compared with the reference population of older women with estrogen receptor–positive tumors (number of events/number of patients are shown in parentheses).
From Goldhirsch A, Gelber RD, Yothers G, et al. Adjuvant therapy for very young women with breast cancer: need for tailored treatments. *J Natl Cancer Inst Monogr* 2001;30:44–51, with permission.
ER, estrogen receptor.

women with lymph node–negative breast cancer (68). Women were randomized to goserelin for 24 months (n = 346), six courses of "classic" CMF (cyclophosphamide, methotrexate, 5-fluorouracil) chemotherapy (n = 360), or six courses of classic CMF followed by 18 months of goserelin (CMF → goserelin; n = 357). (A fourth no-adjuvant treatment arm with 46 patients was discontinued early.) Of patients, 20% were age 39 years or younger and median follow-up was 7 years. Patients with ER-negative tumors had better DFS if they received CMF (5-year DFS for CMF = 84%, 95% confidence interval [CI], 77%–91%; 5-year DFS for CMF → goserelin = 88%, 95% CI, 82%–94%) than if they received goserelin alone (5-year DFS = 73%, 95% CI, 64%–81%). By contrast, for patients with ER-positive disease, chemotherapy alone and goserelin alone provided similar outcomes (5-year DFS for both treatment groups = 81%, 95% CI, 76%–87%), whereas sequential therapy (5-year DFS = 86%, 95% CI, 82%–91%) provided a statistically nonsignificant improvement compared with either modality alone, primarily because of the results among younger women (Fig. 85-3). The DFS results shown in Figure 85-3 according to treatment group illustrate that outcomes for older premenopausal women with ER-positive disease cannot be used to define appropriate treatment choices for younger women (in this example, ≤39 years). For some young patients, endocrine therapy alone may suffice, or a combined endocrine therapy approach may be optimal (69,70).

Tamoxifen

Tamoxifen, the most thoroughly studied selective ER modulator (SERM), has not been specifically investigated in very young patients. This drug typically increases the estradiol secretion from premenopausal ovaries. The updated EBCTCG meta-analysis of all randomized trials of adjuvant tamoxifen has revealed that 2 to 5 years of treatment has similar efficacy in all age groups, including patients less than 40 years of age (71). However, several analyses have suggested that the youngest women in various treatment groups seem to get less benefit from tamoxifen alone, which may be due in part to lower adherence to therapy in the very young (11,72,73). These findings suggest an opportunity to improve on treatment results for this patient population. It is also important to note that, although risks associated with tamoxifen (e.g., blood clot, stroke, and uterine cancer) tend to be much lower in younger patients than older patients, younger women are more likely to develop ovarian cysts because of high estradiol levels resulting in ovarian hyperstimulation while on tamoxifen (74,75). Nevertheless, tamoxifen substantially reduces the risk of breast cancer recurrence in women of all ages and recent data from the ATLAS trial demonstrating further improvement in mortality by extending tamoxifen to 10 years when compared to 5 years has opened up a new treatment option for young women who remain premenopausal after 5 years of tamoxifen and are therefore not candidates for aromatase inhibitor therapy (76).

Adjuvant Ovarian Ablation (Suppression) with or without Tamoxifen

The combination of ovarian suppression or ablation and tamoxifen has been tested in advanced disease and proved superior to either treatment alone (77). In a trial conducted in Asia, the combination of oophorectomy and tamoxifen compared with no adjuvant therapy resulted in an 11% absolute

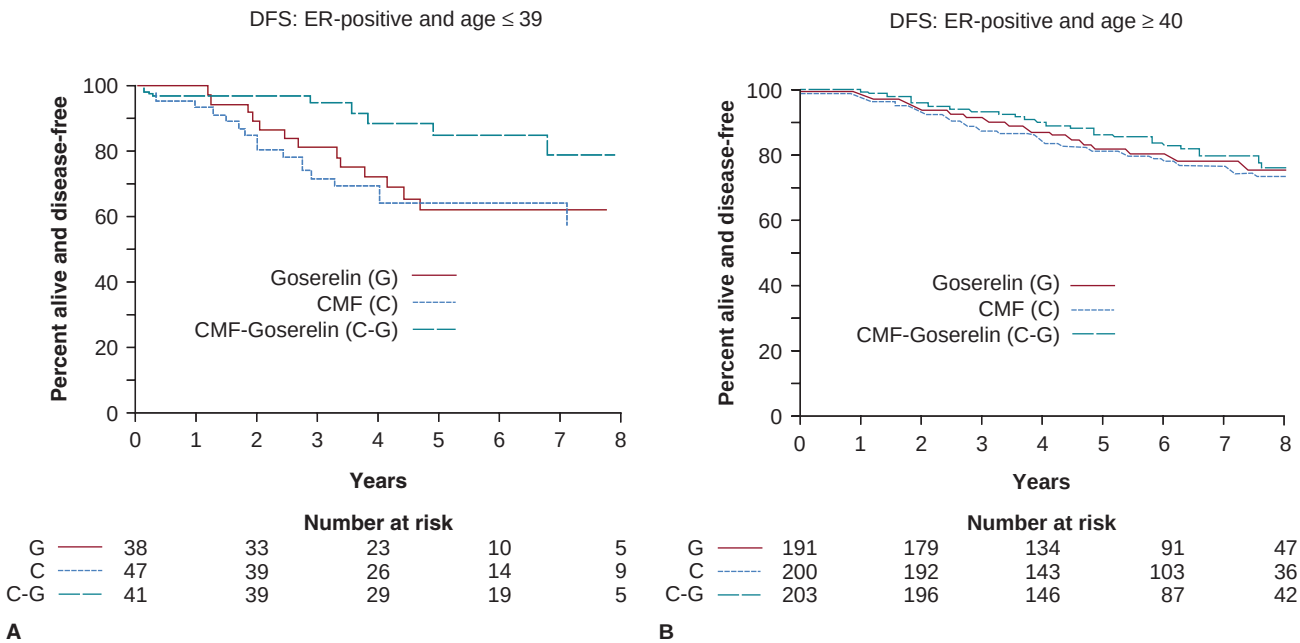

FIGURE 85-3 Kaplan-Meier plots of disease-free survival (DFS) for the ER-positive cohort enrolled in International Breast Cancer Study Group (IBCSG) Trial VIII comparing six courses of cyclophosphamide, methotrexate, and 5-fluorouracil (C), 24 months of goserelin (G), and six courses of C followed by 18 months of goserelin (C-G) at 7 years of median follow-up. Results for subgroups according to age less than 39 years **(A)** and age 40 years or more **(B)** are shown. (From International Breast Cancer Study Group (IBCSG). Adjuvant chemotherapy followed by goserelin versus either modality alone for premenopausal lymph node-negative breast cancer: a randomized trial. *J Natl Cancer Inst* 2003;95:1833–1846, with permission.)

benefit in DFS and an 18% benefit in overall survival (OS) at 10 years (78). In the subset of patients with ER-positive tumors, 10-year DFS probabilities were 66% in the treated group compared with 47% in the control group, corresponding to 10-year OS rates of 82% and 49%, respectively. In a subset analysis from this same study, ERBB2 overexpression appeared to have a favorable influence on response to adjuvant oophorectomy and tamoxifen in women with ER-positive disease (79).

Acceptance of ovarian function suppression, tamoxifen, or the combination may be a significant problem for premenopausal women in general and for younger patients in particular (80). Issues include objective and subjective symptoms of menopause, psychological distress, and adjustment to changes in personal and family plans. Chemotherapy seems easier to offer to younger patients because of its shorter duration and lesser degree of long-term effects on endocrine function than ovarian suppression, although evidence suggests most premenopausal healthy women would choose ovarian suppression over CMF chemotherapy, hypothetically (81). Long-term symptoms of acute ovarian suppression may be a particular problem for some patients. However, in an evaluation of 874 pre- and perimenopausal women in IBCSG Trial VIII (see previous section in this chapter), patients receiving goserelin alone showed a marked improvement or less deterioration in quality of life (QOL) measures over the first 6 months than those patients treated with CMF, yet no differences were seen at 3 years except for hot flashes (82). As reflected in the hot flashes scores, patients in all three treatment groups experienced induced amenorrhea, but the onset of ovarian function suppression was slightly delayed for patients receiving chemotherapy. Of note, in this study, younger patients (<40 years) who received goserelin alone returned to their premenopausal status at 6 months after the cessation of therapy, whereas those who received CMF showed only marginal changes from their baseline hot flashes scores, likely indicative of minimal ovarian dysfunction.

The Suppression of Ovarian Function Trial (SOFT) randomizing premenopausal women with HR-positive disease to tamoxifen, tamoxifen and ovarian suppression, or exemestane and ovarian suppression should further elucidate the role of ovarian suppression, and optimal endocrine therapy in young women with breast cancer. The complementary Trial of Exemestane and Tamoxifen (TEXT) randomizing premenopausal women with HR-positive disease to ovarian function suppression with either tamoxifen or exemestane will also clarify the role of aromatase inhibition for these patients. SOFT and TEXT have completed enrollment of over 5,700 patients and the overall primary endpoint disease-free survival event rate is 2% per year, about one quarter that originally anticipated. The first results of SOFT and TEXT are expected to be reported in 2014 (*www.ibscg.org*). The lack of acceptability resulting in premature closure of the Premenopausal Endocrine Responsive Chemotherapy Trial (PERCHE), a randomized trial evaluating the role of chemotherapy in the setting of combined endocrine therapy, will hamper the availability of more definitive evidence regarding the benefits and risks of chemotherapy in addition to endocrine therapy in very young patients. The fully enrolled TailoRx trial (*www.ecog.dfci.harvard.edu*) and the currently recruiting RxPonder trial (*www.swog.org*) may provide some information on the role of chemotherapy, but are likely to include very few young patients given the current attitude regarding need for chemotherapy in young women. Meaningful results for the very young HR-positive cohort will also require evaluation exclusively in patients who receive optimal endocrine therapy. The optimal duration and the timing of adjuvant endocrine therapy options in very young patients with HR-positive disease remain open questions.

BREAST CANCER DIAGNOSED DURING PREGNANCY

It is more likely that younger rather than older premenopausal women will be faced with concurrent pregnancy and the diagnosis of breast cancer, although the issues are similar, irrespective of age. Cytotoxic treatments have been safely administered, beginning in the second trimester, after the completion of organogenesis, although there are risks (83). Both trastuzumab and tamoxifen are contraindicated during pregnancy, due to risk of perinatal complications and teratogenicity, respectively. However, many babies have been born without obvious abnormality after *in utero* exposure to these agents (84,85), Issues regarding whether to maintain the pregnancy and the timing of breast cancer treatment are complex both from a medical and psychosocial standpoint (for additional details, see Chapter 65).

BREAST DISEASE IN ADOLESCENTS

Breast disease in adolescent females is fortunately uncommon, with most presenting lesions being benign, most commonly fibroadenomas (86,87). For most breast lesions in children and adolescents, open biopsy can be avoided (88). Breast cancer is very rare in this population. Because of this, neither the prognosis nor optimal management of the disease in this age group is clear. Available case series suggest that adolescents with breast tumors comprise a mix of histologic subtypes including cystosarcoma phyllodes and, more commonly, adenocarcinomas including invasive intraductal, invasive lobular, signet ring, and secretory adenocarcinomas (89,90). Treatment recommendations should be tailored to the specific histology, and attention to psychosocial issues, including adherence with therapy, is prudent in the care of teenagers with breast cancer.

BREAST CANCER IN CHILDHOOD CANCER SURVIVORS

Young women with a history of treatment for childhood cancer, in particular those treated with chest ("mantle") irradiation for Hodgkin disease, are at dramatically increased risk of early-onset breast cancer (91,92) (see Chapter 19 in this text). Treatment considerations in this unique subgroup may be complicated by previous systemic therapy, recommendations against further radiation therapy, and psychosocial issues.

TREATMENT OF YOUNG WOMEN WITH ADVANCED DISEASE

Very young women who present with metastatic disease are generally treated using an algorithm reflecting the general incurability of the disease, and employing ovarian function suppression together with other treatment options if the disease is endocrine-responsive (see Chapters 73 and 74 in this text). The sequential use of endocrine therapy followed at the time of disease progression by chemotherapy, similar to the conventional approach in older premenopausal and postmenopausal women, is reasonable, although this has not been specifically tested in younger patients. Young patients with metastatic disease may be particularly vulnerable to psychosocial distress, especially if they have young dependents (93).

QUALITY OF LIFE AND PSYCHOSOCIAL ISSUES

A growing body of evidence suggests that younger women with breast cancer are at increased risk of psychosocial distress compared with older women, both at diagnosis and follow-up (21). In a large prospective cohort study, women age 40 and younger who developed breast cancer experienced significant declines in their quality of life (QOL) compared with age-matched women without breast cancer (94). Adjusting for disease severity and treatment factors, young women who developed breast cancer had the largest relative declines in QOL following diagnosis compared with middle-age and elderly women who developed breast cancer. In a survey of women who were age 50 or younger at diagnosis and disease-free at 6-year follow-up, women generally reported high levels of physical functioning, but the youngest women (ages 25–34 at diagnosis) exhibited the greatest degree of psychosocial distress, particularly with social and emotional functioning as well as vitality (95). Young age at diagnosis as well as motherhood has also been associated with greater fear of recurrence, independent of disease characteristics (96,97) Many young women also feel isolated and lack information (98). When they attend breast cancer support groups, their issues are often substantially different from those of the older women. Others in their age cohort are planning for the future, whereas young women with breast cancer are facing a life-threatening and physically mutilating disease. Little information is available regarding work and life decisions made by these women. And although access to psychosocial support is associated with a better QOL in breast cancer survivors, these results have not been presented separately for the youngest patients and few psychosocial interventions have been evaluated in young women specifically (21,99).

FERTILITY AND PREGNANCY AFTER BREAST CANCER

Young women with breast cancer may face the risk of becoming amenorrheic with treatment, either temporarily or permanently, resulting in potential infertility, onset of menopausal symptoms, problems with sexual functioning, and exposure to long-term risks of early menopause. The risk of amenorrhea is related to increasing patient age and treatment received (100,101) (Fig. 85-4). For some young women, cessation of menses may be welcome and may improve outcomes for women with HR-positive disease. For many young women, however, the threat or experience of infertility may be devastating. Discussion of this important survivorship issue should commence early in the treatment decision process because some women may elect to try to preserve fertility through intervention or forgo some therapy (102). Young breast cancer survivors can be reassured that at the present time there is no clear increased risk of recurrence from having a biologic child (103). However, studies are limited by substantial biases, including the *healthy mother* bias, and concerns remain for some (104,105). Nevertheless, many young women are interested in pregnancy after breast cancer and an international effort is currently underway to evaluate the safety and efficacy of taking a break from tamoxifen therapy in order to try to have a biologic child. The Breast International Group (BIG) – North American Breast Cancer Groups (NABCG) Endocrine Working Group is developing a prospective trial for women 37 years old or younger at diagnosis of HR-positive breast cancer to assess pregnancy success following tamoxifen interruption after 18 to 30 months of treatment (coordinated by IBCSG) (*www.ibcsg.org*). Pregnancy after breast cancer is a very complex and personal decision for a woman who remains at risk for recurrent disease (for additional details, see Chapter 90, Reproductive Issues in Breast Cancer Survivors).

MENOPAUSAL SYMPTOMS AND SEXUAL FUNCTIONING

Menopausal symptoms and sexual dysfunction are common in breast cancer survivors (101). To date, most breast cancer survivors included in evaluations of sexual dysfunction have been over age 40, reflecting the demographics of breast cancer. Little information is available focusing on sexual dysfunction in very young breast cancer survivors, and no intervention studies have been conducted. Research has, however, identified risk factors for sexual dysfunction in breast cancer

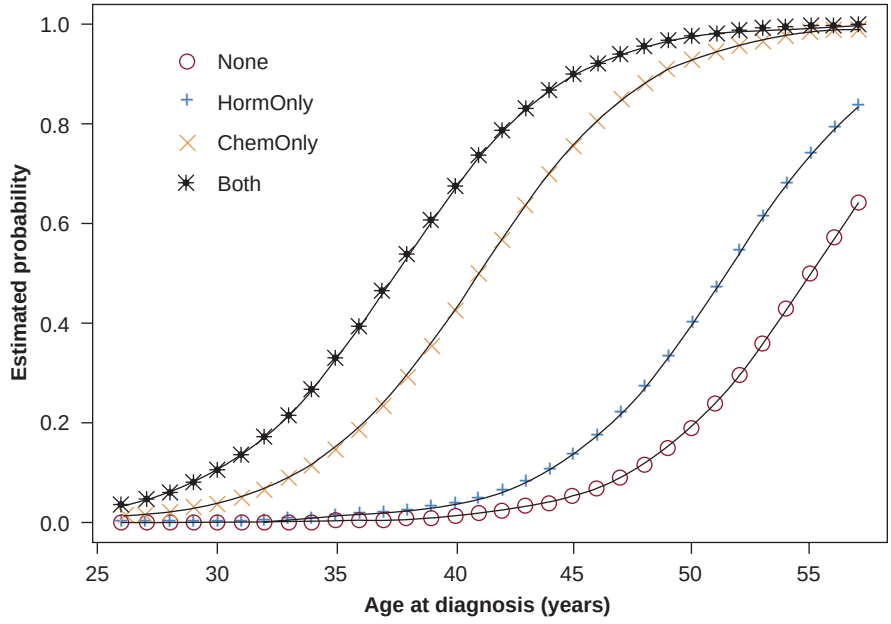

FIGURE 85-4 **Probability of menopause during the first year after diagnosis (according to a model).** (From Goodwin PJ, Ennis M, Pritchard KI, et al. Risk of menopause during the first year after breast cancer diagnosis. *J Clin Oncol* 1999;17:2365–2370, with permission.)

survivors including younger age, premature menopause, and the use of chemotherapy (106). The use of tamoxifen and type of breast surgery may also have an impact on sexual functioning, especially in young breast cancer survivors. In a survey of 371 women diagnosed with breast cancer age 40 and younger (mean age at diagnosis 33 years and mean age at follow-up 36 years) where 77% of these women were premenopausal at follow-up, many reported bothersome sexual functioning or menopausal-type symptoms (107). In particular, 46% of women reported hot flashes and 39% reported dyspareunia. Current ovarian suppression, menopausal status, baseline anxiety before the diagnosis, pregnancy after the diagnosis, prior chemotherapy, and lower perceived financial status were associated with more bothersome symptoms. Evidence indicates that intervention to improve menopausal symptoms and sexual functioning is effective, although limited research to date focuses on very young women (108).

CONCLUSIONS

When a very young woman is diagnosed with breast cancer, she may face several threats to her future health and well-being. Most concerning, a young woman with breast cancer is more likely than an older woman to have an adverse prognosis. The differential in prognosis by age may reflect, in part, biological differences between breast cancer that develops in a younger compared with an older woman. Prognosis may, however, also be affected by suboptimal therapy, particularly endocrine therapy, in the youngest patients who are least likely to lose ovarian functioning as a result of systemic therapy. Because of the relative rarity of breast cancer in young women, large pooled analyses and multinational clinical trials are necessary to address the many controversies and improve therapy for younger patients. Late health and psychosocial effects of breast cancer in young women should also be considered, and recent advocacy and public efforts to increase awareness of and support for young women with breast cancer should improve their outcomes (*www.cdc.gov/cancer/breast/*; *www.youngsurvival.org*).

MANAGEMENT SUMMARY

In general, treatment of the young patient with breast cancer is similar to other patients and is determined by the characteristics of the tumor and the patient, with some special considerations.

Local Therapy

- Consider preoperative systemic therapy for women with locally advanced disease or those with large tumors who desire breast preservation.
- Careful attention to margin status and boost irradiation after lumpectomy is warranted to minimize the higher risk of local recurrence associated with young age.

Systemic Therapy

- Consider the endocrine as well as the direct cytotoxic effects of chemotherapy.
- Optimize endocrine therapy, including consideration of adherence issues, given evidence for benefits in young women with hormone receptor–positive disease.

Psychosocial and Survivorship Issues

- Evaluate concerns about future fertility early on and refer for consideration of fertility preservation strategies as needed before systemic therapy.
- Consider genetic testing (e.g., *BRCA1* or *BRCA2* testing), early on if it would have an impact on a woman's treatment decisions.
- Provide psychosocial support, referrals, and informational resources (e.g., *www.youngsurvival.org*) given the increased distress often seen in young women with breast cancer.

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CHAPTER 86

Breast Cancer in Minority Women

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CHAPTER CONTENT

INTRODUCTION: A FRAMEWORK FOR UNDERSTANDING BREAST CANCER DISPARITIES

The study of breast cancer in minority women is inevitably linked to the study of healthcare disparities. The Institute of Medicine has defined healthcare disparities as "racial or ethnic differences in the quality of healthcare that are not due to access-related factors or clinical needs, preferences, and appropriateness of intervention" (1). In the context of breast cancer, disparities occur when a group within the breast cancer population experiences unequal access to cancer screening and diagnostic care, inferior cancer treatment, lower rates of response to anti-cancer therapies, poorer short term outcomes such as treatment toxicities or complications, or poorer long-term outcomes including breast cancer recurrence and death. The determinants of breast cancer disparities are complex and include biologic, behavioral, socioeconomic, provider, and structural factors. Breast cancer disparities are seen in a number of vulnerable populations including elderly and poor women, but have been best documented among racial and ethnic minorities and particularly among black women. In this chapter, we will summarize the existing literature regarding racial disparities in breast cancer, explore the most pronounced disparities among other vulnerable groups, and discuss potential areas for intervention and future research.

African American women with breast cancer die at significantly higher rates than their white counterparts, and this racial gap in survival persists despite overall improvements in breast cancer mortality over time (2). This core fact has motivated much of the breast cancer disparities research in the United States over the past three decades. From this core finding, a number of questions immediately arise. These questions and their answers can be imagined as layers to be unearthed in the search for the roots of breast cancer outcome disparities. Are racial differences in breast cancer mortality best explained by differences in cancer stage at diagnosis, tumor biology, treatments received, response to treatment, subsequent experiences during survivorship, or a combination of these factors? These questions are the starting point for the study of breast cancer disparities.

Known differences in stage at presentation, tumor biology, receipt of treatment, response to therapy, and survivorship care are the basic elements contributing to breast cancer outcome disparities. Once these basic elements are established, we turn to understanding the factors underlying each element. For instance, do black women present at a later stage due to inherently more aggressive disease, less effective screening, or delays in diagnosis? Do black women receive different breast cancer treatments for equivalent disease across the spectrum of care, including diagnostic and staging evaluation, surgery, radiation, chemotherapy, and endocrine therapy? And do they respond to such treatments differently, in terms of both efficacy and toxicity?

Once the key drivers of breast cancer outcome disparities are defined, we can examine which factors may be amenable to change. As one example, a woman who presents with advanced breast cancer due to lack of screening may not have undergone breast cancer screening because she believes herself to be at low risk (behavioral factor),

because she cannot afford the cost of screening (socioeconomic factor), because her provider has not recommended screening (provider factor), or because there is no screening facility within a reasonable distance of her home (structural factor). This woman's story is an example of a basic element of breast cancer outcome disparity (advanced stage at presentation) potentially explained by a particular factor (lack of screening) which in turn may have a number of drivers at the patient, provider, or health system level. To the extent that these drivers vary by race, ethnicity, age or other patient characteristics, they contribute to health disparities. Complex interactions between factors are also to be expected in the study of health disparities. A conceptual model of the multilayered factors contributing to breast cancer disparities is presented in Figure 86-1.

OVERVIEW OF DISPARITIES IN BREAST CANCER

In the United States, new diagnoses of breast cancer are slightly more common in white women, but breast cancer mortality is higher among black women (2). In 2005–2009, the age-adjusted incidence rate of breast cancer was 127.3 per 100,000 women among whites and 121.2 per 100,000 among blacks, while age-adjusted death rates were 22.4 and 31.6 per 100,000 women among whites and blacks respectively (3). Although breast cancer incidence and mortality rates have declined for all racial groups over time, the gap between black and white patients has not closed and in fact appears to be widening (4). Figure 86-2 demonstrates the trends in breast cancer incidence and mortality among black and white women. Racial and ethnic trends in breast cancer incidence and mortality vary depending on age. Specifically, younger black women (those <50 years old) have a higher incidence of breast cancer compared to younger white women, but beginning around the time of menopause, incidence rates among white women surpass rates of black women, and remain higher throughout the older years (5,6). Although advanced stage at presentation will be discussed in this chapter and clearly contributes to poor breast cancer outcomes, a marked stage-specific survival gap remains after controlling for basic stage and hormonal status differences among newly diagnosed patients, as depicted in Figure 86-3. Race remains an independent predictor of poor survival after controlling for tumor size, grade, and year of diagnosis (7). In this chapter, we will examine in detail the major factors underlying disparities in breast cancer mortality—differences in stage at presentation, biology, receipt of treatment, treatment response, and survivorship care—and their drivers.

DISPARITIES IN PRESENTING STAGE

One well-documented contributor to higher breast cancer mortality among black women is advanced stage at presentation. Table 86-1 shows the percentage of women in the national Surveillance Epidemiology and End Results (SEER) database presenting with various stages of breast cancer between 2000 and 2009. Black women present more often than their white counterparts with regional or distant breast cancer, and less often with localized or early stage breast cancer (3). Given that cancer stage at diagnosis is a strong predictor of breast cancer survival (7), it is straightforward to understand why advanced presenting stage is associated with poor outcomes among black women. Less clear are the reasons why black women present at a later disease stage. Differences in screening patterns, diagnostic trajectory after a cancer is suspected, and risk of aggressive cancers that may arise in the interval between regular screenings may all contribute to late-stage diagnoses.

Screening Disparities

Modern mammography screening clearly reduces the risk of late-stage breast cancer diagnosis (8). Late-stage diagnosis of breast cancer in black women has historically been attributed to screening behaviors, specifically underuse of screening mammography or lack of diagnostic follow-up after an abnormal mammogram result (9). Overall use of screening mammography has risen over the past two decades, but the equivalence of mammography use among racial/ethnic groups is a subject of ongoing debate, with some studies showing equivalence and others suggesting that black women remain less likely to get mammograms at the recommended 1- to 2-year interval (9,10,11). Although screening is associated with early diagnosis among all racial groups, this association appears weaker in black women (12) and differential performance of mammography does not appear related to higher mammographic breast density among black women (13). This finding may instead be explained in part by the quality of mammography services received; one recent study found that black and Hispanic women were less likely than white women to have their mammograms at academic centers, facilities that used breast imaging specialists to interpret mammograms, and facilities with digital mammography (14). Provider factors also may contribute to disparities in receipt of mammography. Black women more often than white women cite lack of physician referral or recommendation for mammography as the reason they failed to receive the test (15).

Disparities in Diagnostic Workup

Completion of a diagnostic workup is an important step intervening between a screening or physical exam abnormality and initiation of treatment. Evidence suggests that racial disparities exist in the timeliness of diagnostic workup for breast cancer. Two studies in vulnerable populations have suggested that even among uniformly low income women, and after controlling for the effect of insurance status and income, black women experience longer delays between initial abnormal mammogram or exam findings and the final determination of a pathologic diagnosis (16,17). Large population-based studies confirm race as an independent predictor of diagnostic delays, with a greater disparity among women who present with physical symptoms compared to screening abnormalities (18,19). Cultural beliefs and attitudes, for example, the fear that cancer can be spread through the air during a diagnostic procedure, have been found to partially explain racial disparities in timeliness of diagnostic workup (20). Longer times between symptom onset and definitive pathologic diagnosis are associated with higher mortality (21).

RACIAL DIFFERENCES IN BREAST CANCER BIOLOGY

Persistent survival gaps between blacks and whites diagnosed at similar stages of illness (22) and with similar access to healthcare (23) have led researchers to suggest that breast cancer in black women may be fundamentally biologically different from that in white women. Early observations supporting this hypothesis include findings that, within a given stage, black women are more likely to have larger tumors and positive lymph nodes. However, McBride

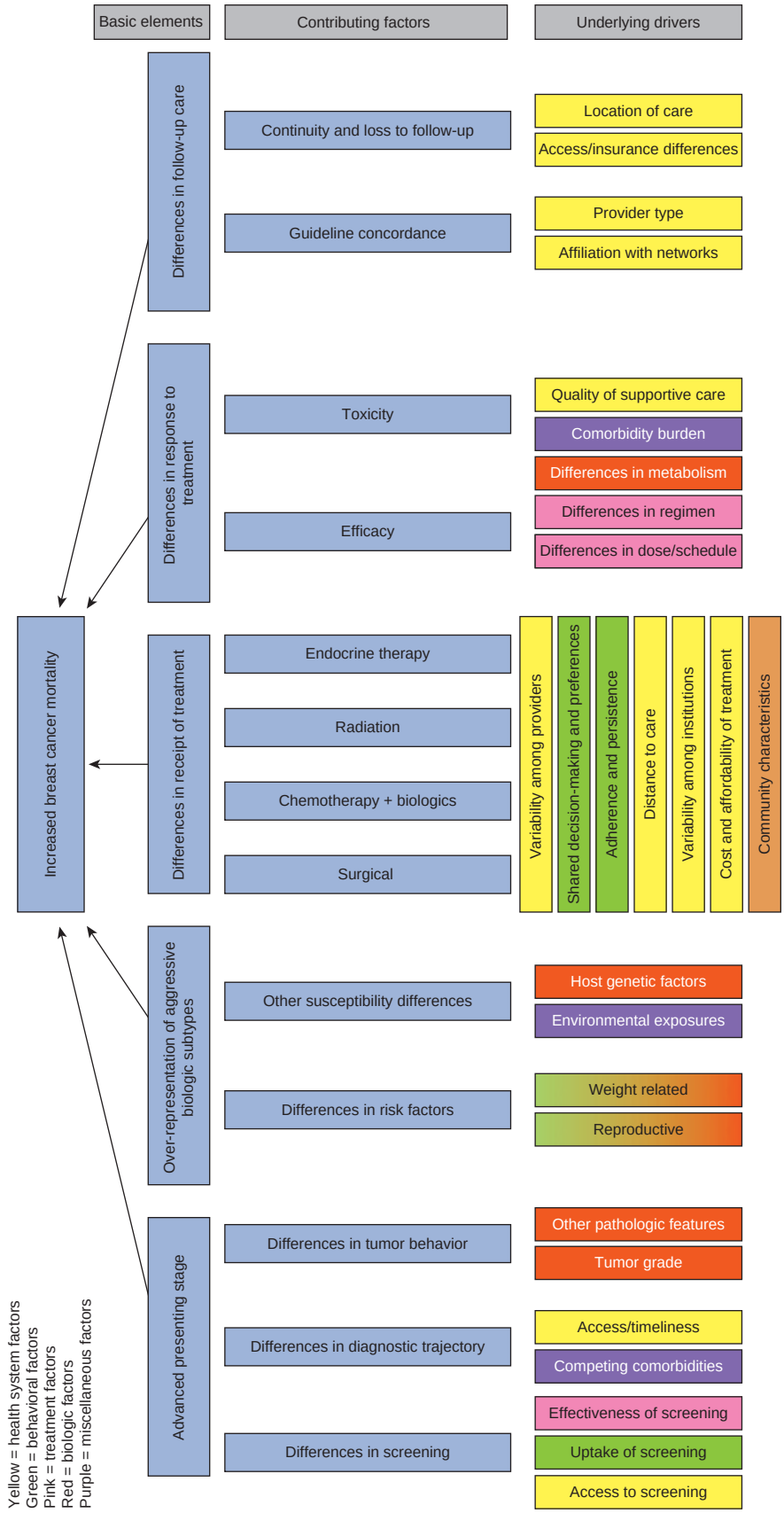

FIGURE 86-1 Key elements contributing to disparities in breast cancer mortality are pictured in *blue*. Underlying contributors are depicted in *yellow* (health system factors), *green* (behavioral factors), *pink* (treatment factors), *orange* (biologic factors), and *purple* (miscellaneous factors).

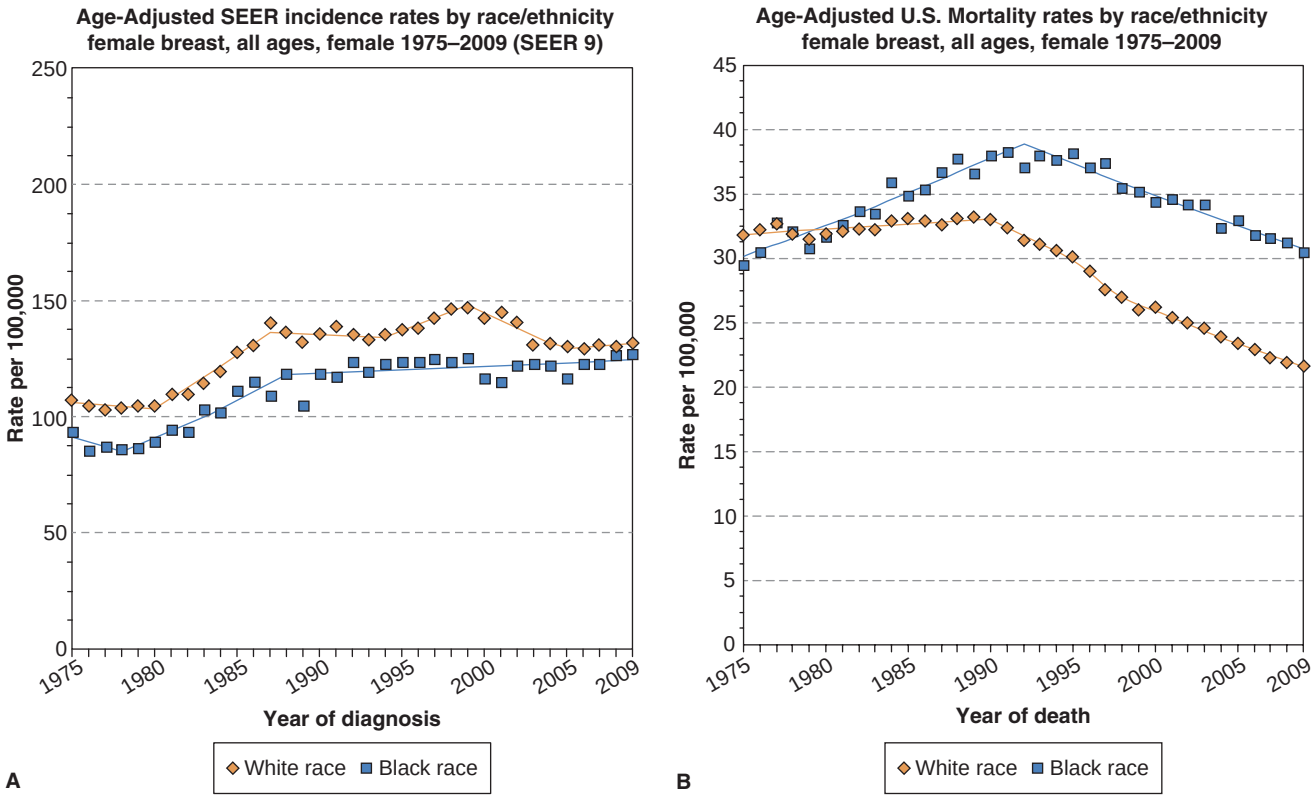

FIGURE 86-2 Age-adjusted incidence rates **(A)** and mortality rates **(B)** for U.S. women with breast cancers diagnosed from 1975 to 2005. White patients (*red lines*) have higher incidence but lower mortality than black patients (*blue lines*), and the mortality gap has increased over time. (Data from Fast Stats: an interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute. http://seer.cancer.gov/faststats.)

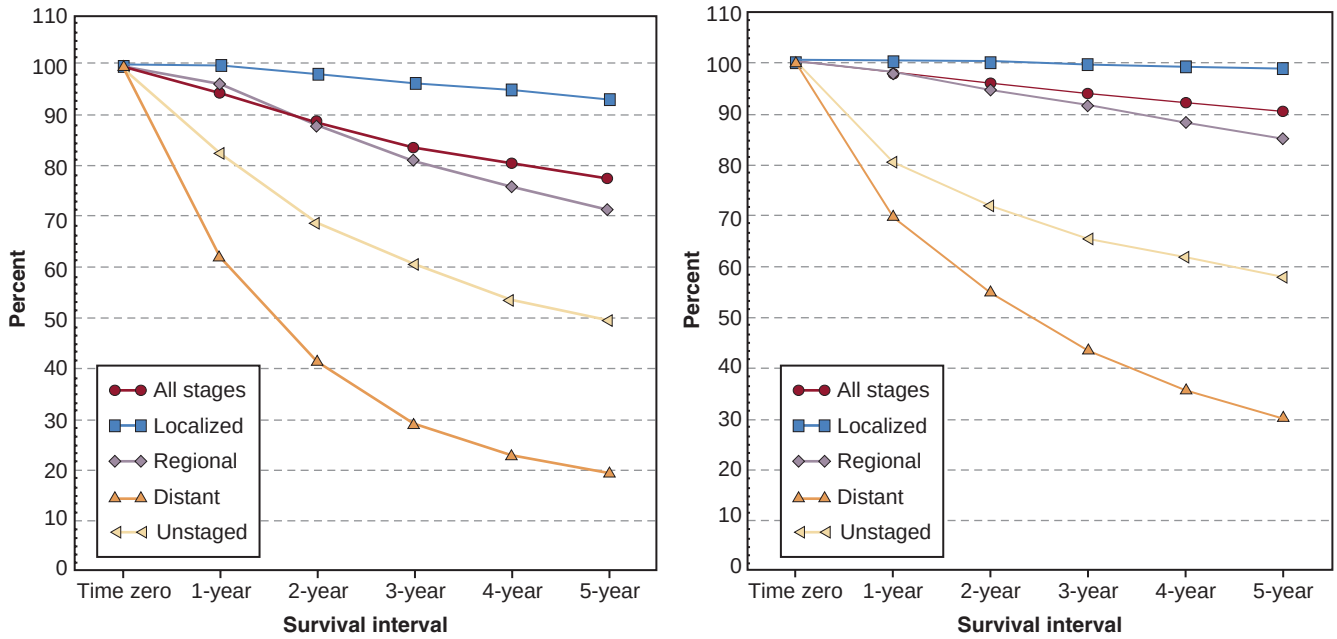

FIGURE 86-3 Relative 5-year survival of breast cancer patients by stage and race in United States SEER 9 (Surveillance Epidemiology and End Results) registries, diagnosed 1975–2005. Black patients are depicted on the *left*, white patients on the *right* hand graph. (Data from Fast Stats: an interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute. http://seer.cancer.gov/faststats.)

TABLE 86-1

Percentages of Women in SEER 18 Registry Regions Presenting with Localized, Regional, and Distant Disease 2000–2009

	Localized	*Regional*	*Distant*	*Unstaged*
All	61.3%	31.1%	5.0%	2.6%
White	62.4%	30.4%	4.6%	2.5%
Black	52.0%	37.0%	8.1%	3.0%

Data from Fast Stats: an interactive tool for access to SEER cancer statistics. Surveillance Research Program, National Cancer Institute. http://seer.cancer.gov/faststats.

and colleagues found that controlling for such within-stage differences did not attenuate differences in mortality (24). Thus, racial differences in outcome among similar-stage women do not appear to be due primarily to more advanced disease among black women within each stage grouping.

Histologic features of breast cancers also vary by race and ethnicity. While differences in presenting stage largely disappear when mammography is received equally, black women still have significantly more high-grade breast cancers (10). Chen and colleagues found that after adjusting for age, stage, socioeconomic status, body mass index, reproductive history, insurance status, and location, black women with invasive breast cancer were more likely to have high grade nuclear atypia, high grade tumors, and more necrosis compared to white women (25). Black women are also more likely to have overexpression of cell-cycle regulators, such as Cyclin E, p16, and p53, and polymorphisms in nucleotide excision repair genes (26). All of these results provide a strong argument for biological differences between black and white women in breast cancer.

Perhaps the most striking example of biological differences between breast cancers in black and white women occurs in biologic "subtype," which refers to the profile of cell surface receptors expressed by the cancer, including estrogen receptors (ER), progesterone receptors (PR), and human epidermal receptor type 2 (HER2). Immunohistochemical analyses of tumors from women in the Carolina Breast Cancer Study (CBCS) and other population-based studies have found that a significantly lower proportion of black women have favorable prognosis ER or PR-positive, HER2-negative breast cancer compared to whites, and a correspondingly higher proportion of black women, particularly younger black women, have poor prognosis triple negative (ER-, PR-, and HER2-negative) breast cancer (27–29). Similar analyses of a West African cohort of breast cancer patients also found a high incidence of triple negative breast cancer (30). As molecular subtyping of breast cancers becomes more widespread, we expect that previously unappreciated biologic differences by race may also be found.

Recent studies have shed light on potential epidemiologic differences underlying racial differences in distribution of breast cancer subtypes. Reanalysis of the CBCS and other epidemiologic studies have suggested that the effect of traditional breast cancer risk factors, including reproductive history and weight-related factors, vary by biologic subtype (31,32). Some risk factors, including early age of menarche, centripetal obesity, or the protective effect of breast-feeding, are far stronger for basal-like breast cancer (the molecular correlate of triple negative breast cancer) than for hormone receptor-positive, HER2-negative breast cancer. Other factors actually appear to have opposite effects in different subtypes. For example, multiparity and young age at first full-term pregnancy, which have historically been identified as protective factors in breast cancer epidemiology, appeared protective only for luminal breast cancer (the molecular correlate of hormone receptor-positive breast cancer), while both appeared to be risk factors for basal-like breast cancer (31). These studies suggest that race-associated differences in lifestyle or hormonal exposures may partially explain variations by race in breast cancer subtype. Recent genome-wide association studies implicate novel risk variants for breast cancer in women of African ancestry as another contributor (33). It is clear, however, that biological factors cannot explain all of the racial disparity in morbidity and mortality because black women experience worse long term outcomes even when compared to white women with biologically similar disease (9,22,27).

DIFFERENCES IN RECEIPT OF TREATMENT

Background on Cancer Treatment Quality

Although presenting stage and biologic factors are important determinants of breast cancer prognosis and treatment, these factors do not fully explain racial disparities in outcomes. If minority women receive less-than-standard treatment, we might expect to see continuing differences in outcomes, even after controlling for stage at presentation and biologic differences. Differences in treatment are now the focus of many studies examining breast cancer disparities. A large body of research shows that racial disparities exist in overall receipt and timeliness of treatment as well as monitoring of treatment-related toxicities (34–37). Failure to receive appropriate treatment is an important cause of racial disparities in breast cancer mortality (38).

Evidence of Racial Variation in Quality of Breast Cancer Treatment

Evidence-based guidelines for the treatment of breast cancer (39) and metrics to evaluate breast cancer care quality (40) are widely available in the United States. Despite the existence and widespread dissemination of these guidelines and quality metrics, many patients—in particular, black women—do not receive high quality, guideline-concordant care. Studies of treatment disparities have focused on the receipt of mastectomy versus breast conserving therapy (BCT, defined as breast conserving surgery [BCS] followed by radiation therapy), receipt of radiation when breast conserving surgery is chosen, receipt of adjuvant chemotherapy, and receipt of endocrine therapy when appropriate. Some studies have also attempted to use aggregate measures of high quality breast cancer care. The ability to accurately measure these treatments and to adequately control for confounders of the race-treatment relationship, such as socioeconomic status and comorbidity, varies from study to study depending on the data source. We describe some of the most significant studies documenting treatment disparities, their findings, and limitations.

Using inpatient and outpatient medical records from six New York City hospitals, Bickell and colleagues found that 34% of black women and 23% of Hispanic women, compared to 16% of white women, failed to receive appropriate adjuvant therapy for early stage breast cancer. Appropriate treatment included radiation therapy after BCS, adjuvant chemotherapy after definitive surgery among patients with hormone receptor-negative tumors at least 1 cm in size, and

endocrine therapy among patients with hormone receptor-positive tumors at least 1 cm in size (34). In multivariate models, poor quality care was significantly associated with black or Hispanic racial/ethnic status, lack of medical oncologic referral, having more comorbid conditions, and lack of insurance. Black and Hispanic women were more than twice as likely to receive poorer quality care, after controlling for all other factors. Consulting with a medical oncologist attenuated but did not entirely eliminate the racial disparity (34).

Lund and colleagues examined first course of treatment among women diagnosed in 2000–2001 with invasive breast cancer in five Atlanta SEER counties (2008). In this analysis, black women were four to five times more likely to experience significant treatment delays. Black women also were less likely to receive cancer-directed surgery, radiation therapy after BCS, and endocrine therapy for hormone receptor positive tumors, after controlling for age, tumor size, stage, lymph node involvement, and ER/PR status (36). As with many observational studies, this analysis was limited by lack of information about treatments beyond the 4-month time window after diagnosis, inability to capture HER2 status, lack of information about comorbidities, and lack of information about provider and system-level characteristics.

In a study of newly diagnosed stage I and II breast cancer patients 65 and older using Surveillance Epidemiology and End Results (SEER)-Medicare data, investigators evaluated disparities in receipt of BCT, documentation of hormone receptor status, surveillance mammography during remission, and a combined measure of adequate care (41). In adjusted comparisons, Hispanic women were 33% less likely to receive adequate care, and black women were 23% less likely to receive adequate care, compared to white women. Black/white disparities actually worsened over time. Older women and those from rural areas were also significantly less likely to receive standard quality care, controlling for other factors. Banerjee and colleagues assessed receipt of BCT, endocrine therapy, and chemotherapy by conducting comprehensive medical record reviews of women diagnosed with breast cancer in Detroit at the Karmanos Cancer Institute and found that for local disease, white and black women received equivalent care, but for regional disease, black women were less likely to receive guideline-recommended endocrine therapy and chemotherapy. The authors did not find a racial disparity in receipt of BCT versus mastectomy, but they did note that women with Medicare or Medicaid insurance were more likely to receive mastectomy than those with private insurance. They also found that black women had far more comorbid conditions than white women, highlighting the need to control for comorbid illnesses in future analyses to avoid potential confounding (42). Because this study was limited to one institution in an area with many older, insured, black women of low socioeconomic status, the effect of variations in rural/urban residence, income and education, neighborhood racial composition, insurance status, and ethnic identity could not be easily assessed.

In a study by Freedman and colleagues (2009), SEER data from 1988 to 2004 were used to assess definitive local treatment (i.e., mastectomy or BCT) for early stage cancers. Over time, rates of mastectomy decreased as BCT diffused into practice; however, in adjusted models, rates of any definitive treatment remained lower for black and Hispanic women compared to white women, and no reduction of this disparity was observed over time (35). This analysis controlled for biologic tumor features, year of diagnosis, and region, but lacked information about employment, insurance status, and comorbidities, and did not control for possible organizational confounders.

Several studies have also found that black women more often experience delays in adjuvant therapy, which may affect longer-term health outcomes (18,37,43,44). One study using SEER-Medicare data explored variation in timing of receipt of radiation therapy after BCS and found that a substantial minority of breast cancer patients 65 years and older never received guideline-recommended radiation therapy after BCS. Further, among those women who did receive radiation therapy, black women more often experienced delays in initiation of therapy (37). After controlling for region-level resources, hospital facility-level factors, and patient-level factors, delayed initiation of radiation after BCS remained more common among black women compared to white women, although the Hispanic disparity resolved (37). Other studies have documented delays in time to first treatment among black women. Among young women with incident breast cancer (ages 20–54) in Atlanta, 22% of black women compared to 14% of white women experienced delays of greater than 3 months from diagnosis to first treatment. Access to care and poverty partially accounted for these delays, but significant racial differences in delays remained even after adjustment for all other factors (45).

Disparities also exist in the use of novel surgical techniques for breast cancer. Multiple studies have documented that black women are less likely to receive sentinel lymph node biopsy (SLNB), a less morbid but more technically challenging alternative to axillary lymph node dissection (46–48). This disparity does not appear to be explained by differences in clinical factors, insurance status, type of hospital, teaching status of hospital, or age. Despite increasing overall use of SLNB between 1998 and 2005, racial/ethnic gaps in receipt of SLNB have remained largely the same over time (48). Participation of the treating institution in cooperative research groups appears to promote use of SLNB roughly equally among black and white women (47).

Evidence suggests that after adjustment for known confounders such as hormone receptor status, stage, age, and insurance type, black women are equally likely to receive chemotherapy compared to non-Hispanic white women (49), and Hispanic women may actually be more likely than whites to receive adjuvant chemotherapy (49). However, other evidence suggests that black women more often delay or fail to complete adjuvant chemotherapy (50–52), have early dose reductions (53) or receive nonstandard chemotherapy regimens (54). Although completion of a full course of treatment is clearly important, clinically appropriate variation across patients in dosage, timing of cycles, and administration makes assessment of therapy completion difficult. As a result, it is sometimes difficult to determine whether such variation in chemotherapeutic administration is clinically valid or indicative of treatment disparity.

Initiation of trastuzumab-based adjuvant regimens, which has been standard of care for HER2-positive cancers since 2005, does not appear to differ by race, but completion of the prescribed year of infusional therapy is only half as likely among black women. Completion rates appear similar between non-Hispanic white and Hispanic women (52).

For hormone receptor positive patients, long-term endocrine therapy (ET) with tamoxifen or aromatase inhibitors is the cornerstone of adjuvant treatment to prevent recurrence. Unfortunately, evidence is beginning to emerge that many women either do not initiate ET or become nonadherent to therapy at some point after initiation, and this under-treatment is linked to higher mortality (55–58). Racial differences in ET adherence are an emerging topic of interest in breast cancer disparities, because differential initiation of, and adherence to, ET may explain noted racial heterogeneity in outcomes among hormone receptor positive patients.

Studies of endocrine therapy utilization generally examine initiation (beginning to take the medication), persistence (continuing to take the medication), and/or adherence (taking the medication at a percentage of the prescribed dose and schedule thought to be associated with acceptable efficacy, generally >80% of doses). In a uniformly insured cohort of Kaiser-Permanente patients, initiation of endocrine therapy in hormone receptor-positive patients was similar between black and white women, but significantly lower among Hispanics (59). Several studies in the Medicaid population have suggested that among low-income women, rates of ET initiation are uniformly low but not differential by race (60–62). Two studies of persistence to ET, one in a commercially insured population and one in Medicaid patients, suggest that race does not affect likelihood of continuing to take ET once a woman has started the medication (60,63). However, several studies suggest that among women continuing to take ET, black or non-white women are less likely to be adherent after adjustment for other factors. In the Kaiser-Permanente cohort mentioned above, black women were equally likely to persist in taking ET, but significantly less likely to be adherent to more than 80% of their doses (55). Similarly, Neugut and colleagues found lower odds of adherence among black women in a commercially insured cohort receiving medication via Medco pharmacies (63). In the Medicaid population, reports concerning adherence have been conflicting; one study in New Jersey patients found lower adherence among non-white women (58), while similar studies in New York, North Carolina, and South Carolina patients found no difference in adherence by race (60,62,64). Existing studies in this area have been limited by lack of population-based samples, lack of data on older women, and small minority sample sizes. More studies are needed with sufficient numbers of black women from a broader socioeconomic and geographic range in order to statistically support subgroup analyses by race of long-term ET adherence.

Potential Explanations for Racial Variation in Treatment

The role of comorbidities in explaining treatment and survival disparities between white and black women is very important. Higher rates of comorbidity among black women may explain some disparities in overall survival after breast cancer. However, Tammemagi and colleagues found that although comorbidity burden was partially responsible for racial disparities in overall survival, comorbidities did not explain differences in breast cancer-specific survival (65).

Beyond the obvious role of comorbidities in reducing life expectancy, higher comorbidity burden among blacks could lead to competing priorities in health care seeking-behavior. If, for example, a woman with uncontrolled diabetes and/or a serious disability has limited time and resources to attend healthcare appointments, she may prioritize certain health visits over others. Furthermore, if her functional status or mental health status is compromised by comorbid condition(s), these may additionally inhibit health-seeking behaviors for her cancer diagnosis, particularly if she feels she is at low risk for metastasis or death. Patient-level factors other than comorbid conditions may also help explain why different racial subgroups receive different treatments, including health literacy and personal preferences (66); insurance and socioeconomic status (67); cognitive and social network correlates (68); experience with/trust of the health care system; and fatalistic beliefs and health-seeking behavior (67).

Health system factors are also important potential explanations for why different subgroups of patients receive differential quality of care. Health services organization and structure are closely related to adoption of high quality, evidence-based practices and may play a role in explaining treatment disparities. The interplay between health system factors, community-level factors and patient-level factors can be complex. Characteristics of local communities, including population density, local resource capacity, and neighborhood racial/ethnic composition, may affect the types of organizations that locate in particular settings. In addition, patients' choice of residence, utilization of particular organizations or services, and access to well-trained health professionals may be influenced by their sociodemographic characteristics (69,70). As a result, access to medical innovations and new technology may be distributed unequally, influencing quality of care.

Generally, elements of the healthcare system are described in terms of provider-level factors (e.g., provider specialty, age, race/ethnicity, board certification), facility-level factors (e.g., type, size, profit status, procedural volume, teaching status), and system-level or structural factors (e.g., location, dispersion, and availability of health services, healthcare financing, technology investment, existence of quality monitoring systems). Several studies have investigated the effects of these factors on guideline-concordant practices in cancer care, but rarely are racial/ethnic and other patient-level variables considered in the context of the design and operation of the health system. One study showed that black cancer patients were more likely than white patients to be treated by physicians who lacked board certification, experience, and technical resources (71). Moreover, physicians treating black patients more often reported that they were unable to provide high quality care to their patients (71). Bao and colleagues have discussed the importance of distinguishing "within" physician differences from "between" physician differences, suggesting that the problem of one physician practicing poorly across all his/her patients is quite different from the problem of one physician providing worse quality care to certain patients, while providing better quality care to others (72). The exploration of these factors in the specific context of breast cancer care is described in the following paragraphs.

Despite strong evidence for racial disparities in breast cancer outcomes, few empirical studies have explicitly considered the modifying or confounding effect of health services factors on the relationship between race and breast cancer care. One publication by Jerome-D'Emilia and Begun using information from the National Cancer Database (NCDB) examined diffusion of BCS and highlighted the importance of hospital teaching status, regional supply of radiation oncologists, surgical volume, and ratio of specialists to generalists in predicting receipt of breast conserving surgery over time (73). After controlling for these health system-level factors, race did not have a significant effect on receipt of breast conserving surgery. In another study examining variation in timing of radiation therapy after BCS, researchers found evidence that characteristics of the health system, such as facility location, type/ownership, and institutional affiliations, play a role in determining timing of receipt of radiation therapy and that these factors, when omitted from analyses, likely confound the effect of race/ethnicity (37). For example, increasing distance to the nearest radiation facility generally was associated with lower odds of ever receiving radiation therapy, and distance to radiation facilities varied significantly by race. This study demonstrated that health system-level factors accounted for some, but not all, of the racial differences in timing of radiation therapy. However, racial/ethnic differences in *ever* receiving radiation therapy disappeared after controlling for health system factors and other potential confounders (37).

Access to insurance and ability to pay for treatment also may vary by race and lead to racial differences in outcomes. In general, uninsured/underinsured and low income women suffer serious problems of access to breast cancer care due to lack of ability to afford out-of-pocket deductibles and copayments, lack of reliable or free transportation, and competing demands. Long-term costs associated with breast cancer treatment can be staggering, which may affect receipt and completion of treatment. Uninsured or underinsured cancer patients are especially sensitive to high costs of care, and black women are more often uninsured or under-insured than white women. Regardless of insurance status, hidden costs of cancer care, such as transportation to treatment centers; loss of income due to diminished productivity or loss of work days; and out-of-pocket premiums, deductibles, and copayments can be especially burdensome to the cancer patient (74). Due to the difficulty of measuring person-level socioeconomic status and out-of-pocket expenses in large claims-based datasets, the effect of such factors on the relationship between race and breast cancer care is understudied.

Although racial disparities in breast cancer treatment are generally well-documented, more racially specific data are needed in some areas. With respect to stage IV or advanced breast cancer, many treatment options exist, and treatment options have rapidly changed over the years; more studies are needed to examine racial/ethnic, socioeconomic, geographic, and structural/organizational variation in the complex treatment of advanced disease. Additionally, racial differences may exist in receipt of post-mastectomy radiation therapy (indicated at a minimum for tumors greater than 5 cm or with multiple positive nodes). Punglia and colleagues examined receipt of radiation therapy after mastectomy in elderly women during the 1990s and found that trends in use differed significantly across practice settings, but more updated examinations by race are needed (75).

Differences in treatment can potentially explain a large portion of the racial and ethnic disparities in breast cancer, particularly among patients eligible for radiation and endocrine therapies. In many cases, however, racial differences in mortality remain even after controlling for treatments received, and racial differences persist in health systems with equal insurance coverage and access to care (23). These realities suggest a need to explore other factors that may contribute to poorer outcomes among minority breast cancer patients, including differences in treatment response and survivorship care.

DISPARITIES IN RESPONSE TO TREATMENT

Differences in Toxicity

One potential mechanism by which racial disparities in breast cancer can arise is through differential treatment toxicity in women of different races, leading to more frequent discontinuation, delay, or dose modification of treatment regimens. Such toxicity could be attributable to inherent race-based variations in susceptibility, or to differences in comorbid conditions that influence a woman's ability to tolerate cancer treatments. Both possibilities have been explored most thoroughly in the area of chemotherapy treatment.

Concerns have been raised for greater hematologic toxicity of chemotherapy among black patients due to lower baseline white blood cell counts (51). However, research suggests that hematologic toxicity of breast cancer chemotherapy is actually similar between blacks and whites (76), although more treatment modifications and dose reductions are seen in blacks. A single institution cohort study found lower baseline and posttreatment white blood cell counts among black women, and these lower counts were associated with reduced chemotherapy dose intensity due to dose reductions. Rates of serious chemotherapy-associated side effects including neutropenic fever and toxicity requiring a treatment delay did not appear to differ by race within a clinical trial population (77), though treatment delays for any reason were significantly more common in black women. The effect of toxicity-mediated disparities in treatment intensity on recurrence and survival outcomes is not yet understood.

Black women may also experience a disproportionate side effect burden from treatments other than chemotherapy. Black race has been reported as an independent risk factor for the development of lymphedema, or swelling of the arm after breast cancer surgery (78). Additionally, black and Hispanic women are more likely than white women to experience inadequate pain management and management of serious side effects of treatment (79).

Differences in Efficacy

On the whole, evidence suggests that black and white women receiving similar breast cancer treatment experience similar outcomes. Patients treated with neoadjuvant chemotherapy (chemotherapy given before definitive breast cancer surgery) have been a logical population in which to study this question, because pathologic findings at surgery provide a quantifiable patient-specific measure of response to chemotherapy. In a series of patients with triple negative breast cancer treated with neoadjuvant chemotherapy at MD Anderson Cancer Center, rates of pathologic complete response to chemotherapy and recurrence-free survival were similar among white and black women (80). However, in a larger MD Anderson cohort that included neo-adjuvantly treated patients of all biologic subtypes, black patients with hormone receptor-positive, HER2 negative disease did have significantly inferior recurrence-free survival after controlling for pathologic response to chemotherapy (81). This analysis was not able to control for receipt of, or adherence to, endocrine therapy. Similarly, a single institution study of a multiracial population of stage II–III patients treated at the University of North Carolina with anthracycline/taxane-based neoadjuvant chemotherapy found no difference in pathologic complete response between black and white patients, but significantly worse relapse-free and overall survival among blacks, especially those with hormone receptor-positive tumors (82). No significant difference in outcome was seen in patients with hormone receptor negative tumors, again raising the question of whether access or adherence to long-term endocrine therapy may influence disparities among women with hormone receptor-positive tumors.

Similar patterns of response have been observed in patients receiving adjuvant rather than neoadjuvant chemotherapy. A large cohort study of women participating in National Cancer Institute adjuvant chemotherapy trials found no racial disparity in outcomes among women with triple-negative and HER2+ cancers after controlling for receipt of therapy, but inferior outcomes among black women with hormone receptor-positive, HER2-negative cancers compared to whites (28). In a retrospective study of patients participating in Southwest Oncology group clinical trials, black women were more likely to discontinue or have delays in adjuvant chemotherapy, but even after controlling for these factors and other clinically relevant covariates, black women had inferior

disease free survival (77). No interaction between race and receptor subtype was found in this study, suggesting a consistent effect across breast cancer subtypes, but the strength of this finding is limited by a relatively small sample size.

In summary, the evidence suggests that response to chemotherapy in women with similar disease characteristics is comparable across races, and that observed differences in long-term breast cancer recurrence and survival outcomes after chemotherapy are most prominent in hormone receptor-positive subtypes, where outcomes may be affected by differences in use of endocrine therapy. It is also possible that within-subtype biologic differences explain worse outcomes among black women with hormone receptor-positive tumors, suggesting a need for more research focused on molecular characterization of these tumors.

DIFFERENCES IN SUPPORTIVE AND SURVIVORSHIP CARE

Potential racial differences in long-term sequelae of treatment and survivorship care of breast cancer survivors are dramatically understudied. Older studies suggested that black survivors might have more difficulty with resumption of daily tasks and long-term adjustment compared to whites (83), but research to substantiate or add detail to these findings is lacking. There is some evidence that minority women receive less adequate supportive care during the survivorship period. In one survey study, black and Hispanic women were less likely than whites to report talking with other survivors, and more likely to report wanting more contact with other breast cancer patients (84). Black and Hispanic breast cancer survivors in another survey of survivorship care were more likely to report an unmet survivorship-related need, such as menopausal symptoms, difficulty sleeping, or arm problems. Both cost/insurance and barriers and problems in communicating about needs with providers were cited by women as reasons for unmet needs (85). Overall health utilization among black women after breast cancer may also lag that of white women. In a large cohort study, black breast cancer survivors were less likely than their white counterparts to receive preventive healthcare services, such as influenza vaccination, lipid screening, and screening for other cancers, after adjustment for age, comorbidity and a variety of disease-related and socioeconomic factors (86). Although there is little research regarding the underlying causes of these disparities in survivorship care, it is reasonable to hypothesize that patient-, provider-, and structural-level factors affecting receipt of high quality care during initial treatment may have similar effects during survivorship.

SPECIAL ISSUES IN BREAST CANCER DISPARITIES

Women with Multiple Vulnerabilities

The problem of health disparities in breast cancer care and outcomes is not limited to racial disparities among black women compared to other groups. Organizational, structural, economic, and sociopolitical dynamics of the American health system contribute to complex racial/ethnic, socioeconomic, age-related, and geographic health disparities. Particularly vulnerable groups include the elderly, the uninsured and under-insured, low-income women, and women living in rural or under-resourced areas. Being in more than one of these subgroups likely corresponds with even higher risk of poor quality care and poor outcomes. Elderly, rural-dwelling, less educated, poor, disabled, and Hispanic and/or non-English speaking women all experience significant disparities in breast cancer detection and survival after diagnosis (87). Interactions among these patient-level factors may have an additive or multiplicative negative effect on health outcomes. For example, the issue of distance to care has been found to be more problematic for older women (88) and Hispanic women (37), perhaps suggesting that transportation to care is particularly problematic in these subgroups. High quality data as well as complex analytic methods are required to correctly understand interrelationships among multiple patient-level factors affecting the quality of breast cancer care.

It should be noted that the relationship between race and other factors that affect breast cancer risk and cancer care utilization is complex and that the needs or challenges of breast cancer patients of a given race may differ based on factors linked to, but distinct from, race. To cite one example, multiple studies have documented that use of adjuvant endocrine therapy is uniformly lower among Medicaid patients, who typically have low income and poor healthcare access, than has been reported in other patient populations, and this underuse is uniform across Medicaid patients of different races despite the over-representation of black women in Medicaid (58,60). In this case, socioeconomic vulnerability, not race, is likely the driver of underutilization and attenuates racial differences. Conversely, within-group heterogeneity in racial minorities is often understudied such that the variations in utilization within minority populations are masked. For instance, although Asian women in Northern California have been reported to initiate adjuvant endocrine therapy at similar rates compared to whites, further sub-group analysis identified that Chinese woman actually initiate endocrine therapy at lower than average rates, while other Asian subgroups including Japanese, Filipino and South Asian women initiate at average rates (59). Within-group heterogeneity in breast cancer also occurs within immigrant populations; U.S.-born Hispanic women have higher rates of incident breast cancer than foreign-born Hispanics, and higher socioeconomic status and residence outside an ethnic enclave have also been associated with higher breast cancer incidence, suggesting that these women may have changes in risk factors based on their length of residence in the United States (101). Paradoxically, U.S.-born Hispanic women have lower rates of advanced-stage breast cancer diagnosis than foreign-born women, but somewhat lower breast cancer-specific survival (102). These complex relationships illustrate that disparities in breast cancer among minority women are indeed multifactorial and likely will require equally complex solutions.

Breast Cancer Care in the Elderly

Age and breast cancer are closely and meaningfully correlated (5). The majority of breast cancer diagnoses occur in women older than 60, and the median age at breast cancer diagnosis is 62 years. Breast cancer incidence rises dramatically and nonlinearly with age and levels off around the time of menopause, a trend that is biologically explained by the important role of reproductive factors and ovarian estrogens in breast cancer etiology (6). Further, behavioral and morphologic characteristics of the cancer itself differ by age. As discussed earlier in this chapter, younger women tend to have more aggressive tumors and worse prognosis, whereas older women typically have more indolent disease with better prognosis (5). Important age-specific racial/ethnic trends in breast cancer incidence and mortality are also observed. Specifically, young black women (<50 years old) have a higher incidence of breast cancer compared to young

white women, but around the time of menopause, a crossover occurs and incidence rates among older white women surpass rates of older black women (6).

Age-related disparities in cancer treatment are well-documented in the literature, but the implications of such disparities are muddied by poor representation of elderly breast cancer patients in clinical trials (89). Due to insufficient accumulation of clinical trial evidence about the effects of radiation and chemotherapy in older women, cancer quality metrics have been limited to women younger than 70. Many experts agree that such an age-specification sets a low bar for quality, given observational evidence showing that older women benefit as much as younger women from these therapies (89). Studies have shown that women older than 70 are less often treated with chemotherapy and less often receive radiation therapy after breast conserving surgery (37,90), but the implications of this under-treatment are unclear and need further study. Importantly, randomized trials demonstrate that older women derive the same benefit from chemotherapy as younger women (91), and that women older than 65 treated with less aggressive, nonstandard adjuvant chemotherapy fare worse (89). Choice of treatment and supportive medications matter. In an older study of women over 70 treated with the first-generation chemotherapy regimen oral CMF, only 65% completed all 6 cycles; nonpersistence with treatment was associated with toxicity (92), highlighting the importance of side effect management in this vulnerable population.

Disparities in Research Participation

Black women enroll in clinical trials much less often than white women and thus may have poorer access to life-prolonging treatment offered by many cancer trials (93). As a result, diffusion of research-related innovations may be disproportionately benefiting certain women as compared to others. In addition, Mitchell and colleagues found that few breast cancer randomized trials reported or analyzed outcomes based on race/ethnicity, indicating a failure to report data that may help evaluate and overcome health disparities (94). Under-representation of elderly and minority women may also lead to under-recognition of toxicities that are race or age specific.

INTERVENTIONS TO ADDRESS BREAST CANCER DISPARITIES

The elimination of healthcare disparities is a national public health priority, and a number of interventions at the policy level have attempted to narrow breast cancer disparities. The national Breast and Cervical Cancer Early Detection Program (BCCEDP), begun in 1991, is one such program in which federal and state matching funds are allocated to provide cancer screening to low income women, and more recently to provide coverage for treatment in the event of a cancer diagnosis (95). Data from the early years of the program indicated a positive effect, with the greatest increases in mammography screening rates among black women in the under-65 age group (96). Rates of mammography among blacks continued to rise through the year 2000, and the age of the BCCEDP program at the state level was an independent predictor of higher mammography usage among white women, though the effect was not statistically significant for black and Hispanic women, likely due to smaller sample sizes (95).

A number of interventions at the patient- and provider-level have also been tested to increase use of screening mammography. A systematic review by Masi et al found that simple patient reminder-based interventions were not generally effective in raising screening rates in populations that included large numbers of black women and/or patients with low income or low educational attainment. Provider-targeted reminders, however, were more successful in improving screening rates in minority populations, and multifaceted interventions that addressed barriers such as transportation cost in addition to providing reminders and educational material have also been successful in minority populations (97,98). None of these interventions examined effects of the intervention on long-term outcomes such as breast cancer mortality, and such an evaluation is not likely to be feasible given the extended study timeframe required. Patient-level interventions to address disparities in diagnostic work-up or receipt of appropriate treatment have been tested less often than interventions to increase screening. In five studies of diagnostic testing interventions, Masi and colleagues found that some form of case management shortened the time from mammogram to diagnosis or biopsy among black (four studies) and Hispanic (one study) women (97). A more recent study of case management through a patient navigator among urban minority women with abnormal mammograms demonstrated improvements in time to diagnostic resolution, anxiety, and patient satisfaction with patient navigation compared to usual care (99). Similarly, a case management based intervention increased receipt of BCS with radiation therapy in a racially diverse cohort and eliminated disparities in rates of stage-appropriate treatment (100).

FUTURE DIRECTIONS

The decision by an individual patient and her providers to undertake a particular diagnostic and treatment path is complex. Treatment decisions leading to differential quality of care may arise from patient-level, provider-level, facility-level, and structural characteristics (37). Improving patient-level psychosocial or behavioral correlates of treatment disparities, such as health-seeking behavior and trust in the healthcare system, will require creative and sensitive interventions. Provider-level, facility-level, and structural correlates of treatment decision-making, however, should be distributed relatively similarly across patients. For example, access to specialists and facilities capable of providing modern procedures, such as sentinel lymph node biopsy or radiation therapy, should in theory be equally available to black, Hispanic, and non-Hispanic white patients, but this may not be true in reality. Of course, individuals can choose to forego guideline-recommended therapy, but as a rule, treatment options should be made equally available and accessible to all breast cancer patients with clinically similar tumors.

Clearly, race-specific genetic susceptibility to more aggressive cancers may not be affected by public health efforts; however, recognizing that there are racial differences in tumor biology may suggest the need for more tailored screening approaches or for focus on identifying environment-gene interactions that lead to strategies for cancer prevention. Additionally, health system/structural-level correlates of racial disparities in breast cancer outcomes such as access to insurance coverage may be slow to change over time, but are likely to improve with recently enacted health reform legislation. Health reform is an opportunity to redesign healthcare systems and policies in order to improve the quality of care for *all* breast cancer patients. The possibilities are numerous. For example, interventions designed to provide transportation to radiation therapy or chemotherapy appointments for racial/ethnic minorities and elderly women

without regular access to transportation could be tested and reimbursed by insurers should they prove effective in reducing barriers to access. Similarly, telemedicine strategies currently under study may be useful in building collaboration between tertiary centers and smaller community hospitals whose advanced breast cancer patients can benefit from inter-institutional tumor board meetings. Finally, greater emphasis on, and evaluation of, the training and use of patient navigators are needed to encourage early initiation of adjuvant therapy and to limit underuse of adjuvant therapy in racial/ethnic minorities and elderly patients.

Despite gains in our understanding of breast cancer disparities, many nagging questions remain regarding how to ensure optimal treatments and outcomes for all patients. Among these are questions about the best use of innovative gene expression profiles or detailed molecular studies in directing patient care, improvements in surgical and radiation techniques, optimization of adjuvant systemic therapies incorporating novel biologic treatments, whether structural interventions can improve receipt of guideline-concordant treatment by removing barriers to access, and whether behavioral interventions can increase initiation and long-term adherence to adjuvant therapy. As new treatment innovations emerge and new guidelines are developed, it will be increasingly important to monitor uptake and to ensure that vulnerable subpopulations have equal access to these evidence-based advances in care. The field of cancer disparities is evolving from one which builds observational evidence of differences in presentation, treatment, response, and survivorship to one which designs and tests novel interventions to remedy the underlying causes of these differences.

Finally, systems thinking could be used to build, parameterize, and validate models that help coordinate breast cancer care across diverse breast cancer patients, health facilities, and providers. Recognizing that the supply of oncologists and other cancer specialists is limited and that cancer prevalence may be increasing given the aging American population, optimal use of cancer resources is important. For example, earlier stage, uncomplicated breast cancer patients may be treated sufficiently well at lower volume, community-based facilities, whereas advanced stage patients with significant clinical complications or comorbidities may benefit from being treated at higher volume, academic medical facilities. Because there are fewer of the latter, we should seek to optimize patient allocation so that clinical expertise, technical resource capacity, transportation/travel, and case complexity can be delivered in the areas of greatest need. Such a systematic approach will ensure the best outcomes for all patients, regardless of race/ethnicity, age, or socioeconomic status. Creative optimization models drawing upon the methods used in industrial engineering and operations research may be useful in this context.

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SECTION XIV

Issues in Breast Cancer Survivorship

CHAPTER 87

Nursing Care in Patient Management and Quality of Life

Karen Meneses and Deborah K. Walker

CHAPTER CONTENTS

Nurses have an integral role in the interdisciplinary management of patients from prevention, screening, and early detection through diagnosis, treatment, recurrence, and survivorship. This chapter is divided into patient care management along the cancer continuum with specific focus on patient management during the various therapeutic approaches to care. Each section emphasizes patient management related to education, symptom management, and psychosocial support.

PREVENTION, SCREENING, AND EARLY DETECTION

Prevention, screening, and early detection are important strategies in reducing the breast cancer incidence, particularly in high-risk women. The emphasis on lifestyle interventions along with routine screening has led to significant improvement in early detection of breast cancer.

Prevention

There are many risk factors for the development of breast cancer in women, but few can be modified. Table 87-1 lists risk factors. Lifestyle modifications are one area where nurses can be proactive and educate on strategies for risk reduction. Encouraging healthy nutrition, increased physical activity, weight management, and limited alcohol consumption are interventions that can reduce a women's risk of breast cancer (1–3). Although diet has not specifically been linked with an increased risk of breast cancer, obesity and weight gain have demonstrated an increased risk among postmenopausal women (4). Maintaining a healthy body mass index (BMI) through eating healthy and physical activity is important, not only for positive effects on body weight, but also for better psychological and quality-of-life outcomes (5). History of alcohol consumption is important to assess. As little as one drink per day of alcohol has been associated with an increased risk of breast cancer (6). Nurses involved in screening and early detection activities can educate on the risk of excess alcohol consumption, and recommend less than one drink per day (7).

Other prevention strategies for moderate- to high-risk women (i.e., *BRCA1* and *BRCA2*) include risk reduction surgery or using a selective estrogen receptor (ER) modulator such as tamoxifen. Risk reduction surgery may include a bilateral mastectomy and/or bilateral salpingo-oophorectomy. Surgery is usually recommended in women with either the *BRCA1* and *BRCA2* mutation or in women at high risk (8). Surgery may have a negative impact psychologically, so counseling is vital prior to the procedure. Counseling should include the risk and benefits of surgery and discussion of other options, if available (i.e., reconstruction).

In women 35 years or older, tamoxifen has be used to decrease the risk of a second primary contralateral breast cancer (9). Nurses can educate women about the benefits of tamoxifen that include reducing the risk of invasive and noninvasive breast cancer, and reducing risk of a new primary contralateral breast cancer (9). Symptom management education while on tamoxifen is also important, and should include hot flash management, risk of thromboembolic events, and increased risk for endometrial cancer (9).

TABLE 87-1

Risk Factors
Age—risk increases with age
Reproductive factors
Age at menarche—early increases risk
Age at menopause—late increases risk
Age of first live birth—late first pregnancy
Nulliparity—increases risk
History of benign breast disease
Oral contraceptive use
Current or prior use of hormone replacement therapy
Alcohol consumption
Increased body mass
Ionizing radiation to chest before the age of 30
Family history
Personal history of breast cancer—lobular carcinoma *in situ*

From National Comprehensive Cancer Network (NCCN). Fort Washington, PA: NCCN, Inc., 2012.

Educating women about risk factors is ideally done by the health care team. Patients often turn to their nurses for information. Nurses can share information about modifiable and nonmodifiable risk factors (i.e., age, family history, etc.). This knowledge would help nurses identify those at risk for breast cancer and provide help when they counsel about prevention strategies.

When addressing risk factors and prevention strategies with women, there is the potential for psychological concerns. Women may overinterpret their risk with resultant increase in anxiety or stress which may lead to ignoring symptoms or recommendations for screening. Alternatively, women may see improvement in overall health when they follow the recommendations for lifestyle modification and screening for breast cancer.

Screening and Early Detection

Recommendations for breast cancer screening vary slightly depending on the recommended guidelines that are followed. The general consensus among all recommendations is that not one screening modality should be used alone. Breast self-awareness, clinical breast exam, and mammography should be used together, along with clinical reasoning to screen individuals for breast cancer (7,10–12). Nurses should be familiar with the recommendations supported by their institution and educate women accordingly.

Breast biopsy is performed when an area of suspicion has been identified on diagnostic evaluation. Fine-needle aspiration, core needle, and excisional biopsy are commonly used methods (7). Patients should be educated about the specific method, recovery period, and when follow-up occurs. Fine-needle aspirations are typically done when there is a low suspicion for malignancy. It is the least invasive and can be performed in the office using a needle and syringe to aspirate contents of the mass. Recovery is quick and patient usually does not have any limitations. If the result is benign, follow-up occurs within a few months to monitor for reaccumulation of fluid.

Core needle biopsies are done more frequently to obtain large tissue samples for analysis. After local anesthetic, a large-gauge hollow needle is inserted into the suspicious area and several samples are obtained. During the sampling process a "clicking" sound may occur as the sample is retrieved. The patient may feel pressure during the procedure, but not major pain. Bruising may occur at the needle insertion site.

An excisional biopsy of the breast is invasive and may be done with a local anesthetic, under IV sedation, or rarely, general anesthesia. The patient should be informed accordingly regarding any restrictions prior to the type of procedure; for example, nothing to eat after midnight on the day before surgery. Because this procedure is invasive, patients may have a visible scar and/or a noticeable change in breast shape or size. This procedure can take about 1 hour with a recovery period of less than 2 hours. For a few days the patient can expect to be sore and have some swelling to the area. Patients should also be informed about the risk of infection from the invasive procedure and to call with fever, pain, erythema, or bleeding from the incision. Recovery is about 1 to 2 weeks for the incision to heal. Follow-up is needed in 10 to 14 days if sutures need to be removed.

Additionally, the nurse should provide education on breast self-awareness including the proper way to perform a self-breast exam (SBE). Although SBE is controversial and has not been shown to decrease breast cancer mortality (12), it is important that women become familiar with their breasts to help identify problems in between clinical examinations. The patients should also be given information to help them understand their own risk for developing breast cancer and the recommendations for ongoing surveillance. This information should be individualized and based on their medical and family history, as well as clinical exam findings. There are numerous online resources in both English and Spanish that can be used as education materials.

A review of a meta-analysis found that screening and early detection for breast cancer may cause fear and anxiety among individuals (13). Often individuals do not go for screening because they fear a mass might be found, they may have a recurrence, or a second breast cancer. To help alleviate some of those concerns, nurses should be proactive in offering recommendations and education on the use of screening as a tool to identify areas of concern early. Early identification may lead to early intervention and better outcomes.

PATIENT CARE MANAGEMENT OF LOCAL AND REGIONAL DISEASE

Education

Practice guidelines for the treatment of early-stage breast cancer are well publicized and are available to patients and their families (7). Patients who are best able to make decisions about treatment are those who can express and communicate their beliefs, feelings, and preferences, who actively listen to information shared by their oncology team, and who search out additional information or second opinions from trusted and respected sources (14). Likewise, clinicians who are best able to assist patients in making reasonable decisions about treatment are those who recognize that decision making is a process that occurs over time and who acknowledge patients' vulnerability in making decisions (15).

While there are numerous patient teaching materials available in print (e.g., books, pamphlets, and brochures), there has been a significant increase in electronic and

web-based education formats about breast cancer treatment (16). In addition, electronic support groups, face-to-face support groups, counselors, and individual networking efforts contribute to helping patients find information (see appendix for web sites). Clinicians can foster patient decision making by ongoing assessment of their patients' developmental stage, educational level, degree of anxiety, energy level, personal coping styles, past experiences, and family history. Nurses can help patients and their families discern what is useful during this stressful time and what can be used at a later date by knowing what resources are available in their institution, in the community, regionally, and nationally.

Preoperative Teaching

Specific preoperative teaching focuses on information about the procedure, incision and drain care, pain management, lymphedema prevention and management, and prosthetic devices (17). In the United States, length of hospital stay for mastectomy is about a day. Thus, preoperative teaching ideally begins in the surgeon's office. Patients generally find that a simple pamphlet, brochure, or video that illustrates the surgical experience beginning with admission, surgery, and recovery helps orient them to the surgical facility and procedures.

Patient teaching before surgery may include instructions about stopping use of any aspirin-containing products, vitamin E, and herbal preparations for at least 7 days preoperatively. Some postoperative pain medications contain opioids that can cause constipation; it is helpful for patients to drink several glasses of water before midnight the night before surgery. Similar to other surgical procedures, no solid food or drink may be ingested at least 6 hours preoperatively. On the day of surgery, patients may feel comfortable wearing a loose-fitting blouse with front tab buttons for ease of comfort, particularly when axillary node dissection is planned. Harris et al. recently evaluated guidelines for breast cancer rehabilitation with an emphasis on lymphedema and concluded that there is a pressing need to update the guidelines on upper extremity musculoskeletal impairments and lymphedema (18).

Symptom Management after Mastectomy

Incisional Wound and Drain Care

Nurses provide specific information about dressing changes, measurement and recording of drainage, monitoring for signs and symptoms of infection, and personal hygiene. Patients generally prefer a description of what their surgical incision will look like, and an appropriate visual diagram or photograph helps illustrate the anticipated results. Postoperatively, patients need instruction on drain care and how to minimize unnecessary pressure or prevent accidental dislodgement. Patients may feel mild to moderate discomfort and soreness. Having a family member or friend available to help them with physical care and personal hygiene and to monitor for potential postoperative complications (i.e., seroma, hematoma, increased pain or discomfort, or fever). Light foods such as clear broth or soup, fruit juices, and soft foods may help ease postanesthesia effects such as nausea. For general comfort, pillows to support the affected arm and back are helpful.

Pain Management and Comfort Measures

Postoperative pain varies widely, depending on individual and cultural characteristics, the surgical procedure, and pain medication relief (19). Some patients have relatively little discomfort with lumpectomy and require mild analgesics, whereas others may have pain after mastectomy and reconstruction that requires stronger analgesia. A plan for postsurgical pain management is best individualized between the clinician and patient with regular monitoring of pain relief.

Postoperative sensations and pain, such as muscle tightness, difficulty in lifting of the arm, and soreness around the shoulder, are to be expected (20). Support for the arm and shoulder during the first 24 postoperative hours and avoidance of active stretching or pulling until after the drains are removed are helpful. Gentle stretching exercises can usually begin soon after surgery (usually 48 hours) and should be individualized to reflect the extent of the operation, the presence of drains, and the preoperative capabilities of the patient. For patients who will receive radiation therapy as part of their treatment, regaining adequate range of motion is extremely important because the radiation treatment position requires the arm to be abducted at a 160-degree angle. Since lymphedema is a major side effect of treatment, the reader is referred to Chapter 40 for extensive information about the topic.

Prosthetic Fitting

Prosthetic fitting for women who have had mastectomy and reconstruction is generally done around the first postoperative follow-up appointment or when the incision has healed. However, women benefit from receiving specific information about how, when, and where to purchase a prosthesis and from having a temporary prosthesis in hand before hospital discharge. Many different prosthetics are available, such as soft forms and self-adhering forms, in a variety of colors and textures. There are also stylish and specially designed lingerie and bathing suits that can accommodate the prosthesis. Having a sample of a breast prosthesis and mastectomy bra to use during preoperative teaching is useful.

Care after Breast Reconstruction

After reconstruction, patients may start home exercises such as brisk walking, stationary bike riding, and gentle stretching exercises. Avoiding high-impact aerobics, jogging, and lifting weights above 5 to 10 pounds is recommended for several weeks after reconstruction (20). Patients should avoid the use of health spas and public swimming pools until after the incision lines and drain sites are healed (20). Although breast reconstruction approximates the look of the natural breast, it cannot duplicate the same look and feel (20).

Psychosocial Recovery

Detailed discussions of patients' psychological reaction and support programs are found elsewhere in the text. Specific preoperative discussions in which clinicians can engage with their patients include attending to the emotional impact of the initial diagnosis and treatment of breast cancer and acknowledging that the surgical experience marks the beginning of a long recovery period. Other psychosocial strategies include the following: helping patients to reframe their time sequence; reordering priorities about work, family, and social activities; and encouraging short-term thinking (e.g., practice 1 day at a time, practice thought-stopping that provokes anxiety, and think through the process of the events of the week and the time it takes to accomplish tasks).

PATIENT CARE MANAGEMENT DURING RADIATION THERAPY

Education

Teaching patients about radiation therapy ideally begins during the consultation visit, when the role of radiation therapy in the overall treatment plan, additional diagnostic

studies needed, and treatment planning are discussed. Patients may be apprehensive about starting radiation but generally are relieved to learn that side effects are well tolerated (21). Information about radiation treatment planning includes the rationale for simulation, the need to minimize radiation dose to vital organs such as the lung and heart, and the construction of immobilization devices to keep the limbs in consistent position during treatment. Patients must plan to spend sufficient time for the simulation procedure, must be prepared to feel some discomfort while lying on a hard simulation table, must understand that the radiation therapist will place a permanent tattoo or skin markings (e.g., the size of a freckle) directly on their skin surface to help reproduce the treatments on a daily basis, and must realize that simulation is *not* a radiation treatment.

After simulation is completed, patients receive an appointment to start treatment that will be given daily, 5 days a week. Patients find it helpful when the radiation oncology nurse gives information about a typical day or week's treatment so that they can obtain a mental picture of the experience. Patients also find it helpful to keep a diary of daily activities and appointments. Some patients prefer to bring a CD player or other device to listen to their relaxation tapes or music during treatment. The first treatment generally takes about 30 to 45 minutes; subsequent treatments take about 15 minutes. They may be disconcerted by the sounds emanating from the radiation treatment machine. Patients may need reassurance that although they are alone during treatment, the radiation therapists remain in contact with them by screen monitor and intercom. Radiation oncology departments are often located on the ground floor, with natural light, serene wall colors, and artwork. Soothing background music helps allay patients' anxiety.

Symptom Management during Radiation Therapy

Symptom management includes teaching about the potential side effects of radiation therapy, self-care measures to manage the side effects, and managing the overall radiation therapy experience. The acute physical side effects of radiation therapy are skin reactions and fatigue.

Skin Reactions

Radiation-induced skin effects range from slight peeling, dryness, tanning, itchiness, and breast tenderness and fullness to moist desquamation (21). The severity of skin reactions is related to radiation factors (i.e., total dose, fractionation, energy beam, bolus treatment, and volume of tissue treated), patient factors (e.g., breast size, age, nutritional state, presence of comorbid disease), and treatment factors such as previous or concurrent chemotherapy. Particularly susceptible areas of skin breakdown include the inframammary fold and supraclavicular areas.

Teaching patients self-care skin management during radiation ideally begins before or at the start of treatment. The radiation oncology team examines patients for acute side effects on a weekly basis and as needed as therapy progresses. In a recent update to evidence-based skin care management in radiation therapy for breast cancer, McQuestion indicates that there is insufficient evidence with respect to topical or oral agents in the prevention of skin reactions. Further, calendula cream may reduce the incidence of grade 2 or 3 skin reactions (21).

Cancer-Related Fatigue

Fatigue is recognized as one of the most prevalent symptom of cancer and its treatment (7). Fatigue can be a chronic problem that results from several causes (i.e., treatment and pathophysiologic, behavioral, and emotional factors). It occurs during treatment and persists even after treatment ends. Patients with cancer report that fatigue has a negative influence on quality of life: It can impair the ability to function or maintain daily routines (e.g., weakness, no energy), influence emotional reaction (e.g., sadness, irritability), and interrupt work schedules (e.g., poor attention or concentration). Although rest can restore a normal level of functioning in the healthy person, this restorative capacity is diminished in patients with cancer. Patients receiving radiation therapy report a usual pattern of fatigue that gradually rises by the third week of treatment and gradually declines after therapy ends. Some patients experience less fatigue on weekends, when radiation is not delivered.

The National Comprehensive Cancer Network (NCCN) practice guidelines for cancer-related fatigue (7) use a treatment algorithm of regular patient evaluation and a brief screening instrument. Basic cancer-related information is given after initial screening. A more focused evaluation is done when the patient has moderate or higher levels of fatigue. Patients are evaluated based on five factors known to be associated with fatigue: pain, emotional distress, sleep disturbance, anemia, and hypothyroidism. The presence of any of these factors requires treatment with patient reevaluation. If none of the factors is present or if the fatigue is unresolved, a more comprehensive assessment is recommended, including a thorough review of systems, review of medications, assessment of comorbidity, nutritional and metabolic evaluation, and assessment of activity level.

Specific causes of fatigue such as infection, fluid and electrolyte imbalances, or cardiac dysfunction are treated accordingly. Nonpharmacologic and pharmacologic treatment of the fatigue is considered when specific causes are not identified. Nonpharmacologic interventions may include a moderate exercise program to improve functional capacity and activity tolerance, restorative therapies to decrease cognitive alterations and improve mood state, and nutritional and sleep interventions for patients with disturbances in eating or sleeping. Pharmacologic therapy may include drugs such as antidepressants for depression or psychostimulants that have been reported to improve fatigue but are still investigational (7).

Patients may also experience problems with physical functioning, sleep, and attention. Effective management of cancer-related fatigue involves an informed and supportive oncology care team that assesses patients' fatigue levels regularly and systematically and incorporates education and counseling regarding strategies for coping with fatigue (7).

Psychosocial and Family Support

Radiation treatments require daily visits over a 4- to 5-week period that may require adjustment in work, family, and social patterns. Patients may need assistance in helping to reorganize work schedules to accommodate daily treatment. Strategies include scheduling radiation treatment at either the beginning or end of the workday, shortening the workday schedule when possible, or even taking a temporary leave of absence from work during radiation. Because of the daily imposition of the radiation treatment schedule, other patients may need assistance with home management and child care. Older patients or those with mobility problems may additionally require assistance in traveling to and from daily treatment.

PATIENT CARE MANAGEMENT DURING SYSTEMIC THERAPY

Education

Breast cancer treatment has become increasing complex. With a better understanding of the biology of breast cancer and the various types that have been identified (i.e., triple negative), new treatment strategies have been implemented. New drugs, new combinations, and the order in which the various treatment modalities are delivered is continuously being studied and implemented.

With these advances comes increased responsibility for the nurse in management of the patient with breast cancer. At a minimum the nurse should be familiar with treatment goals, the various drugs used in treatment (including the protocol), and potential side effects of the various drugs. This knowledge can help the nurse provide relevant patient education and appropriate nursing management.

Patients can receive therapies in the adjuvant, neoadjuvant, or metastatic setting, so goals may vary from cure, control or palliation. The therapies used in breast cancer treatment can also vary in side effects and toxicity, so education should be tailored to the patient and their individual response to treatment. The section will discuss a few selected symptom management strategies for breast cancer patient's being treated with endocrine therapy, chemotherapy and targeted therapy.

Endocrine Therapy

Tamoxifen and aromatase inhibitors (AIs) have similar side effect profiles with both classes of endocrine therapy showing similar effects on quality of life. Side effects include hot flashes and sexual dysfunction, such as vaginal dryness and dyspareunia, and sexual dysfunction. Increased bone turnover, reduced bone density, and increase in fractures are reported with AIs particularly among older women (22). Long-term adherence to endocrine therapy remains a challenge (23).

Chemotherapy

Symptom Management during Chemotherapy

The most common physical symptoms experienced are bone marrow suppression, nausea and vomiting, hair loss, fatigue, weight gain, mucositis, neurotoxicity, and menopausal symptoms. Managing vascular access devices (VADs) and decreasing risk of extravasation are also important aspects of clinical care.

Bone Marrow Suppression: Neutropenia is a dose-limiting toxicity of chemotherapy. The nadir is predictable and occurs about 10 to 14 days after treatment, with recovery occurring about 3 to 4 weeks later. Signs and symptoms of infection include fever, pain and tenderness, change in elimination of urine and stool, lethargy, myalgia, and malaise. Observed signs of infection are generally absent in moderate to severe neutropenia because of the lack of circulating neutrophils.

Ongoing and early assessment, identification, and patient education about the signs and symptoms of infection, hand washing, and meticulous personal hygiene are essential components in preventing and reducing neutropenia-related infections (7). The NCCN Myeloid Growth Factors Guidelines examined therapeutic efficacy and clinical benefit (7). The practice guidelines include risk assessment, prophylaxis of high-risk patients, and judicious use of myeloid growth factors.

Chemotherapy-Induced Nausea and Vomiting (CINV): With the widespread use of serotonin antagonists, nausea and vomiting are manageable side effects of chemotherapy. Chemotherapy-induced nausea and vomiting are categorized as acute (during treatment), delayed (more than 24 hours after therapy), and anticipatory (a classic conditioned response as a result of inadequate antiemetic therapy). The risks of nausea and vomiting are related to the type and dose of chemotherapy used and individual patient factors such as female gender, younger age, previous chemotherapy, and history of motion sickness. The emetogenic potential of chemotherapeutic agents is classified from high to low. Typical chemotherapeutic agents used to treat breast cancer, such as cisplatin, cyclophosphamide, doxorubicin, and methotrexate, have either moderate to high emetogenic potential. Although several antiemetic regimens are available, they must be individualized for each patient. Inadequate control of nausea and vomiting during treatment can lead to anticipatory nausea and vomiting, which is more difficult to manage.

Guidelines suggest that serotonin antagonists be used either alone or in combination with corticosteroids (7). These agents are highly selective for 5-HT_3 receptors and are best used with highly emetogenic chemotherapeutic regimens. The serotonin antagonists do not have the extrapyramidal reactions more commonly associated with dopamine antagonists. Other classes of antiemetics include dopamine antagonists (i.e., metoclopramide, phenothiazines, and butyrophenones), neurokinin 1 antagonist, corticosteroids, benzodiazepines, and cannabinoids.

Metoclopramide and dexamethasone have improved efficacy compared with the serotonin antagonists with delayed nausea and vomiting. Benzodiazepines have some efficacy in anticipatory nausea and vomiting.

Mucositis: Mucositis is a general term that refers to an inflammation of the mucosa (24). Agents that are considered highly stomatotoxic are the antimetabolites, anthracyclines, plant alkaloids, and taxanes. Patient factors that are considered to confer a higher risk of developing mucositis include older age, alcohol and tobacco use, poor oral hygiene, poor nutritional status, use of ill-fitting dentures, and compromised renal function (24–25).

Consistent use of an oral care regimen offers the best protection against mucositis. Pretreatment strategies to prevent and decrease the incidence of oral complications include a baseline oral assessment, treatment of preexisting dental disease, and patient education (25). Effective oral care protocols include a combination of a cleansing method, use of lubricants, measures to relieve pain and inflammation, and measures to prevent or treat infection (25).

Neurotoxicity—Acute Pain Syndrome: Patients receiving agents such as 5-fluorouracil, the taxanes, or eribulin mesylate are at risk of neurotoxic complications (26). Peripheral neuropathies present with loss of sensation that begins at the fingertips and spreads to the wrist and starts from the toes and spreads to the ankles. With additional therapy, progressive muscle pain, weakness, motor changes, and hypersensitivity to heat and intolerance to cold can occur (26).

Neurotoxicity associated with these agents includes numbness and paresthesias in the hands and feet that can worsen over time with treatment. Treatment of neurotoxicity has included changes in dose and timing (26). Smith et al. reported on the development and testing of the Neuropathic Pain Scale to assist practitioners in assessing neuropathy in clinical practice (27).

Arthralgia and Myalgia: Arthralgias and myalgias can occur in patients receiving taxanes (28). Symptoms are dose related, may be associated with mild discomfort, or more

severe discomfort and pain with higher doses. Effects occur 48 to 72 hours after infusion and can persist for up to 7 days. Effects occur primarily in large joints, but they can involve the whole body. Pharmacologic interventions, such as nonsteroidal analgesics or narcotics, are usually required. Nonpharmacologic interventions include warm baths, relaxation techniques, and massage therapy.

Alopecia: Alopecia includes body hair loss (e.g., eyelashes and eyebrows, axillary, and pubic hair). The literature continues to demonstrate that hair loss remains one of the most distressing side effects of chemotherapy (29). Although a mastectomy scar is devastating, hair loss can be publicly stigmatizing. Hair loss is often viewed as an assault to one's physical appearance, body image, self-esteem, and sexuality. Although patients may cognitively prepare for hair loss, the actual occurrence is most often a difficult emotional experience.

Different chemotherapy agents have the differential ability to induce hair loss based on their route of administration, dosing schedules, and peak blood levels. For example, doxorubicin is most commonly linked to alopecia. Patterns of doxorubicin-associated hair loss generally occur 2 to 3 weeks after initial treatment, with continued hair loss occurring over time. Conversely, taxane-associated hair loss often occurs dramatically and suddenly. Methotrexate and fluorouracil are associated with minimal hair loss. Oral cyclophosphamide is related to hair thinning, particularly at the crown.

Patient teaching should stress and reassure that hair loss is temporary. Useful interventions for hair loss and tips before hair loss occurs includes: cutting hair in a manageable and easy to maintain style before chemotherapy, using a mild protein-based shampoo and conditioner, using an electric hair dryer on the lowest setting, avoiding electric curling irons or curlers, and dye that can increase the fragility of hair, avoiding excessive brushing and hair combing, and purchasing a wig to fit one's normal hair color and style. After hair loss occurs, suggestions include: protect the exposed scalp from excessive temperature changes; use emollient or lotion regularly to moisturize the scalp, reduce scalp itching with an oatmeal-based colloidal soap, and scarves and turbans as an alternative to wigs.

Behavioral Symptoms: Behavioral symptoms during adjuvant chemotherapy and after treatment include changes in energy, sleep, mood, depressive symptoms, and cognition (30). Behavioral symptoms are related to a serious disruption in quality of life and can persist for many years after treatment. Treatment and cancer survivorship plans include information about the range of anticipated time that behavioral sequelae occur. Behavioral symptom management strategies include psychoeducational support, and cognitive-behavioral strategies.

Chemotherapy Administration Management

Evidence-based guidelines for the administration of chemotherapy have been issued jointly by the American Society of Clinical Oncology (ASCO) and the Oncology Nursing Society (ONS), and a separate statement by the Infusion Nurses Society (31). The most recent 2012 ASCO/ONS guidelines contain information about standards related to staffing, chemotherapy practice, chart documentation, chemotherapy orders, drug preparation, patient consent and education, chemotherapy administration, monitoring and assessment (31).

Preventing Extravasation

Extravasation is a serious complication, causing pain, swelling, erythema, paresthesias, and ulceration of tissue. Factors influencing the degree of extravasation include the type of vesicant, the dose, and the concentration (32). Chemotherapeutic agents are classified as either vesicants (drugs causing tissue damage if extravasated), irritants (drugs that cause redness and inflammatory reaction at the injection site without necrosis or ulceration), or nonirritants (33). The anthracyclines are the chemotherapeutic agents used in breast cancer that are classified as vesicants (32). Because vesicants cause extensive tissue damage, major efforts are made to prevent that complication. When extravasation occurs, antidotes differ depending on the chemotherapeutic agent (32–33).

Vesicants used in breast cancer include doxorubicin, epirubicin, and mitomycin; irritants include fluorouracil, mitoxantrone, and etoposide. Irritants are more readily metabolized, removed from the injection site, and excreted compared with vesicants. Assessment parameters to differentiate extravasation from irritation or flare reaction include pain, redness, ulceration, swelling, and blood return. Key strategies to prevent extravasation include: ensuring patency of the vein or central line, avoid infusing vesicants over joints, bony prominences, or antecubital fossa, avoid giving a vesicant in an area where lymphatic or venous circulation is poor (33). An extravasation kit and extravasation policy and procedures should be readily available in any area where chemotherapy is administered.

Hypersensitivity Reactions

Hypersensitivity reactions are rare, yet can occur within a few seconds after the start of taxane infusion. Hypersensitivity reactions range from a rash, erythema, flushing, or dyspnea to severe cardiopulmonary reactions (34). Since most hypersensitivity reactions occur within the first 10 minutes of paclitaxel infusion, the reaction is most likely caused by Cremophor EL which is associated with histamine release and hypotension. Premedication regimens of oral steroids, diphenhydramine, and cimetidine have decreased the incidence of hypersensitivity reactions.

Symptom Management of Targeted Therapies

Targeted therapies have a different side effect profile compared with chemotherapy. Trastuzumab, the first EGFR targeted drug indicated for the treatment of *HER2* overexpressing breast cancer can cause heart damage and must be used cautiously in patients receiving anthracyclines (35). Cardiac status is monitored regularly with MUGA or ECHO scans. Lapatinib is a small-molecule TKI indicated in advanced breast cancer setting. The drug is taken orally and can cause side effects such as diarrhea, acneiform skin reactions, and pain in hands and feet (36). Patients on herbal products such as St. John's wort should discontinue use while on lapatinib. Patients must contact their oncologist immediately with symptoms of dehydration. They are also restricted from eating grapefruit or grapefruit juice while on lapatinib.

Psychosocial Support during Chemotherapy and Targeted Therapy

Psychosocial response during chemotherapy varies. Patients need encouragement to pace their activities, to incorporate their treatment into their daily family and work routines, and most of all, to be encouraged to ask for and receive assistance. Many patients appreciate the support they receive from others who have been there or who are going through similar experiences. Others take comfort in their family and interpersonal relationships. Breast cancer patients also use electronic support through chat rooms and blogs (37). Most patients prefer to maintain a normal lifestyle during chemotherapy. They may continue to work

as long as they desire, but may request a treatment schedule that permits recovery from side effects on days off from work. Other patients may request that their chemotherapy treatment be given on weekends or evenings.

PATIENT CARE MANAGEMENT IN METASTATIC BREAST CANCER

Metastatic disease can present at initial diagnosis or can develop after adjuvant treatment of breast cancer. Despite screening efforts, women unfortunately can present with metastatic breast cancer (MBC). Although treatment for breast cancer has advanced over the years with many new therapies, metastasis can occur at any point following initial treatment. Patients may have a local recurrence to their chest wall or a distant recurrence in the bone, liver, lungs, or brain. When there is potential for disease recurrence, a biopsy must confirm the diagnosis (7). Treatment focus in MBC is to control the disease and any symptoms that the patient may be experiencing. Nurses can routinely assess about bone pain, neurologic changes, shortness of breath, and obtain patients weight to monitor for possible progression or recurrence of disease (38). Lab values can also indicate site-specific metastatic disease and should include liver function studies, alkaline phosphatase, and calcium.

Some of the same treatment options in the adjuvant setting are appropriate in the metastatic setting including endocrine therapy, targeted therapies, and chemotherapies. Treatment decisions are based on several factors including prior therapy, tumor type (e.g., triple negative or estrogen positive) performance status, toxicities, quality of life, patient preferences and patients' ability to adhere to a specific regimen. No matter what the therapy, treatment goals are to extend survival and improve overall quality of life. Patient management will depend on the therapy and be similar to management in the adjuvant setting, with a stronger focus on supportive care measures.

Bisphosphonate therapy is considered for patients with bone metastasis. Nurses' should monitor renal function, if indicated, each time the medication is administered, noting any signs of renal insufficiency. Calcium levels should be followed to ensure that levels do not drop to low. Hypocalcaemia should be corrected with calcium and vitamin D supplements. Osteonecrosis can occur in patients on bisphosphonates, so nurses should perform a good oral exam before initiation of treatment. Any invasive dental work should be avoided, as healing may be compromised.

Along with the health care team, the nurse should assess the psychosocial aspects of care with the patient, family, and/or significant other. Patients with MBC often experiences feelings of distress, anxiety and depression, fatigue, and even fear (39). These issues often may lead to a poor quality of life and should be discussed with interventions implemented to help alleviate some of their concerns. Referrals may need to be made for a more structured psychosocial evaluation. Education should be provided regarding the illness and symptoms they may experience, which may reduce their psychological symptoms.

PATIENT CARE MANAGEMENT IN LONG-TERM SURVIVORSHIP AND SURVEILLANCE

The end of primary treatment is associated with a decline in acute physical side effects (e.g., nausea and vomiting, hair loss, and bone marrow suppression) and a corresponding increase in physical late effects such as (e.g., infertility, menopausal symptoms, fatigue), and less frequent long-term effects (e.g., second cancers, lymphedema, osteoporosis) associated with a return to some semblance of order and routine. Breast cancer survivors describe psychosocial adjustment to living beyond breast cancer survivor. Periods of adjustment that include some level of psychosocial distress are common.

The Institute of Medicine recommended the use of survivorship care plans summarizing the type of cancer treatment, suggestions for management of late effects, cancer surveillance, and health maintenance (40). Yet, more than 5 years after the recommendations were released data indicate that less than half of oncology providers recently reported that they have implemented the guidelines (41). However, major breast cancer advocacy organizations such as Living beyond Breast Cancer, Komen Foundation, and others contain a wealth of practical information for management of late effects and offer webinars for updates.

Health promotion includes smoking cessation, nutrition, and physical activity. The American Cancer Society recently issued an update of its recommendations on nutrition and physical activity for cancer survivors (42). General recommendations for nutrition and physical activity are to maintain a healthy weight, be as lean as possible without being underweight, avoid excess weight gain, maintain regular physical activity, and limit alcohol intake. The American Cancer Society issued smoking cessation guidelines practical advice and the information is available at http://www.cancer.org/acs/groups/cid/documents/webcontent/002971-pdf.pdf.

Return to Work

Work issues can be major hurdles in adjustment after breast cancer (43). Breast cancer survivors may desire to continue working or may seek new work or professional employment after treatment ends. Worry about health insurance and benefits poses a high-priority concern. Several cancer advocacy organizations, particularly the National Coalition for Cancer Survivorship, have excellent pamphlets and books that discuss the insurance, employment, legal, and financial matters of high concern to cancer survivors that are well worth the cost of having copies in one's organization patient lending library.

SUMMARY

In summary, the human dimension of living through and beyond the breast cancer experience is more than management of acute physical side effects. It is the careful attention to *persons* with breast cancer, their unique personality, preference, choices, decisions, experiences, and insight that give meaning, shape, and form to the illness and disease. On a day-to-day basis, oncology nurses are a vital component to the oncology team by helping coordinate patient care, manage symptoms and psychosocial distress, manage the daily patient ebb and flow, evaluate quality-of-life outcomes, and add the critical dimension of caring to oncology care.

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CHAPTER 88

Overview of Survivorship Issues

Ann H. Partridge and Larissa Nekhlyudov

CHAPTER CONTENTS

OVERVIEW

Cancer survivorship has been defined as the period of time from diagnosis through the balance of a person's life (1). However, most care and research in this area has focused on the post-early treatment phase, and broadly encompasses not only the physical, but the psychosocial and economic sequelae of the diagnosis and treatment of cancer for individuals, their families, and society. The vast majority of people diagnosed with breast cancer will become survivors in the short term and most also in the long term. Breast cancer survivors are the largest group of cancer survivors in the United States, comprising nearly a quarter of the recently reported 13 million cancer survivors; the number is expected to grow over the next decade (2). It is not surprising, therefore, that much of the survivorship research to date has focused on this population of women, resulting in a large and growing literature in this area. Yet, there remain significant limitations in our understanding of cancer survivorship care. This chapter presents the components of survivorship care for patients with a history of breast cancer, highlights evidence-based recommendations, and acknowledges areas of uncertainty.

The general goals of follow-up care for patients with breast cancer are to: (i) detect recurrence or new primary disease and reduce the risk of future breast cancer events including encouraging adherence to surveillance and chronic adjuvant therapy; (ii) monitor, prevent, and/or treat long-term, late effects related to diagnosis or treatment, including medical and psychosocial risks; (iii) provide breast cancer-related decision-making support (e.g., regarding duration of hormonal therapy, future fertility, or optimal contraception); (iv) educate and support patients to continue or adopt optimal health behaviors that may improve outcomes; and (v) assure that patients seek appropriate and timely non-cancer related care, such as management and prevention of comorbid medical conditions (see Fig. 88-1).

DETECTION OF DISEASE AND RISK REDUCTION

Breast cancer survivors are at risk for locoregional or distant disease recurrence, as well as new primary breast cancer in remaining breast tissue or the contralateral breast. The risk of locoregional or distant recurrence for an individual patient is dependent on a number of disease, treatment and patient characteristics. (See Chapter 28, Clinical and Pathologic Prognostic and Predictive Factors.) In follow-up care, providers should promote and facilitate the continuation of chronic treatment (e.g., adjuvant endocrine therapy) and/or other strategies such as surveillance mammography that have been proven to lead to reduced rates of recurrence and breast-cancer mortality. For the average breast cancer survivor, the risk of developing a second primary tumor in the contralateral breast is low, approximately 0.5% to 1% per year for the first five years (3). Even though this is higher risk than for the general population, because of competing risks and the lack of clear evidence that contralateral mastectomy improves outcomes, removal of the contralateral breast is not routinely recommended. Women with genetic mutations, for example, *BRCA1* or *2* mutation carriers are at dramatically increased risk of contralateral breast cancer; thus, screening for genetic risk is warranted where personal or family history suggests a potential mutation. In women who harbor a mutation or who have history suggestive of such, consideration of prophylactic efforts to reduce cancer risk in this high-risk population is standard. (see Chapter 17, Genetic Testing and Management of Patients with Hereditary Breast Cancer).

In order to detect recurrence or new primary disease, evidence-based guidelines recommend regular history and physical exam as well as mammography in follow-up but no additional screening for recurrence in the absence of prompting signs or symptoms (4). There is some controversy about the role of MRI in screening remaining breast tissue in survivors, particularly for women who are very young and/or have dense breast tissue. At the present time, while women who are at very high risk of developing new primary breast cancer (e.g., *BRCA1* or *2* mutation carriers) are recommended to undergo additional breast surveillance with MRI, while this is not recommended for women at average risk (5). Given research to date suggesting lack of benefit, no additional imaging or laboratory testing (i.e., tumor markers) are recommended (see Chapter 67, Surveillance of Patients Following Primary Therapy).

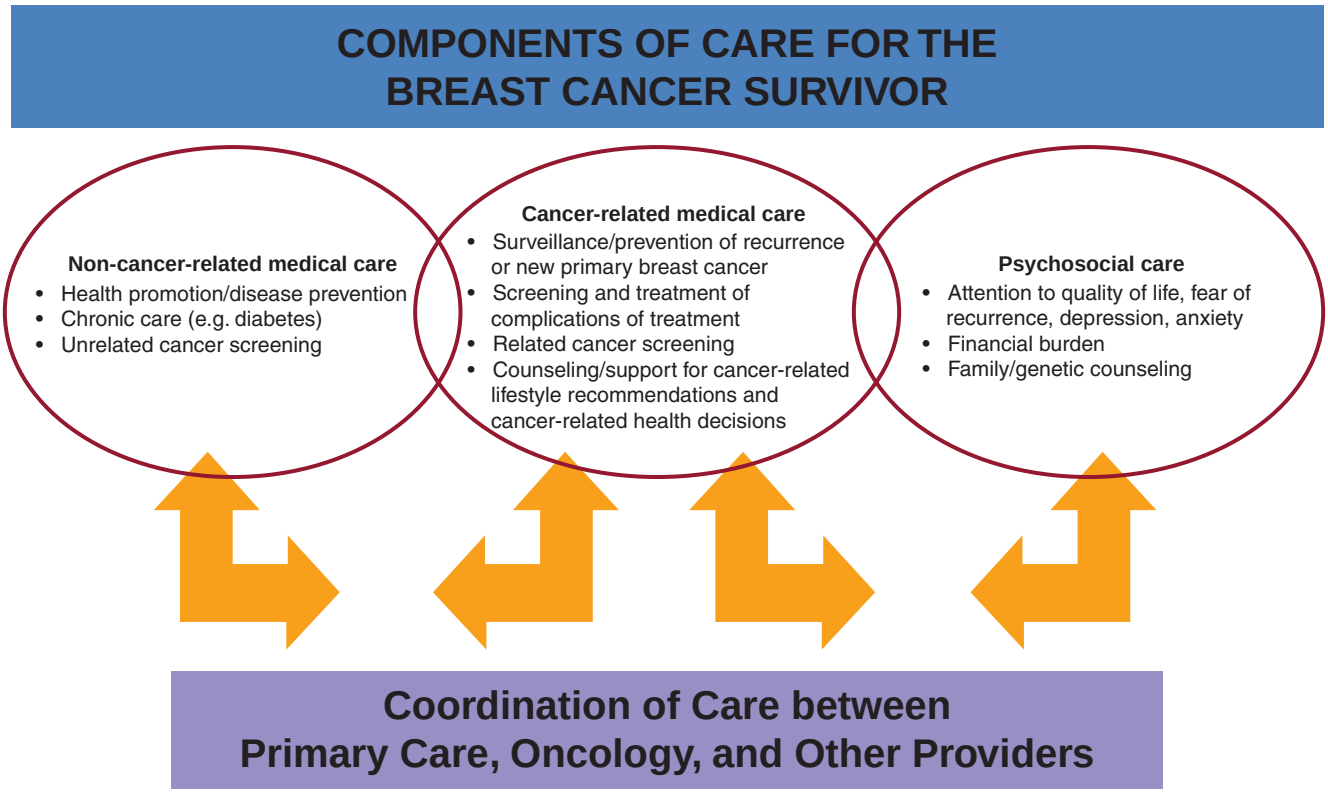

FIGURE 88-1 Components of care for the breast cancer survivor.

MANAGEMENT AND PREVENTION OF LONG-TERM, LATE EFFECTS

Breast cancer survivors may face a number of long-term and late effects from treatment. Long-term effects are problems that become apparent during treatment and persist (e.g., taxane-related neuropathy), while late effects are those that manifest after treatment has ended (e.g., osteoporosis due to premature menopause from chemotherapy or treatment-related leukemia). Figure 88-2 presents common long-term/late effects from breast cancer treatments as they relate to local therapy with surgery and radiation, and systemic therapy, including chemotherapy, biologic therapy, and hormonal therapy. Most patients receive multimodality treatment and clear attribution of problems can be difficult for some symptoms such as fatigue. Further, problems may be pre-existing and may be exacerbated by the diagnosis and treatment of breast cancer (e.g., obesity, diabetes, hyperlipidemia, arthritis). Regular screening for long-term/late effects in survivors as part of a standard history and physical, and prevention and palliation where appropriate is warranted to improve symptoms, quality of life, and potentially future risks and outcomes (see Chapter 49, Implications of Obesity in Breast Cancer; Chapter 51, Management of Menopausal Symptoms in Breast Cancer Survivors; Chapter 52, Long Term and Late Effects of Primary Curative Intent Therapy: Neurocognitive, Cardiac, and Secondary Malignancies).

Psychosocial distress, including depression, anxiety, and fear of recurrences, sexual dysfunction, financial, work and family stressors, and overall impairment of quality of life (QOL) may be one of the most insidious of the long-term, late effects on breast cancer survivors (see Chapter 89, Psychosocial Adaptation during and after Breast Cancer). In the year following a diagnosis of breast cancer, many women will experience difficulties, particularly as they transition to survivorship (1,6). And while there are substantial improvements in psychosocial morbidity over time, some women will experience long-term impairment, particularly those who have received prior chemotherapy (7). Given the evidence for benefits from psychosocial interventions, oncology and primary care providers should be attentive to these concerns in breast cancer survivors and provide support and refer patients to resources or specialists for additional counsel as needed.

BREAST CANCER RELATED DECISION SUPPORT

Patients with a history of breast cancer may face a number of issues in follow-up that are not related to breast cancer per se, but may have consequences for breast cancer risks. For example, young survivors who are interested in future fertility and pregnancy will desire oncology input regarding feasibility, risks, and timing both at diagnosis and in follow-up (see Chapter 90, Reproductive Issues in Breast Cancer Survivors). A history of breast cancer may also affect the risk-benefit ratio of various treatments for problems associated with menopause, in particular including menopausal symptoms, dysfunctional uterine bleeding, or diseases such as osteoporosis. It is incumbent on oncology providers to counsel survivors and coordinate with other specialists regarding these issues.

OPTIMIZING HEALTH BEHAVIORS

Lifestyle factors including diet, alcohol consumption, weight and weight gain, physical activity, as well as smoking have all been found to be associated with the risk of developing

LONG-TERM AND LATE PHYSICAL EFFECTS IN BREAST CANCER SURVIVORS

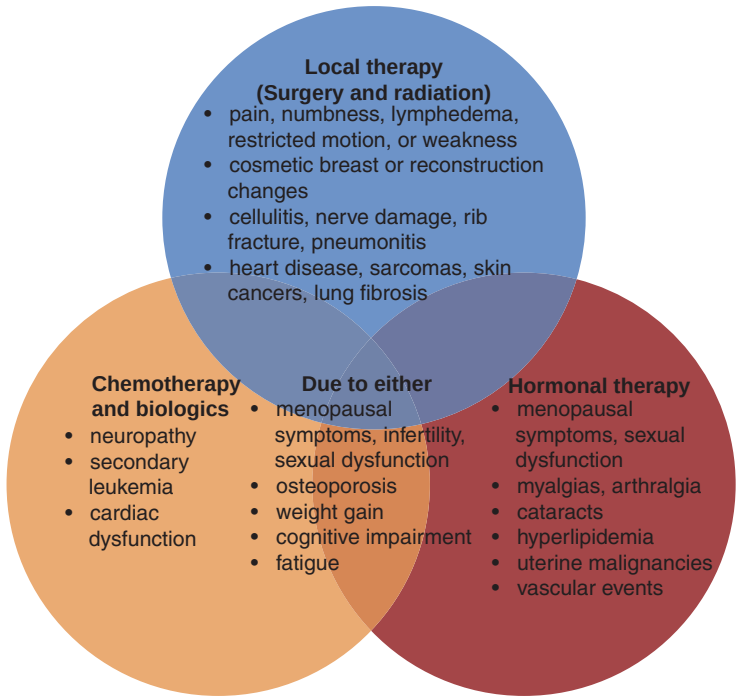

FIGURE 88-2 Long-term and late effects of breast cancer treatment.

breast cancer and increasingly, to prognosis after a diagnosis (8). Further, suboptimal health behaviors may have important consequences for the medical and psychosocial health of survivors (see Chapter 50, Life Style Issues in Breast Cancer Survivors). Although evidence is limited, an increasing number of intervention studies have revealed that improved health behaviors after a breast cancer diagnosis may promote improved quality of life including less fatigue, and possibly decrease risk of cancer recurrence (8). During the early survivorship period, breast cancer survivors may be particularly amenable to making positive health behavioral changes given the anxiety and stress associated with a diagnosis and desire on the part of the patient to improve their likelihood of a good outcome. However, providers should be aware that women may continue to pursue only limited activity, due to persistent symptoms and weight gain and should encourage incremental changes. Counseling survivors regarding optimal energy balance and the potential reduction of risks of recurrence, morbidity and/or mortality, and recommending exercise and weight management or reduction, as well as alcohol reduction and smoking cessation if appropriate, may capitalize on the "teachable moment" and help them to make lifestyle changes (9).

COORDINATION OF CARE AND NON-CANCER CARE MANAGEMENT

Breast cancer survivors are at risk for substantial morbidity, decreased survival, and impaired quality of life from both the cancer and from cancer treatment. Thus, attention to their unique issues in follow-up care is clearly warranted. However, previous research has revealed that there may be substantial gaps in the follow-up care of breast cancer survivors both for cancer and non-cancer-related health concerns (10). Breast cancer survivors are at increased risk of obesity and its related sequelae, such as hyperlipidemia and diabetes. Given the association between diabetes and poorer outcomes in women with a history of breast cancer, it is particularly important that survivors are counseled, monitored, and treated for metabolic syndrome-associated problems (11). Women with osteoporosis or those who may be at risk of developing osteoporosis due to chemotherapy and/or adjuvant aromatase inhibitors also need to be monitored for bone health and treated as necessary. As breast cancer survivors may be cared for by primary care providers in addition to the oncology clinician, it is important that optimal communication and coordination occurs. Various models of care, often encouraging the provision of treatment summaries and survivorship care plans have been promoted as methods to facilitate communication among providers across care transitions and improve access to, and receipt of, quality survivorship care (1). However, research supporting the feasibility of implementing these practices and their effectiveness in enhancing health outcomes is limited with one recent trial showing no beneficial effect of survivorship care plans on outcomes (12). Ultimately, the optimal approach for addressing the comprehensive health needs of the growing population of cancer survivors may be risk-based care as it involves a personalized, tailored systematic plan of periodic screening, surveillance, and prevention relevant to the cancer experience for a given individual (13).

MANAGEMENT SUMMARY

- Standard follow-up for women with a history of early stage breast cancer should include routine history and physical exam and elicitation of symptoms and mammography for remaining breast tissue.
- Attention to long-term and late physical and psychosocial effects of breast cancer is warranted to palliate symptoms and potentially prevent future problems.
- Education and counseling patients regarding optimal health behaviors and lifestyle modifications should be a standard part of breast cancer survivorship care.
- Breast cancer survivorship care requires good communication and coordination of care with primary and other subspecialty providers to assure recommended cancer surveillance and monitoring as well as optimal non-cancer related care.

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CHAPTER 89

Psychosocial Adaptation during and after Breast Cancer

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CHAPTER CONTENTS

INTRODUCTION

Breast cancer is the most common form of cancer among American women, with advances in detection and treatment leading to increases in disease-free survival. However, unlike treatment for other chronic diseases, many treatments for cancer are toxic and intensive, adversely affecting patients' physical, psychological, and social resources, both short and long term.

Because of improvements in screening technology that allow the diagnosis of breast cancer at earlier stages; new developments in treatment approaches; the greater use of preoperative systemic therapy, and increased awareness about potential late effects of chemotherapy and radiation, more women are confronted with a variety of treatment choices, emphasizing her role in the decision-making process and the critical role of patient-doctor and family communication in breast cancer care. The identification of genetic markers of breast cancer risk and the evaluation of chemopreventive agents adds to the psychological toll on unaffected women who are at increased risk for this disease. With the publication in 2008 of the Institute of Medicine's report, *Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs*, a new standard has been set for oncology practice, one that acknowledges that the patient herselfis as important as, and at times more important than, the tumor in planning and delivering optimal care (1).

Although breast cancer is a major stressor for any woman, there is great variability in women's psychological responses. This chapter outlines the range of women's psychosocial responses to breast cancer and factors that may increase a woman's risk for poor adaptation. In addition, the role of family supports in adaptation, and concerns related to sexual functioning and posttreatment survivorship are addressed.

Although very little research has been done in male, compared to female, breast cancer, male breast cancer survivors have been found to have long-term deficits in physical and mental health status, compared to noncancer controls (2). There may be similarities in the challenges men and women face in coping with their cancers, however, there is a clear difference in that compared to women, men likely experience their cancer within the context of lower social awareness and higher social isolation. Male breast cancer is reviewed more fully in Chapter 61.

FACTORS THAT AFFECT PSYCHOLOGICAL IMPACT

A patient's psychological response to her disease is affected by her surrounding sociocultural environment, her underlying psychological characteristics, and medical factors (Table 89-1). Comprehensive care requires individualized attention to, and assessment of, each of these areas, as needed, throughout the illness trajectory.

Sociocultural Context and Psychosocial Issues in Decision-Making

The national visibility afforded to cancer has resulted in increasing attention to the patient's role in medical decision-making. As a result, women today have more information about, understanding of, and resources to manage their breast cancer illness and recovery than ever before. Although increasing patient awareness and understanding continues to be the goal, it is important to note that some women may feel they have "too much" responsibility in treatment decisions, up to 21% in one study (3), which was associated with poor baseline knowledge and 6-month decision regret. Thus, the need for physicians to tailor their communication and information-sharing with patients, especially those with low health literacy, is significant.

TABLE 89-1

Factors That Contribute to the Psychological Responses of Women to Breast Cancer

1. Current sociocultural context, treatment options, and decision-making
   a. Changes in surgical and medical management from a uniform approach, e.g., breast-conserving management; introduction of sentinel node biopsies and neoadjuvant therapy; more therapeutic options and acknowledged uncertainty
   b. Social attitudes
   c. Public figures openly sharing their breast cancer experience
   d. Autobiographic accounts of and "how to" guides for dealing with and surviving breast cancer in the popular press
   e. Ethical imperative for patient participation in treatment issues; legal imperative for knowledge of treatment options
   f. Variations in care by ethnicity, location, age
   g. Public awareness of treatment and research controversies; advocacy for more funding and lay oversight
2. Psychological and psychosocial factors
   a. Type and degree of disruption in life-cycle tasks caused by breast cancer (e.g., marital, childbearing, work)
   b. Psychological stability and ability to cope with stress
   c. Prior psychiatric history
   d. Availability of psychological and social support (partner, family, friends)
3. Medical factors
   a. Stage of cancer at diagnosis
   b. Treatment(s) received: mastectomy/lumpectomy and radiation (plus/minus immediate/delayed reconstruction), adjuvant chemotherapy, hormonal therapy
   c. Availability of rehabilitation
   d. Psychological (partner, support groups)
   e. Physical (reconstruction; arm mobility and lymphedema prevention)
   f. Psychological support provided by physicians and staff

Over the course of care, women face three major decision-making periods. The first is encountered at the time of initial discovery of a lump or symptom suspicious for breast cancer, at which time a woman must decide if further evaluation is needed. A woman's decision is informed by her access to, and cost of, specialized care; her age, her level of education or knowledge, her attitudes and beliefs about cancer; her personality and coping style; and the nature of the existing doctor-patient relationship (4). Delays in seeking care have been attributed to age (>65 years), a symptom other than a breast lump, not sharing the symptom with others, negative attitudes toward, or a poor relationship with, the healthcare professional, fear of cancer and related treatments, low perception of risk, less spirituality, and a willful ignorance of symptoms (4,5). Independent of health insurance, stage of diagnosis, and age, black and Hispanic patients have been shown to have higher risks of 30-, 60-, and 90-day treatment delay than white patients (6,7). Medicare beneficiaries may be at increased risk for delay in definitive treatment in particular (8). Language barriers, inadequate resources, and inaccurate beliefs may disproportionately affect Latina and African American women (9,10). In at least one study, treatment delays experienced among low-income women led to worse survival outcomes (11). If a delay in early detection has occurred, personal guilt or anger at her physician can interfere with a woman's adaptation to treatment. Reinforcing the value of care she is receiving may be important in her engagement in the recovery process.

The second major set of decisions is set in motion at the time of consultation with a surgeon about local treatment options, which may be followed by multiple consultations with other cancer specialists. Women may choose between mastectomy versus limited resection and irradiation, plus or minus immediate reconstruction. If systemic therapy is indicated, an additional cascade of decisions must be made. Differences in the types of breast cancer treatment received by a woman exist, based on geography, age, socioeconomic status, and race. For example, African American women with less education are at risk for receipt of non-guideline-concordant adjuvant chemotherapy regimens, potentially contributing to worse outcomes (12). Women living in rural areas, particularly those who are older, may be less likely to receive recommended radiation therapy in association with their breast cancer treatment (13). Breast-conserving therapy is more likely to be performed in academic settings, in the Northeast, and among younger women (14).

The time between diagnosis and initiation of treatment is one of the most stressful periods in the breast cancer experience. The emphasis on informed decision-making places a responsibility on the physician to be cognizant of the individual woman's physical and psychological needs and to tailor accordingly the discussion and recommendations made. At times, it may mean addressing a woman's demands for unrealistic treatment, acquiescing to another woman's desire to defer a final decision to her physician or significant other, or in some cases reassuring a woman that she need not reach a decision immediately but can research her options and come to an appropriate choice. During this time, she may opt to seek a second opinion to aid in her decision-making. As desire for information and preference about decision-making roles can change over time, asking about them periodically is important. Treatment information can be provided as printed or videotaped materials, and reputable websites may be recommended to patients and families. For women feeling overwhelmed or pressured to make a surgical decision, it may be helpful to postpone surgery and meet with a member of a psychosocial support team who could facilitate a discussion about underlying concerns and fears.

Psychological Variables in Adaptation

In 1980, Meyerowitz (15) delineated three broad areas of psychosocial impact of breast cancer: (a) psychological discomfort (anxiety, depression, and anger); (b) behavioral changes due to physical discomfort, marital or sexual disruption,

and altered activity level; and (c) fears and concerns related to body image, recurrence, or death. Although women diagnosed today have many more treatment options and resources for support, the psychological concerns remain the same (16). In addition to these variables, the life stage at which the cancer occurs, previous emotional stability (personality and coping style), and presence of interpersonal support also affect adaptation (see Table 89-2).

Age at time of diagnosis is important in considering a breast cancer patient's distress (17,18). Concerns about the threat to life and future health, as well as fears of potential disfigurement, disability, and distress associated with treatment, are common for women of all ages but may be heightened in younger women with breast cancer. In younger patients, beyond disruption to multiple active roles, there is the perception that they have more to lose due to the threat to their future, including the potential loss or delay in having or building a nascent career or family. Worse outcomes in quality of life and depressive symptoms have been shown to be more frequent and severe in breast cancer survivors aged 50 years or younger when compared with the general age-matched population of women without cancer and to older women (aged >50 years) with breast cancer (19). Concerns about premature menopause, menopausal symptoms, and infertility were common in younger women and have a role in the level of posttreatment distress. Additionally, the younger breast cancer patient often presents with more advanced disease and typically is treated more "aggressively" surgically, which further affects psychological adjustment. (See Chapter 85 on Breast Cancer in Younger Women.) Research has not focused as much on women older than 65, despite their representing almost half of current breast cancer survivors (20). Although one may assume an older woman's distress regarding her breast cancer may be buffered by her greater life experience and familiarity with medical settings, she may experience the diagnosis in the presence of other major losses and concurrent chronic medical conditions. Older women with breast cancer experience poorer health-related quality of life and lower psychosocial well-being than unaffected peers (21) and are at risk for significantly higher rates of decline in upper body function (22). This pattern, coupled with the observation that older women are significantly less likely to receive appropriate surgical care or rehabilitation (23,24), suggests that patients at both ends of the age continuum are at increased risk for problems in adaptation. Finally, although threats to body image, sense of femininity, and self-esteem may be greatest in younger women, particularly those who are single or without a partner, these threats are concerns of many older women as well (25). (See Chapter 84 on Breast Cancer in Older Women.)

Personality and coping styles affect adaptation to breast cancer. Women who are flexible and employ active problem-solving approaches have better moods and adaptation (26). Women who are able to draw on and use available social resources and support adapt better and may even live longer than women who do not (27). In contrast, women who are passive, helpless, hopeless, or pessimistic in the face of illness; are rigid in their coping style; and isolate themselves or reject help when it is offered adapt more poorly. Women who manifest persistent depressive symptoms in the face of cancer may be at risk not only for poor quality of life but also premature death (28,29) and should be considered promptly for professional psychological assessment and support. Women with a history of resolved major depression have been found to be at increased risk of developing greater depressive symptoms during treatment, which in turn predicts declines in physical functioning during chemotherapy, compared to those with no history of depression (30), highlighting the importance of identifying such women as early as possible and ensuring that adequate resources are in place for them. The relationship between attitude and cancer risk and/or survival remains an area of public interest and active research. Because breast cancer is so prevalent, is associated with significant negative psychological impact, and has inadequately defined causative factors, the possible role of psychological variables in vulnerability to breast cancer and its progression has been explored in medical studies. It also has received considerable attention from patients and the media. Stewart et al. (31) found that 42.2% of the 378 breast cancer survivors surveyed believed that stress caused cancer and 27.9% felt that stress reduction could prevent a recurrence, confirming work done 20 years earlier. Such beliefs can become an added psychological burden and lead some women to pursue unproven therapies. Although epidemiologic studies have failed to find an association between stress and breast cancer development (32) or survival (33), it is nonetheless important to mitigate chronic stress when it is identified. Education regarding the lack of evidence of stress causing cancer is an important component of integrated oncological care. Other important factors in adaptation are a patient's prior experiences with breast cancer and body image. Levels of psychological distress can be affected by the memory of a friend's or family member's suffering with breast cancer. Some women cannot tolerate the idea of loss or damage to a breast and may delay seeking consultation for a symptom, especially if their community views cancer as stigmatizing.

TABLE 89-2

Risk Factors for Poor Adaptation

1. Medical
   - More advanced disease
   - More intense or aggressive treatment
   - Other/multiple co-morbid medical conditions
   - Fewer rehabilitative options
   - Poor doctor/patient relationship
2. Personal
   - Prior psychiatric history
   - Past trauma history (especially physical or sexual abuse)
   - Rigid or limited coping capacity
   - Helpless/hopeless outlook
   - Low income/education
   - Multiple competing demands (e.g., work, child or other family care, economic)
   - Poor marital/interpersonal relationship
   - Younger age (<40) or older age (>80)
3. Social
   - Lack of social support (and/or religious affiliation)
   - Limited access to service resources
   - Cultural biases
   - Social stigma or illness taboo
4. Breast cancer specific
   - Prior breast cancer experience
     - Recurrence or second breast cancer
     - Loss of family or friends to breast cancer
   - High investment in body image, in particular breasts

Adapted from Weisman D. Early diagnosis of vulnerability in cancer patients. *Am J Med Sci* 1976;271:187.

A woman's sociocultural background can further influence her breast cancer experience. Although the interpretation of between-group differences in ethnicity often is confounded by variables such as income, education, and treatment (34), it is worth noting two historically understudied minority groups: lesbian breast cancer survivors and survivors living in rural communities. (For a full discussion of this topic, see also Chapter 86, Breast Cancer in Minority Women.)

Sexual orientation appears to have little effect on quality of life among breast cancer survivors (35). Some data suggest that lesbian breast cancer survivors may be more comfortable with body image and perceive greater social support than their heterosexual peers. However, they also may tend to experience more difficulty interacting with physicians (36). Survivors in rural areas are at greater risk for relationship problems, lack of support, and feelings of isolation (37). Finally, adjustment depends on the actual and perceived level of support, as well as the patient's ability to rely on that support (e.g., attachment security). For example, women who recalled childhood abuse were more likely to experience their surgeon as unsupportive (38).

Prolonged anxiety or depression is not an expected reaction to a cancer diagnosis (39).The common stress reactions around the time of diagnosis and onset of treatment usually can be evaluated and managed by the patient's physicians, nurses, or social worker. However, some women have greater problems and can benefit from psychological management by psychiatrists and psychologists, who often are collaborating members of the treatment team (Table 89-3).

If a patient's anxiety or insomnia interferes with functioning, low-dose anxiolytic medication (e.g., lorazepam [0.25 to 1.0 mg orally two to four times a day] or clonazepam [0.25 to 1.0 mg orally twice daily]) or a hypnotic (e.g., zolpidem [5 to 10 mg]) usually are effective. When anxiety and insomnia cannot be controlled with these medications or when surgical or medical staff observe symptoms of depression—such as frequent crying episodes, loss of interest and/or motivation, irritability, inability to concentrate, or remarks indicating hopelessness, helplessness, or suicidal thoughts—psychiatric consultation is indicated. Psychiatric consultants assess all of the factors contributing to a woman's distress, including any family or relational issues, combining psychopharmacological interventions with psychosocial support for the patient and family. The selective serotonin reuptake inhibitors (SSRIs; e.g., fluoxetine, paroxetine, sertraline, fluvoxamine, citalopram, escitalopram) and novel or mixed action antidepressants (venlafaxine, duloxetine, bupropion, mirtazapine) are considered first-line treatment because they are better tolerated in patients with comorbid depression and medical conditions. Venlafaxine currently is believed to be the antidepressant that should be prescribed to the depressed woman (or the woman with hot flashes) who is taking tamoxifen, due to its relative lack of impact on tamoxifen metabolism. (See Chapter 51 for information on management of hot flashes.)

TABLE 89-3

Women with Breast Cancer Who Should Be Considered for Psychiatric Evaluation

1. Those who present with current symptoms or a history of the following:
   - Depression or anxiety
   - Suicidal thinking (attempt)
   - Substance or alcohol abuse
   - Confusional state (delirium or encephalopathy)
   - Mood swings, insomnia, or irritability from steroids
2. Those who:
   - Have a family history of breast cancer
   - Are very young, old, pregnant, nursing, single, or alone
   - Are adjusting to multiple losses and managing multiple life stresses
   - Seem paralyzed with cancer treatment decisions
   - Fear death during surgery or are terrified by loss of control under anesthesia
   - Request euthanasia
   - Seem unable to provide informed consent

Medical Variables in Adaptation

The stage of breast cancer at diagnosis, treatment required, prognosis, and available rehabilitative opportunities constitute important medical variables that influence psychological adjustment. However, central to successful adaptation is a woman's relationship to her treating physicians and the degree to which they are sensitive to her individual concerns, communicate clearly, and monitor emotional and physical well-being. The length and intensity of current treatments and the recognition that women treated for breast cancer must be followed for extended periods of time have placed an added burden on healthcare providers. Depending on the setting, nurse clinicians or psychosocial clinicians may provide supportive care. Preliminary guidelines for psychosocial care across the cancer continuum have been developed, albeit for highly resourced comprehensive cancer centers, with adherence to, or adaptation of, these guidelines known to be quite low (40,41). Further, concerns about the cost of providing the recommended psychosocial and supportive care and who should pay for this continue to be significant barriers to optimal service delivery.

Surgery

Mastectomy Mastectomy is now performed in fewer than half of women diagnosed with early-stage breast cancer. Of late, however, there has been an increase in the number of women selecting ipsilateral mastectomy with contralateral prophylactic mastectomy (CPM), in part due to the greater use of pre-operative magnetic resonance imaging (MRI) (42,43). Further, for women who do undergo mastectomy, more will undergo breast reconstruction than previously, although data suggest that many mastectomy patients are not made aware of their reconstruction options. Considerable research exists on the impact of loss of one or both breasts on women's physical, social, and emotional functioning. Among the effects documented are feelings of mutilation and altered body image, diminished self-worth, loss of a sense of femininity, decreases in sexual attractiveness and function, anxiety, depression, hopelessness, guilt, shame, and fear of recurrence, abandonment, and death. Historic data indicate that women who are well adjusted before they have a mastectomy and whose disease is in an early stage can expect at 1 year to have a quality of life equal to that of unaffected peers. Today, a woman's persistent issues generally have less to do with the type of surgery received and more to do with her personal and social characteristics and the adjuvant therapy given. Issues related to the latter are discussed in the treatment-specific chapters and in the section Breast Cancer Survivors, later in this chapter.

Research suggests that, in addition to a number of medical factors (e.g., tumor size, location, and aggressiveness), several other characteristics may distinguish women who have mastectomy from those who receive breast-sparing surgery. These include older age, fear of irradiation, preferring to have no therapy beyond surgery, being black or Hispanic (or possibly low income), and among older women, living with extended or nonfamily members or in an assisted-living setting (10).

Contralateral Prophylactic Mastectomy Rates of CPM have increased dramatically in the past two decades, mostly in patients without any identified risk factors, such as genetic predisposition (*BRCA1/2* mutation) or a prior history of radiation (44). Independent predictors of CPM in a large retrospective analysis at a leading cancer center in the United States included white race, immediate reconstruction, family history of breast cancer, MRI at diagnosis, age younger than 50 years, noninvasive histology, and prior attempt at breast conservation (44).

Similar to all treatment decisions, the patient contemplating a CPM should be fully informed regarding her individual risk and given adequate time and information to make the decision, including the option to use a patient decision tool. An individualized approach includes incorporating a patient's personal values regarding risk aversion and anticipated regret into the ultimate treatment decision (45). A Cochrane review has found that there is insufficient evidence that CPM improves survival (46). However, those who chose bilateral prophylactic mastectomy (BPM) had lower levels of anxiety after BPM, compared to their baseline worry and to those who chose surveillance (46).

Breast-Conserving Therapy or BCT (Lumpectomy and Irradiation) A significant factor in what type of surgery is performed is the nature of the care that is available, including the availability of high-quality irradiation therapy. Further, restricted access to plastic surgeons can limit the availability of reconstructive options. Another factor determining choice is the knowledge and availability of genetic testing for mutations in *BRCA1* and *2*; patients with mutations now generally undergo bilateral mastectomy. Cultural and ethnic values also may direct or even dictate choice, although their role is poorly understood. Physician recommendation continues to exert the most significant influence on treatment choice for most women. Early reports suggested that women in BCT groups manifest a somewhat better overall adjustment than those in mastectomy groups (47). However, longer-term follow-up of more current cohorts of breast cancer survivors has failed to show differences in overall quality of life based on type of surgery alone (48). A consistent finding is that psychosocial variables are, for the most part, much stronger predictors of psychosocial outcomes than are medical factors (49). These latter studies further suggest that benefits to sexual function associated with BCT may be less than previously believed. Because BCT often is selected because it is perceived as less disfiguring than mastectomy, it is problematic when the surgical results do not meet expectations. A significant confound to examining the impact of surgery on women's quality-of-life outcomes is that younger women, known to be at increased risk for psychosocial problems in adapting to breast cancer, tend to elect to undergo BCT. These young patients also are more likely to receive adjuvant chemotherapy, which has a significant negative impact on sexual functioning. What we have learned is that BCT is not a psychosocial panacea; rather, it is a surgical and cosmetic option that may facilitate adaptation for many women. Two critical factors that continue to influence the surgical decision-making process are attitudes about cancer and irradiation. The thought of leaving tumor cells in the breast is intolerable for some women, who feel more secure with mastectomy. Other women fear irradiation or are unable to devote 6 weeks to daily irradiation treatments. Women undergoing irradiation are at risk for psychological distress, either related to treatment-associated fatigue, or persistent fears about their disease and the risk of recurrence. Providing a reassuring environment, orientation to expected side effects, and strong support promotes optimal adaptation. Most women who undergo radiation therapy experience initial anxiety related to the treatment, which diminishes after a few treatments, only to return toward the conclusion of therapy because of fear of tumor re-growth without treatment, and the loss of close medical surveillance. To ease this transition, patients should be made aware of the paradoxical increase in feelings of distress. Staff should remain available by telephone and through follow-up appointments.

When discussing women's reactions to irradiation, one additional factor that is important to consider is the risk for upper extremity lymphedema. Women who develop lymphedema are at high risk for problems in both psychological and social functioning (50). Fortunately, the proportion of women affected by this problem has decreased with the use of sentinel node biopsy. (See Chapters 40 and 42 for more details regarding lymphedema and radiation, respectively.)

Reconstruction Postmastectomy breast reconstruction is an important rehabilitative option pursued by a significant subset of women undergoing mastectomy. However, there is some evidence that reconstruction is not being routinely addressed in the surgical decision-making process. In their SEER-based sample, Alderman and colleagues found that only a third of patients reported that their general surgeon discussed this option with them during the decision-making process (51). Younger, more educated women with larger tumors were more likely to report that this discussion took place. Further, patients whose surgeon did cover this option were four times more likely to have a mastectomy. Relatively few studies have systematically examined the psychosocial impact of mastectomy alone compared with mastectomy plus reconstruction. Contemporary studies seek to evaluate psychosocial and sexual outcomes for women selecting each of the three different surgical options (lumpectomy vs. mastectomy alone vs. mastectomy with reconstruction). Parker and colleagues describe similar subtle differences in early adaptation among women undergoing each of the three different procedures, but note that few differences could be seen among groups 2 years after treatment (48). In general, aspects of quality of life other than body image are not better in women who have undergone BCT or mastectomy with reconstruction. In what remains the largest three-way comparison study, investigators found no differences in women's emotional, social, or role functions by type of surgery (52). Consistent with others' findings, women in the mastectomy with reconstruction group were most likely to report that breast cancer had a negative impact on their sex lives (45.4% vs. 41.3% for mastectomy alone, and 29.8% for lumpectomy). An important factor in women's sexual outcomes is that mastectomy with or without reconstruction results in permanent loss of sensation in the area. Further, as discussed in Chapter 42, the use of postmastectomy radiation therapy generally decreases the cosmetic results with reconstruction, particularly with implants. At the same time, the use of immediate breast reconstruction can compromise effective and safe delivery of postmastectomy radiation therapy.

Research suggests there are sociodemographic differences between women who do and do not undergo postmastectomy reconstruction. Women undergoing mastectomy with reconstruction generally are younger, better educated, have higher incomes, are more likely to be partnered, and have an earlier stage of disease (52,53). Women who are older, Hispanic, or born outside of the United States appear less likely to have reconstruction (54). Fewer African American women undergo reconstruction; this often may be due to economic and access barriers, but also potentially is related to lower interest in having reconstruction (55). Asian women also are less likely than white women to undergo reconstruction. There is some data to suggest that among sexual minority women (self-identified as lesbian or bisexual), there may be more decisional regrets among those who choose reconstruction versus mastectomy alone, leading to more adjustment problems (56). Regrettably, few efforts have been made to understand the psychological variables associated with who does and does not seek reconstruction, in particular in the present era in which autologous tissue procedures and immediate reconstruction represent standard options for care. Further, additional research is needed on the impact on women's satisfaction and functioning related to the extent of surgery performed and procedures used to achieve good symmetry.

In addition to local treatment choice (e.g., BCT vs. mastectomy with or without reconstruction), the impact on psychosocial function of the timing and type of reconstruction performed has been examined.

Timing of Reconstruction: Immediate versus Delayed Research with women undergoing immediate reconstruction has shown high levels of patient satisfaction with surgical results and less psychosocial morbidity than in those who undergo mastectomy alone, although as noted in earlier discussions, these differences diminish over time (57). Patients undergoing immediate reconstruction report being less depressed and anxious and experience less impairment of their sense of femininity, self-esteem, and sexual attractiveness than their peers who delay or do not seek reconstruction, but these initial differences in adjustment may be minimal and disappear over time. At least one study has suggested that satisfaction with technical aspects of the reconstructive outcome may be slightly lower among women undergoing immediate versus delayed reconstruction (59). This may reflect the fact that women with immediate reconstruction compare the result with their original breast, whereas those undergoing delayed surgery use the mastectomy site as their basis for comparison.

Type of Reconstruction: Implant versus Transverse Rectus Abdominus Myocutaneous Flap (TRAM) The research evaluating psychosocial outcomes for women undergoing reconstruction using TRAM surgery also has been an area of interest. No differences were seen between groups undergoing implant versus TRAM surgery in satisfaction with the appearance or feel of their breasts or the overall impact of breast cancer on their sex lives, although there was a consistent tendency for the women with TRAM reconstructions to report greater comfort and satisfaction (59). This pattern is consistent with others' findings and the observation that timing of reconstruction may be more influential than type of procedure on women's long-term adaptation (57). However, women who had an implant were significantly more worried about having a problem with their reconstruction (59). Longer-term follow-up of cosmetic outcomes for implant recipients would appear to confirm these fears. Clough et al. (60) report that overall cosmetic outcome was rated as acceptable in 86% at 2 years but had declined to 54% by 5 years in their study sample. Further, 23% of the 334 women in their study underwent implant exchange (excluding those with expanders). A similar pattern was not observed among TRAM reconstructions, in which assessment of cosmetic outcome remained stable over time (60).

Regardless of the type of reconstructive surgery proposed or selected, women need to be well informed about what to expect, including the cost of the surgery, length of time under anesthesia, number of procedures required, cosmetic results achievable, and safety of the techniques used. This may be accomplished through providing patients written materials, including images of reconstructed breasts, as well as referring them to a previously reconstructed patient for more details. Wider availability of video and online tools for decision-making is beginning to provide a unique way to educate women about choices that allows them to tailor the information they receive.

Adjuvant Chemotherapy

A recent systematic review has shown that, of the three breast cancer treatments (surgery, radiation, or chemotherapy), chemotherapy-treated patients have the highest level of anxiety, reaching its peak just before the first infusion, mediated by age and trait anxiety (61). Anticipation of chemotherapy can be difficult, highlighting the importance of patient education by the medical team. Women fear the transient acute sequelae of chemotherapy (e.g., nausea and hair loss). With greater public awareness, fear of chemotherapy's persistent effects (e.g., fatigue, pain, memory problems, sexual dysfunction, sleep disturbance, depression) also can cause major concern (62). Clinical experience suggests that most women cope with the short-term adverse psychological effects by focusing on delayed benefits (e.g., reassurance that they have done everything possible to eradicate their disease). However, clinicians need to be aware that, for some women, declines in health-related quality of life during treatment increase risk for discontinuation of chemotherapy (63). Monitoring for problems and addressing them promptly are important in ensuring adherence to the planned course of care.

Nausea and vomiting, once common side effects of adjuvant chemotherapy and feared and dreaded by patients, now are well controlled with pharmacologic and behavioral interventions (64,65). However, other side effects such as hair loss, weight gain, poor concentration, premature menopause, and fatigue affect psychological adjustment and warrant special attention and early discussions with patients. Information about wigs, the cost of which often is covered by insurers, along with referral to the American Cancer Society's *Look Good…Feel Better* program can help reduce appearance-related distress.

The cause of weight gain with chemotherapy remains unclear. Because of the added insult to self-esteem posed by significant weight gain, as well as data suggesting that obesity leads to worse prognosis (66), greater attention is being paid to diet and exercise. The introduction of exercise programs during chemotherapy is feasible, well tolerated (67), and of benefit in controlling weight gain, improving functional and cardiac status, and potentially enhancing quality of life. (See Chapter 50 for a broader discussion of lifestyle interventions.)

Difficulty with attention, concentration, memory, and processing speed also is reported by many women undergoing chemotherapy. These troubling neurocognitive effects, which also may be chemotherapy-dose related, are the focus of active research (see also Chapter 53 on side effects of systemic therapy). The symptoms may be associated with

the stress of illness, antiemetic drugs, hormonal changes secondary to chemotherapy-induced menopause, and principally with treatment-induced alterations in neurochemical and brain function (68). In some women, this effect may be mediated by a genetic predisposition (69). Important in this literature is the finding that women's complaints about cognitive compromise are not consistently associated with neuropsychological test performance (68). Understanding the true impact of therapy on cognition is challenging as we lack good measures for its role in women's day-to-day functioning. Nevertheless, if cognitive dysfunction is found to persist over time or as some studies suggest worsen this troubling side effect may become a dose-limiting factor in treatment decisions and care (70).

A further troublesome effect of chemotherapy in premenopausal women is premature menopause. (See Chapter 51 Management of Menopausal Symptoms in Breast Cancer Survivors.) The threatened or actual loss of fertility and acute onset of menopause anticipated with adjuvant chemotherapy often cause distress in the woman who is premenopausal at diagnosis. Iatrogenic acute estrogen deficiency may, in a small number of patients, be associated with psychiatric syndromes, depression in particular (71). The hot flashes, night sweats, and vaginal dryness and atrophy caused by chemotherapy-induced menopause can produce severe physical discomfort, including dyspareunia. Although instruction on the use of vaginal lubricants can be helpful, thinning of the vaginal mucosa still may result in irritation on intercourse. Though controversial, use of topical vaginal estrogen may be recommended for women experiencing severe dyspareunia. Studies indicate that the levels of circulating estrogens observed with this intervention are not expected to alter breast cancer recurrence patterns (72).

Hot flashes are among the most common acute and long-term side effects of breast cancer treatment. This symptom is seen secondary to chemotherapy-induced premature menopause, secondary to exposure to tamoxifen or raloxifene, or consequent to cessation of hormone replacement therapy (HRT) following diagnosis. Hot flashes can be profoundly debilitating for some women. Cognitive behavioral therapy (CBT), physical exercise (PE), and these two interventions combined have a beneficial effect on menopausal symptoms and physical functioning, with CBT specifically reducing both the frequency and perceived burden of hot flashes and night sweats (73). The challenge with the CBT group was adherence to the program due to the time commitment required, emphasizing the need for thoughtful, individualized planning with each potential participant. Clonidine, venlafaxine, paroxetine, fluoxetine, mirtazapine, and gabapentin are nonhormonal agents that have demonstrated efficacy in small controlled and uncontrolled trials in reducing hot flashes and should be considered in patients unwilling or unable to take hormonal therapies (74). Some evidence suggests there may be greater patient preference for venlafaxine over gabapentin, although both have similar efficacy (74,75). However, there is an accumulating body of evidence that several SSRI antidepressant drugs, especially fluoxetine and paroxetine, might interfere with tamoxifen metabolism by inhibiting the CYP2D6 enzyme. Venlafaxine minimally affects CYP2D6 activity and, therefore, is the first-line treatment for the tamoxifen-treated depressed patient who is experiencing hot flashes (76). Soy-based phytoestrogens, on the other hand, appear to provide little relief of hot flashes compared to placebo (77). A further effect of chemotherapy is loss of libido, which likely is associated with a reduction in circulating androgens. For many women, loss of desire is the most difficult sequela to treat.

A final troubling side effect of systemic therapy is fatigue. Increased use of multidrug adjuvant therapies that are both more dose-dense and more intense is leading to more women complaining of prolonged fatigue (78). Some studies with duration of follow-up measured in years following treatment completion have found that 15% to 20% of patients may experience fatigue as a chronic effect of treatment (79,80), whereas others have found a near resolution in fatigue levels as soon as 12 months after treatment completion (81). Noted clinically, the prevalence, etiology, and treatment of post-treatment fatigue continue to be areas needing further research. Introduction of molecularly targeted agents, alone or in combination with chemotherapy (e.g., Herceptin), also will increase the need for longitudinal outcome data among treated women, especially given early reports of troubling side effects even with these supposedly less toxic therapies (82). Although overall level of functioning and quality of life among long-term disease-free breast cancer survivors remains high many years after primary therapy, past systemic adjuvant treatment was associated with persistent poorer performance in physical activity and function, pain, and general health (83,84). These findings should be taken into account when counseling women about treatment choice, particularly when disease is limited.

As critical as it is to prepare women well for the commencement of treatment, it is equally important to anticipate and plan for emotional reactions to ending treatment, when fears of recurrence peak. In this regard, women who go on to adjuvant hormonal therapies may gain a sense of relief knowing that they still are doing something active to prevent recurrence. Other factors also contribute to anxiety (see Table 89-4). In recognition of the many persistent effects of modern breast cancer treatment, some clinicians routinely advise women anticipating the end of treatment to allot as many months for their recovery as were spent being treated for their cancer. Two booklets that form part of the National Cancer Institute's *Facing Forward* series, *Life After Cancer Treatment*, and *When Someone You Love Has Completed Cancer Treatment*, provide useful information for the woman and her family about what to expect after initial therapy ends.

Adjuvant Hormonal Therapy

Recommendations regarding the optimal duration of treatment with tamoxifen are unclear, with recent studies suggesting up to10 years may be optimal (85). Although these potential survival and recurrence benefits bring great hope to patients, they also warrant a deeper discussion with the patient regarding the long-term psychological and sexual

TABLE 89-4

Challenges Related to Ending Treatment

1. Fear that the cancer will return
2. Concern about ongoing monitoring (e.g., whom to call if a problem/symptom arises)
3. Loss of a supportive environment (including relationships with staff and fellow patients)
4. Diminished sense of well-being due to treatment effects (often feeling less well than when treatment was initiated)
5. Social demands: "re-entry" problems (dealing with expectations of family and friends that the breast cancer patient will quickly be back to "normal" and resume full function equivalent to pre-illness levels)

impact of this therapy. Once used mostly with postmenopausal patients, tamoxifen now is routinely given to premenopausal women with hormone receptor-positive breast cancer as part of their adjuvant therapy. Thus, when tamoxifen is recommended to a young childless woman who had hoped to regain fertility after 5 years of treatment, she may now have to face the possibility of never having her own biological children.

Some older women find that the associated increase in hot flashes with tamoxifen (or an AI) is a limiting factor in its use. By contrast, some younger patients report that tamoxifen provides relief from the vaginal dryness and decreased libido that accompany chemotherapy-induced premature menopause. Problems with tamoxifen-related hot flashes are more common among women who have a history of moderate to severe hot flashes with menopause and a history of estrogen therapy use. It is important to note that a small subset of women become depressed with use of tamoxifen, which can require temporary or even permanent discontinuation of its use (86). The impact of tamoxifen exposure on brain function also has come under examination (87,88). Rates of discontinuation or nonpersistence of use of tamoxifen, whether due to problems with drug side effects or some other reason, may be higher than believed, ranging from 31% to 73% in a recent systematic review (89). (See Chapter 44 for a discussion of appropriate monitoring for these potential complications.)

Relatively less is known about the psychological and sexual impact of the newer class of hormonal agents, the AIs (90,91). These agents have been associated with troubling joint and muscle pain symptoms. One report found that as many as 10% of women had discontinued AI use because of these side effects (92). The impact of these newer therapies on women's sense of well-being as well as adherence patterns among breast cancer survivors with respect to long-term adjuvant hormonal use are areas warranting future research.

RECURRENT AND ADVANCED DISEASE

With more women living longer after treatment for breast cancer, the numbers of those treated subsequently for recurrent local and distant disease have grown. Despite the physical burden of recurrence, during the year after diagnosis women show steady improvement in psychological functioning, reflecting the adaptive capacity of survivors (93). The distress associated with recurrence can come in many forms and affect multiple quality-of-life domains. Compared with disease-free survivors, women with recurrent breast cancer report poorer physical functioning and perceived health, more impairment in emotional well-being, more problems in relationships with family and healthcare providers, and less hope. Even when disease is localized, significant levels of psychiatric morbidity may occur (93). Women with recurrent disease, whether local or distant, are a particularly vulnerable group for whom active psychosocial intervention is warranted. Family members of these women also experience high levels of emotional distress and may require support.

Supportive care for patients with advanced breast cancer is aimed at comfort and control of symptoms. Different metastatic sites, especially bone, lungs, and brain, present special supportive problems. As discussed in the Interventions section later, participation in support groups may improve quality of survival significantly in this group of women, although the effect of such groups on length of survival appears limited (94).

Advanced care often is provided at home with support from the family or in a hospice setting (see Chapter 73). Central to the success of a home care program is continuity of care with physicians and staff and continued support of family and friends. Psychiatric consultation should be considered when distress (anxiety and depression) is not responsive to the usual supportive measures. Depression and expression of desire for hastened death may present in these settings (95). A management approach that combines psychological support with use of antidepressants and anxiolytics often is helpful. Agitated behavior associated with metabolic encephalopathy, resulting often from hypercalcemia, brain metastases, or narcotic or steroid side effects, may require use of an antipsychotic medication.

Because pain is such a common and feared experience of people living with advanced stages of disease, attention to its management is critical to care. Patients with cancer who experience pain are more likely to exhibit higher levels of mood disturbance and functional disability than those who have little or no pain. Spiegel and Bloom (96) found that for women with metastatic breast cancer, beliefs about the meaning of the pain in relation to the illness predicted level of pain better than site of metastasis. Attitudinal barriers to compliance with medical treatment, including stoicism and fear of narcotic addiction, are common. Thus, addressing the meaning and response to pain from the perspective of the patient is as important as providing an explanation of proposed control techniques.

INTERVENTIONS

The use and variety of psychosocial and behavioral interventions applied in the cancer setting in general and in breast cancer care in particular continue to grow (97). Cancer is one of several chronic illnesses that precipitate the need for, and use of, mental health services (98). Young age at diagnosis, being a younger survivor (younger than 65 years), being formerly married, and having a chronic comorbid illness all are associated with increased use of mental health services in the context of cancer, although as many as one in six survivors may fail to receive mental health services because of cost (100).

Though varying greatly by type (e.g., individual vs. group), orientation (e.g., behavioral vs. cognitive vs. supportive), mode of delivery (in person vs. remote), duration (time limited vs. open ended), and timing (e.g., before, during, or after treatment), as well as target populations served (early vs. advanced, younger than 40 years vs. older, partnered vs. single, or mixed), the fundamental purpose of interventions developed is to provide each woman with the skills or resources necessary to cope with her illness and improve the quality of her life and health. The various types of psychosocial and behavioral interventions used in the cancer setting and their efficacy in improving targeted outcomes are well reviewed elsewhere (99,100). The vast majority of these interventions have been developed specifically for patients with breast cancer or have included patients with breast cancer. A detailed review of the use of different interventions in the care of patients with breast cancer is beyond the scope of this chapter. However, three points must be made regarding the use of such programs in the overall care of patients with breast cancer and their families.

First, researchers have found that patients who received an intervention designed to improve knowledge or coping or reduce distress did better than those who did not. Specifically, those receiving some form of individual or group intervention experienced less anxiety and depression,

had an increased sense of control, had improved body image and better sexual function, reported greater satisfaction with care, and exhibited improved medication adherence (100,101). Significant attention needs to be paid to the development and delivery of psychosocial care models if we are to understand who needs what, delivered by whom, and when in the course of care (102). Further, understanding the economic impact of these programs or services in terms of delivery, changes in healthcare utilization, and out-of-pocket expenses may be critical if we are to expect their broader uptake into routine practice.

Second, use of psychosocial interventions continues to grow, especially in the setting of breast cancer. Use of these services reflects not only patient demand for supportive care, but also growing recognition that addressing psychosocial issues may improve outcomes for patients. At one point, it was hoped that such interventions would result in life extension. The current consensus is that psychosocial interventions do not prolong survival (103,104), but help women "live better," although there are provocative data to suggest that women in the highest medical and psychological risk groups may realize a survival benefit (105). Social well-being in the first year after diagnosis has been found to be a prognostic factor in recurrence and mortality (106,107), although interventions to improve social well-being have not led to improved survival (27). Decreasing depressive symptoms through supportive expressive group therapy over the first year has been shown to be associated with prolonged survival (53.6 months vs. 25.1 months) (108). In breast cancer, because so many women do well or live for longer periods even with more advanced disease, the incremental benefit to survival conferred by receipt of these interventions may be harder to detect.

Provocative, but admittedly preliminary, research in the area of psychoneuroimmunology and cancer suggested that psychological variables (e.g., perceived stress, mood) might modify disease outcomes (109). However, efforts to design interventions to address this interface have produced mixed results. Despite the growing number of trials reported, meta-analyses provide only modest evidence that psychosocial or behavioral interventions reliably alter immune parameters (110). Because of their key role in breast cancer, better understanding of the impact of psychosocial interventions on endocrine functioning and disease outcomes warrants further pursuit.

Third, although it might be argued that an individually tailored intervention should result in the best outcome for any given patient; this may not be feasible, suitable, or even desirable in all cases. Increasing evidence shows that participation in group activity offers a uniquely supportive and normalizing experience, with a small number of older studies finding that groups were as effective as individual sessions in reducing patient distress. Use of communication technologies, including the Internet, teleconferencing, and telephone (111), may be used to provide group support and represent the new frontier in intervention research. These technologies address issues of isolation and allow for anonymity. In addition to providing medical information, the Internet may offer a unique vehicle to improve access to information and social support and reduce isolation (112–114).

Research suggests that four key elements are vital to achieving optimal outcomes for all cancer survivors: (a) access to state-of-the-art cancer care; (b) active coping, in particular active participation or engagement in one's care, even if this means delegating decision-making; (c) use of social support (although it is recognized that the perception that this is available may be sufficient) (115); and (d) having a sense of meaning or purpose in life. Many of the psychosocial and behavioral interventions developed in cancer are designed to foster or reinforce some or all of these core needs. However, access to these remains a problem. Clinician awareness about, and referral of, patients to even such well-established programs as the American Cancer Society's Reach to Recovery is variable (116). Key to the development of an effective intervention is the recognition that, for many women, cancer represents a transitional event. As defined by Andrykowski et al. (117), cancer is "a traumatic event that alters an individual's assumptive world with the potential to produce long-lasting changes of both a positive as well as negative nature." As such, the primary goal in any intervention is to help minimize the negative and enhance the positive impact of the breast cancer experience on the woman's recovery and well-being.

SPECIAL ISSUES

In the remaining sections, the special issues related to the care of other family members, the role of sexual quality of life in rehabilitation, and the well-being of long-term breast cancer survivors are reviewed.

Role and Care of the Family

The quality and quantity of individuals' social connections is linked not only to mental health status, but also to both morbidity and mortality (118). Not surprisingly, social support has been found to be integral not only to positive adjustment, but also to length of survival (119,120) in women with breast cancer. When people are ill, they tend to feel less in control and less confident, especially when they must rely on others. At the same time, serious illness of any kind increases the ill person's need for closeness to others to counteract feelings of insecurity and vulnerability. Absence of social support or the loss of a significant person who withdraws during the patient's illness becomes an additional stressor that may be more painful emotionally than the illness itself.

Active family involvement helps to meet the emotional and practical needs of the patient, while providing meaningful roles and related functional goals toward which the patient can strive. Despite the recognized importance of the role of partners and family in caring for women with breast cancer, this subject remains the focus of only a modest number of studies. Further, even less is known about family adaptation long-term, as the majority of studies conducted have examined the acute or early post-treatment period. Once treatment ends, family members must adapt to the interpersonal and financial changes brought on by cancer, deal with their loved one's lingering effects of illness, and learn to live with potential uncertainty about the future. Family caregivers may experience lower quality of life, more fear of cancer recurrence, and less support than their loved one with cancer does (121). In this study, the strongest predictors for survivors' quality of life were family stressors, social support, meaning of the illness, and employment status, whereas the strongest predictors for family caregivers' quality of life were fear of recurrence and social support. Of note, the quality of life of the survivor and caregiver contributed independently to the quality of life of the other person.

Partners' adaptation, similar to patients', varies over time, as do the sources of distress they face. For example, during treatment, concerns may focus on whether the therapy is working and how to cope with the side effects of treatment and manage a household; whereas after treatment fear of recurrence and trying to make sense of the experience may produce distress. Further, there is a significant correlation

between a patient and her partner's patterns of coping, and these couples' levels of distress are higher than those of couples not facing cancer (122). Predictors of partner distress include: high burden of the illness and caregiving demands, more limited resources available, recency of the marriage, older age, less education, lack of or dysfunctional communication style, heightened fear for the wife's well-being, worry about job performance, and the partner's own baseline level of adjustment (122). One study examining cultural differences found that Asian American women (specifically those of Chinese and Japanese descent) were expected to be self-sacrificing and nurturing of husband and family regardless of illness, whereas European American women were allowed to be more dependent (123). Further, Asian American women emphasized a goal of harmony over intimacy—whereas European American women embraced the reverse—and in communication preferred the nonverbal versus the verbal communication style valued by European American women.

When observed or reported, high emotional distress in a partner or family caregiver warrants immediate attention. Left unaddressed, high anxiety in the partner/caregiver can have a negative impact on the breast cancer patient's adaptation over time; impair the ability of the partner/caregiver to provide optimal patient care; and result in changes in a partner's/caregiver's immune system that can result in adverse health consequences (124). Research on interventions to promote coping conducted with dyads or family caregivers documents significant albeit modest benefits. These include reduction in caregiver burden and improvements in caregiver coping, self-efficacy, and quality of life; coupled with decreased patient symptoms, reduced mortality, and improved patient physical and mental health (124–126). Reflected in these reviews is that many of these interventions seek to promote teamwork and mutual support, foster open communication, encourage caregiver self-care, and enhance education about the illness experience. Although more research in this promising adjunct to quality care is needed, interventions currently exist that would benefit "at risk" couples.

An experience of breast cancer may bring couples closer together and typically does not result in partner abandonment. A history of prior marital discord may put a couple at risk, however. Cancer is very "permission giving" to many survivors. The woman who uses this event to examine her satisfaction with a preexisting partnership may, if she finds it lacking or emotionally dissatisfying, decide to make a major life change and exit the relationship. In a similar vein, desire to reduce the stress in her life, felt by many women to be a causal factor in risk for cancer, may precipitate a drive to make major life changes.

It is critical to remember that support is a two-way street; the source of the problem may arise in the provider of support (family member) and/or in the recipient, and commonly involves both. The impact of cancer can be as devastating to a family member as to the patient herself, and sometimes worse. Whereas the woman can obtain support from multiple sources and control her anxiety by focusing on just getting through treatment, partners often receive less attention and report feeling uncertain as to what to do and helpless in their role as observers. It is helpful for staff to acknowledge the difficult task faced by family members, provide opportunities for them to talk about questions and reactions both with the patient and alone, and ensure that backup supports are available and that efforts are made to give family members relief, especially if care is going to be complex or long term. It also is important to permit family members to limit care to those areas in which they are most comfortable and effective.

Once thought to be traumatic for children, current literature suggests that the experience of cancer in a parent may be more modest in impact. This may be due to greater public dialogue about cancer, greater openness among families dealing with this crisis, and broader availability of resources to help families cope (127,128). Behavioral problems, conflicts with parents, and other symptoms of emotional distress can increase during parental illness. Increased risk of a child internalizing (which can be reflected by feelings of guilt, worry that he/she caused the cancer, and symptoms of depression) is present. A number of factors may affect a child's response to maternal breast cancer, including disease severity, family function and environment, family and child coping reactions (in particular maternal depression if this occurs), and parent and family characteristics, in particular their communication/expressiveness. Relationships to a child's age and gender were inconsistent across studies, although there was a suggestion that adolescent daughters may be more vulnerable when their mother has breast cancer (129).

The monitoring of all dependent children, especially when the mother's breast cancer is advanced, is important. The opportunity for parents to discuss how and what to tell their children about the mother's illness early in the course of care also is important and should include advice on tailoring these conversations to meet the appropriate developmental needs of their offspring. Specific interventions to help a mother and her children cope with illness may be helpful (130). A number of books addressing this topic and an NCI publication, *When Someone in Your Family Has Cancer,* may be useful in this process. Teachers and school counselors can assist in monitoring the child's behavior and response to this family stressor. This task may be more difficult when the offspring is an adolescent. Finally, concern about what impact breast cancer may have on a mother's survival may be complicated by worry about its meaning for an offspring's future well-being. With the growth of high-risk genetic clinics, attention has focused on the overall psychological adjustment and quality of life of female first-degree relatives of patients, which may impact their adherence to such screening programs, an issue addressed in greater detail in Chapter 17. Whereas the information needs of women treated for breast cancer are well documented, those of their family members bear further study.

Quality of Life and Sexual Functioning

The impact of disease and treatment on women's sexual functioning, once rarely discussed or addressed, has garnered significant research attention in recent years. Interest in this important topic is both a function of compelling advocacy by women for greater attention to these issues, and consequent to the large number of women for whom treatment causes significant problems in this valued area of function.

The literature documents a range of changes in women's sexual function after breast cancer, including disruptions in normative sexual processes (e.g., sexual desire, arousal, lubrication, and orgasm), and diminished sexual activity and pleasure. Most of these effects are secondary to exposure to adjuvant chemotherapy and hormonal therapy, with adverse consequences of surgery conferring a more limited impact (e.g., changes in body image, interference with function due to lymphedema or persistent postoperative pain syndromes) (131). AIs, increasingly used in the management of postmenopausal breast cancer survivors, are associated with increased vaginal and vulvar symptoms. In those for whom these side effects are severe, a switch to tamoxifen

may be preferred over adding local or systemic estrogens to the AI regimen (132). In addition to exposure to adjuvant therapies, risk factors for problems in sexual function include poor partner communication, sexual function problems in the partner, depression in either partner, or younger age. Compared to their older counterparts, younger women have distinct concerns about chemotherapy-induced premature menopause and loss of fertility that contribute to their distress; they also report more problems with weight gain and physical inactivity that, in turn, can negatively affect their sense of femininity and attractiveness (133). Because of strong cultural taboos around discussion of women's health issues, young African American women in particular may fail to receive desired education and counseling around the sexual impact of cancer on their well-being (134).

Overall, sexuality declines after initial diagnosis. When breast cancer recurs, although most couples strive to maintain intimacy, further decline may be noted (135). In metastatic breast cancer patients and their partners, sexual problems have been found to be associated with increased depressive symptoms (136). Furthermore, high levels of mutual constructive communication and low levels of demand-withdraw communication may protect against depressive symptoms associated with sexual problems in patients but not in their partners, emphasizing the need for future interventions that target communication patterns in couples.

The range of psychological reactions to cancer that threaten sexual function include threats to (a) sexual identity and self-esteem, such as disturbances of mood, gender, and sexual identity and body image; (b) personal control over body functions, such as disease-related symptoms that interfere with or inhibit sexual functioning; (c) intimacy, such as loss of social contacts that have potential for intimate physical expression, the disintegration of established patterns of achieving physical pleasure and intimacy, or myths related to contagion; and (d) reproductive function, such as the direct impairment of fertility or the fear of recurrence with pregnancy. In addition to these psychological reactions, some women experience less joy and vigor, as well as an underlying uncertainty about their health and the vulnerability of their bodies to further assault. The emotional distress, pain, fatigue, and insult to the patient's body image and self-esteem caused by the diagnosis and treatment of breast cancer can damage sexual functioning, even among individuals who had a strong and satisfying sexual relationship before illness. Despite heightened sensitivity to sexual issues, in practice, provision of effective sexual interventions remains highly variable. Further, research to guide the delivery and evaluate the impact of care in this area is limited.

A central challenge to addressing sexual dysfunction when it occurs is avoidance of this sensitive topic by both provider and patient. In addition to the discomfort most people feel when discussing sex, practitioners must contend with limited time, and at times, privacy to raise these issues, lack of awareness that sexual problems are being encountered, or when present, knowledge about local resources to address them. Currently, this last barrier is dissipating as education about effective therapies for problems such as vaginal dryness, hot flashes, painful intercourse, and lack of desire becomes more broadly acknowledged and available.

Whereas breast cancer survivors appear to attain maximum recovery from the physical and emotional trauma by 1 year after surgery, a number of specific problems persist beyond 1 year, in particular those amenable to sexual rehabilitation (e.g., body image, lubrication, orgasm). A multimodal approach to women's sexual rehabilitation is recommended. This includes use of pharmacologic, nonpharmacologic, and psychosocial interventions as appropriate (137,138). Special training in sex therapy techniques is not a prerequisite for discussing sexual dysfunction; only information about and willingness to refer women for help with these issues is needed. For women still in their childbearing years, there are now American Society of Clinical Oncology (ASCO) guidelines about asking and for referring these individuals for fertility preservation options and counseling (139). (See Chapter 90 Reproductive Issues in Breast Cancer Survivors for a discussion of management of fertility and breast cancer.) Because sexual problems tend to worsen, not improve, over time, sexual rehabilitation needs to start early. Ideally, this should occur before treatment starts for those patients for whom specific impairment of sexual function can be anticipated (e.g., premature menopause in the premenopausal or perimenopausal woman). Raising the topic of sexual function early, by letting the patient know it is an appropriate focus of concern and that the healthcare provider is willing to discuss it, opens the door for future dialogue in this area, and normalizes their distress. It also is important to respect a woman's privacy, and as such, it may be helpful to identify a single staff member to initiate such conversations, often the primary nurse. When specific questions arise, the nurse needs to know what the patient has been told and by whom in order to focus questions for patients, direct their inquiries to the appropriate staff member, clarify or reinforce information provided, and serve as an advocate for the patient. Above all, this designated member should know about resources for help in this area and, as needed, coordinate input with that of others.

BREAST CANCER SURVIVORS

With their numbers expected to grow in years to come (140), more attention is being focused on cancer survivors and the experience of living through and beyond their illness and its treatment (141). Although women vary widely in their response to diagnosis and treatment, most return to lives that are as full as, and often richer personally, than before their illness. Although some women reduce work hours or leave jobs following a cancer diagnosis, either by choice or because of disability, by 12 to 18 months postdiagnosis most patients have returned to work (142). Besides being a vital source of income and often of needed healthcare coverage, work also can be an important source of social support and self-esteem as well as distraction from illness during treatment. Those in manual labor jobs (which often includes women with lower education and income) may experience more limitations, but most find that employers are accommodating of their needs (143), suggesting that many of the myths about cancer's adverse impact on survivors' job performance are beginning to be dispelled. Somewhat troubling, however, is the longer term picture. Continued follow-up of breast cancer survivors suggests they may be at risk of later morbidity that reduces their numbers in the workforce relative to women without a cancer history. Morbidity may be due to treatment-related effects (e.g., lymphedema, decreased functional capacity, cognitive problems) or disease recurrence (142). Population-based data suggest that over time, carrying a cancer history puts survivors at greater risk for experiencing problems in their physical (24.5%) and mental (10.1%) health compared with 10.2% and 5.9% of adults without cancer, respectively (144). Given these findings, a growing case is being made for the need to revisit the idea of rehabilitation after cancer (145). As part of this, assessment of work status and counseling

around work-related issues, with referral for help in negotiating workplace issues as needed, are important in aiding women's continued employment as desired.

Striking to many clinical researchers involved in the conduct of long-term follow-up studies is the enormous resilience evidenced by women; post-traumatic growth as a benefit that may occur after facing a life-threatening illness (146). The growing interest in cancer survivorship, as reflected in the number of programs offered by the NCI-designated cancer centers designed specifically to address survivors' needs posttreatment, is testament that survivors' call to action is being heard (http://cancercenters.cancer.gov/documents/Survivorship%20Appendix%20D.pdf). Services provided focus on two main areas: (a) surveillance, and (b) health and well-being after treatment.

Follow-Up Care and Surveillance Posttreatment

Although concern about disease recurrence may diminish over time, for most breast cancer survivors, this never fully goes away. The degree of worry may fluctuate and be triggered by a variety of sources, including continuing physical problems after treatment (see Table 89-5). Fear of recurrence in the survivor can have an adverse effect on family quality of life; the reverse also is true, with family members' fears negatively influencing the quality of life of the survivor. When activated, fear may lead to disruptive behavior such as heightened body monitoring, anxiety well in advance of a doctor visit, and worry about the future; or in some instances severely disabling reactions including hypochondriac-like preoccupation with health at one extreme, or avoidance and denial at the other, inability to plan for the future, and despair. Interventions are being developed to help women cope successfully with uncertainty (147). Although other interventions that effectively reduce distress and improve a sense of well-being might be expected to result in decreased worry about disease recurrence, this remains to be tested.

Part of this persistent anxiety may be attributable to the fact that breast cancer survivors understand that their cancer could recur at any time after treatment and that medical follow-up must continue for life. Data support the appropriateness of this concern. As women live longer after their initial breast cancer diagnosis, they are at higher risk than women with no cancer history of developing a second cancer, most often a second breast cancer (148). In this context, it is important to note that not all women posttreatment for breast cancer consider or think of themselves as "survivors." Although some women embrace this language and are proud of their status, others reject being so labeled. Still others fear that calling themselves survivors before 5 years might invite a recurrence. More important is that each woman treated recognizes the need for follow-up for life. Decision-making around follow-up care itself represents the third major decision point in the breast cancer patient's illness pathway.

TABLE 89-5

Triggers for Fear of Recurrence

1. Routine follow-up visits and tests
2. Anniversary dates (e.g, date of diagnosis, end of cancer treatment, birthday)
3. Worrisome or "suspicious" symptoms
4. Persistent treatment-related side effects (especially fatigue or pain)
5. Change in health (e.g., weight loss, fatigue)
6. Illness in a family member
7. Death of a fellow survivor/prominent cancer survivor
8. Times of stress
9. Idiosyncratic triggers (e.g., "learned responses" such as the smell of alcohol due to association with receipt of chemotherapy; sight of the treatment center)

Although the value of survivors receiving a treatment summary and plan for future care at the end of treatment has been recognized, the type of follow-up care that should be provided to which survivors and at what periodicity is a major topic of debate (see Chapter 67, Surveillance of Patients following Primary Therapy and Chapter 88 on survivorship). Increasingly, it is recognized that women need to be followed for surveillance of recurrent disease as well as adverse long-term or persistent and late-occurring sequelae of treatment, and psychosocial adjustment, although who should be responsible for this latter aspect of care in particular is unclear (149). Ganz and Hahn provide guidance on how to implement comprehensive care plans for breast cancer survivors transitioning to recovery (150). Among the questions for the future will be to determine where this care is best delivered and by whom: in primary care, specialty clinics, or some combination of these. Research also will be needed on the cost, both economic and with respect to women's sense of well-being, of the models developed for follow-up care.

An important take-home message in all of the research discussed in this last section is that a cancer diagnosis represents for many a "teachable moment" for healthcare providers along with breast cancer survivors themselves, a moment currently being missed by many oncology practitioners (151). The crisis of cancer often creates a window of receptivity during which healthcare professionals can provide patients with educational messages about, and support for, pursuing healthy lifestyle choices. Although these activities, if adopted, may not alter length of breast cancer survival, they do carry the potential to significantly reduce individual risk for treatment-related or other chronic illness-related morbidities and potentially other cancers. To take full advantage of this opportunity to intervene, it will be vital to understand what women identify as important for them to address (e.g., weight, diet, stress, exercise, and tobacco/alcohol use), the types of information and resources needed to promote and maintain change in these identified areas, and how to most effectively deliver these interventions. Encouraging breast cancer survivors to take control of what they can in their lives may enable them to live with better health in, and less fear of, the future.

Health Behavior after Cancer

One of the newest topics in breast cancer follow-up care is the role of health promotion (see also Chapter 51). This is being spurred largely by survivors' interest in, and growing requests for, informed guidance about what they can do to reduce their risk of cancer-related morbidity and mortality. Many breast cancer survivors already report taking better care of themselves in the wake of cancer, with particular focus on adopting healthier lifestyles, reducing stress, eating better, and exercising regularly. In our research with long-term (≥5 years after diagnosis) breast cancer survivors, the areas in which the experience of cancer had the most positive impact were diet, exercise activities, and religious beliefs. The greatest negative impact was felt in the domains of love life and, for younger survivors, work life or career and financial situation (84).

Two areas receiving significant research attention with respect to their impact on women's health outcomes are stress management and physical activity interventions. As noted earlier, many women believe that the stress in their lives can precipitate or exacerbate breast disease. For these survivors, reducing stress is seen as potentially lifesaving. Researchers at the University of Miami's Mind Body Center have developed a standardized 10-week training program that equips women with the cognitive and behavioral skills necessary to identify, analyze, and manage stress (152).

A second avenue to stress reduction is staying active during, or becoming physically active after, cancer treatment. There is increasing evidence demonstrating the association of obesity with: (a) greater risk of contralateral breast cancers (153); (b) development of postmenopausal breast cancer (154); (c) poorer prognosis in early stage disease, with increased recurrences, including distant recurrences (155); and (d) poorer response to adjuvant therapy (156), highlighting the importance of addressing weight control and levels of physical activity (energy balance) in the total care of the breast cancer patient. Often begun during treatment, research shows that physical activity can improve mood (reduce anxiety and depression), enhance cardiovascular function, control weight, improve body image and self-esteem, reduce nausea and fatigue, and potentially alter immune function (157). To date, two observational studies (158,159) and one randomized clinical trial (160) have found a survival benefit for women who became or remained moderately physically active after breast cancer treatment.

As the evidence of their benefits for survivors mounts, lifestyle changes are being recommended posttreatment (161). Although U.S. population-based data suggest that survivors may be more active than their peers without a cancer history, both groups remain well below the recommended levels of daily activity; smoking and dietary practices also lag behind recommended patterns (162). Use of complementary and alternative medicine (CAM), reported by many patients during active cancer treatment, also is seen in the posttreatment setting. Studies suggest that CAM use is more common among younger, better educated women with good health insurance. Reports of poorer psychological functioning among patients with cancer using CAM remedies (163) suggest that some women may be self-medicating for depressive symptoms.

Reducing alcohol exposure also is common in this population. A study investigating postdiagnosis alcohol consumption in 9,329 breast cancer patients over a median 10-year follow-up revealed no association with recurrence or all-cause mortality (164). However, regular drinking, defined as more than three drinks per week, was associated with a higher risk of recurrence but not mortality in postmenopausal women (164). Surprisingly, because few survivorship studies inquire about smoking, we have very little information on women's practices in this regard. Data from the National Health Interview Survey (NHIS) indicate that although overall smoking rates are lower in survivors than adults without a cancer history (19.7% vs. 23.8%), many cancer survivors continue to smoke after treatment. Such behavior appears to be of particular concern among younger survivors (19- to 40-year-olds), in whom the rate of smoking posttreatment (40.5%) was significantly higher than estimates for their cancer-free peers (27.1%) (162). Although limited to date, research points to a positive association between current smoking and breast cancer mortality (165). Given this picture and breast cancer survivors' heightened risk for cardiovascular problems, it is important to remember that it is never too late to realize a health benefit by quitting smoking. Those caring for breast cancer survivors should ask about this behavior and intervene as appropriate.

CONCLUSION

Breast cancer has a unique, and at times complex, psychological impact, with variable emotional responses developing in women and ranging in severity and their impact on functioning. Increasing treatment options have empowered women—and for some, overwhelmed them—emphasizing the need for individualized approaches and treatment discussions with all women. Broader dissemination of information from psychological studies of adaptation to the available treatment options can help in efforts to determine the best treatment to meet patients' physical and emotional needs. Addressing the psychosocial and psychosexual needs of patients with breast cancer improves quality of survival and may even enhance length of survival from other, comorbid conditions and events, even if not from cancer. As newer therapies are introduced, research on their immediate and delayed psychosocial impacts is needed. Finally, with the increasing demand for their involvement in care, special attention must be directed to the psychological well-being of the immediate relatives of women with breast cancer, especially their partners and offspring.

In closing, clinicians should be reminded that their relationship with a given patient remains paramount above all of the considerations outlined previously. A physician's communication style, behavior, attitudes, and beliefs can dramatically affect a woman's experience. Toward this end, it is important for the healthcare professional to view him- or herself as part of the treatment. By acquiring and honing the communication skills necessary to engage a patient in her own care, while being respectful and observant of her needs, clinicians can increase the opportunity to minimize psychological trauma, enhance treatment adherence, and obtain the best possible outcome for each woman treated.

MANAGEMENT SUMMARY

- Although most women diagnosed and treated for breast cancer do well psychologically and socially, one fourth of women with breast cancer have psychological symptoms that warrant psychiatric intervention.
- Clues to identifying women with psychological distress include previous treatment for depression or anxiety, symptoms of depression and anxiety that seem out of the "normal" range, and psychological symptoms that worsen over time.
- Diagnosis and treatment of breast cancer causes psychological distress for all women; recovery from physical and emotional symptoms usually occurs gradually during the 12 months after the completion of cancer treatment. Patients should be told that asking for psychological help is a sign of strength, not weakness.
- Psychological and social support services should be offered to all women (the availability of support services varies depending on the location and type of practice).
- Brief, easily scored distress screening tools could be used periodically across the course of care to help identify women who are most in need of psychological treatment.

- Psychological support comes in many forms and is delivered by many professionals. Available psychosocial support members should be encouraged to become active participants in a multidisciplinary team.
- Symptoms of anxiety and insomnia during the diagnostic, pretreatment, and treatment phases often can be rapidly and effectively treated with low-dose anxiolytics and hypnotics.
- Symptoms of depression should be evaluated by a psychiatrist or a psychologist; safe and effective antidepressants are available for women who are being or have been treated for breast cancer.
- Women who are receiving dexamethasone should be informed that it can cause psychological symptoms (anxiety, depression, mood swings); women should be asked to report these symptoms if they occur because they can be treated rapidly and effectively.
- Family members' responses to a woman's illness are important to her adaptation. These should be monitored and support provided if there are signs of distress.
- The oncologist can play an important role in encouraging the patient's early resumption of sexual activity after breast surgery or chemotherapy. The patient's partner should be encouraged to attend diagnostic planning and follow-up visits. Sometimes partners need referral for psychological support so they can better support the patient.
- Menopausal symptoms are highly distressing for many women. Mood swings, irritability, insomnia, and hot flashes can be treated effectively with a variety of medications. Some patients experiencing these symptoms benefit from referral to a psychiatrist for evaluation.
- Women value communication with their physicians. The most satisfied patients are those who feel they were compassionately warned about potential side effects of treatment.
- Be aware that some women emotionally "sail" through treatment and then develop symptoms of distress; symptoms develop in some of these women at the anniversary of their diagnosis or during the following year. Women should be asked during their 3-month posttreatment and 1-year follow-up visits how they are doing emotionally and referred as appropriate.
- Psychological symptoms such as anxiety are common at the conclusion of cancer treatment. Women feel vulnerable and less protected when not being seen regularly by their radiation or medical oncologist. Women should be provided with information on what to expect when treatment ends.
- It is useful to provide each woman with a survivorship care plan that includes a written summary of the treatments received and recommendations for follow-up care. This can help breast cancer survivors negotiate the transition to recovery and plan appropriately for future healthcare needs.

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CHAPTER 90

Reproductive Issues in Breast Cancer Survivors

Kathryn J. Ruddy and Elizabeth S. Ginsburg

CHAPTER CONTENTS

INTRODUCTION

Breast cancer is one of the most commonly diagnosed malignancies in women of childbearing age. Approximately 10% of women diagnosed with breast cancer are younger than 45, translating to over 23,000 women in the United States yearly and many thousands more worldwide (1). Thanks to improvements in the treatment of breast cancer and an increasing focus on survivorship issues, combined with the sociodemographic trend of delaying childbearing, many young breast cancer survivors are interested in future fertility (2–4). A recent meta-analysis found that concerns about infertility contributed to high levels of distress in young women with breast cancer (5). Breast cancer treatment can diminish or destroy a woman's reproductive potential due to direct gonadal toxicity or due to the natural waning of fertility while she is receiving therapy. However, many young women remain premenopausal and fertile for at least some period of time after breast cancer treatment, and some are interested in interventions to increase the chance that they will be able to conceive (6).

Because of the intricate relationship between breast cancer and hormones, fertility and reproductive issues in this population are complex. Reproductive factors are associated with the risk of developing breast cancer, and hormonal manipulations and medications are a mainstay of breast cancer treatment. Chemotherapy recipients who experience treatment-related amenorrhea have a better prognosis than women who continue to menstruate throughout chemotherapy (7). Nevertheless, for some young women with breast cancer, the threat or experience of infertility may be particularly distressing (6,8). Fertile Hope is an advocacy organization that supports fertility preservation for cancer patients; its founder proclaimed about her cancer diagnosis on www.fertilehope.org, "The thought of being sterile was almost as devastating as my cancer diagnosis itself." Some women are also interested in avoiding potential ill-health effects of premature menopause, including hot flashes, vaginal dryness, bone thinning, cardiovascular problems, and mental health issues (9,10).

EFFECT OF BREAST CANCER TREATMENT ON OVARIAN FUNCTION

Fertility may be adversely affected in several ways in young women with breast cancer. First, the time required to receive systemic breast cancer treatment may be months (e.g., conventional cytoxic chemotherapy) or years (e.g., adjuvant tamoxifen). During treatment, while pregnancy is contraindicated due to risks of teratogenicity, ovarian function and fertility are naturally declining due to aging. (see Fig. 90-1). The average age of menopause in the United States is 51 years, but fertility wanes many years before cessation of menses for most women, so many breast cancer patients diagnosed in their late 30s or 40s will be unable to conceive by the time they complete five to ten years of treatment with tamoxifen.

Second, adjuvant chemotherapy is directly toxic to the ovary, reducing fertility and potentially inducing premature menopause. The degree of damage to the ovaries will determine whether amenorrhea is temporary or permanent. Chemotherapy induces apoptosis in dividing cells in the ovary including maturing follicles (11). Because alkylating agents like cyclophosphamide are not cell-cycle specific, they may also directly kill oocytes and pregranulosa cells of primordial follicles. There is mixed evidence regarding whether chemotherapy given during the follicular phase of the menstrual cycle is more injurious to ovarian function than chemotherapy given at other times (12,13). Chemotherapy-associated premature menopause is thought to occur in 10% to 90% of patients receiving chemotherapy depending on the regimen given, the age of the patients, and the definition of menopause. Most studies are limited by the use of chemotherapy-related amenorrhea (CRA) as a

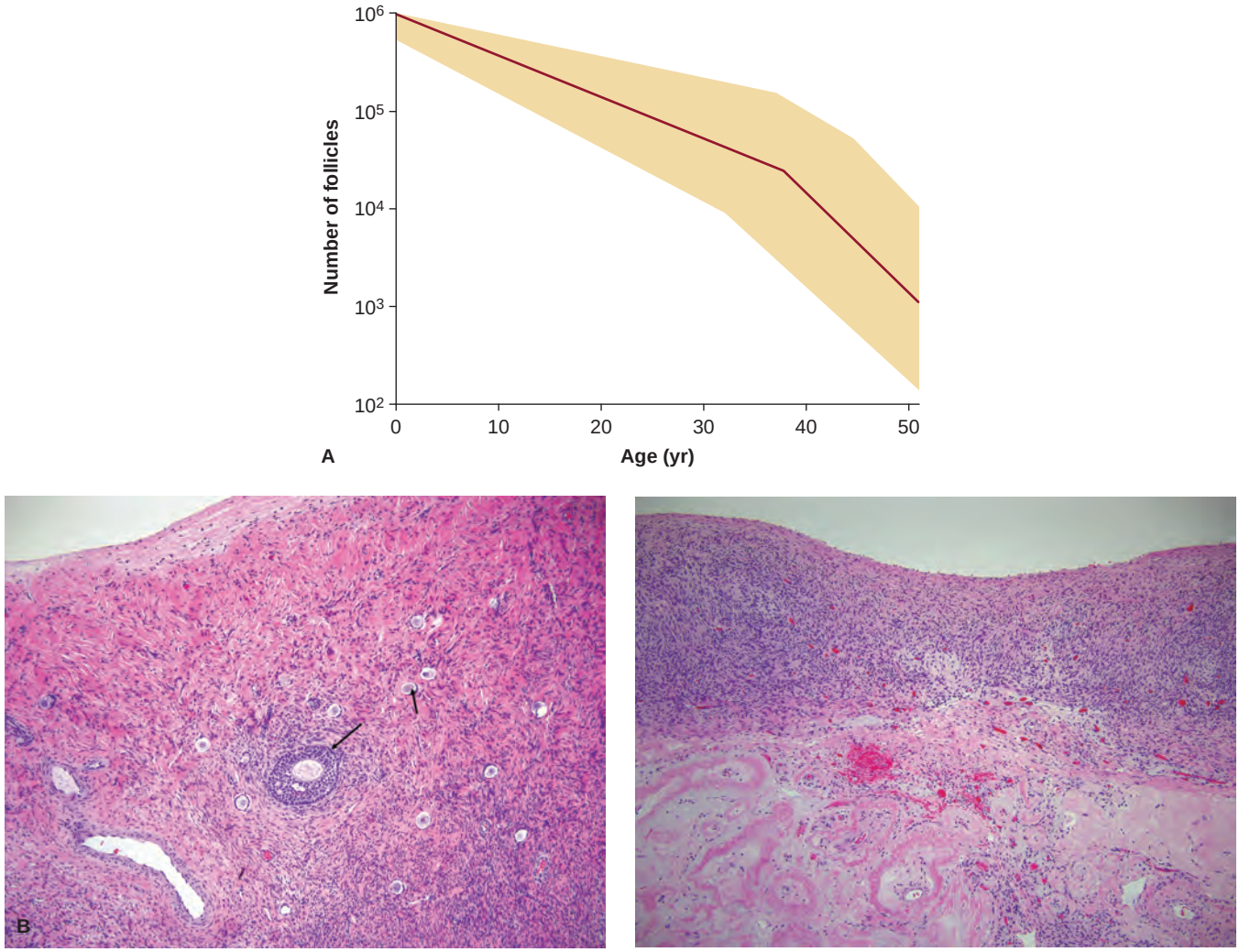

FIGURE 90-1 Natural decline in oocytes over time from birth to menopause. **(A)** depicts the decline in human ovarian oocytes by age (Data from Faddy et al. (74)). **(B)** shows histologic specimens of a premenopausal ovary containing follicles (*arrows*) and postmenopausal ovary without follicles. The expanse of tissue is the ovarian medulla, which does not contain many follicles even in the premenopausal state. (Adapted with permission from Lobo RA. Potential options for preservation of fertility in women. *N Engl J Med* 2005;353:64–73. (Ref. 73); Courtesy Q3 of Cynthia A. Jimenez, MD.)

surrogate for menopause and infertility. Treatment regimens vary substantially, and follow-up is heterogeneous and relatively short. CRA may be temporary, especially in very young women; older women are more likely to have permanent amenorrhea. Chronically anovulatory women may remain fertile even if they are not having menstrual cycles, but, on the other hand, ongoing menses are a poor surrogate for fertility, especially as women age, due to waning egg quality.

Available data confirm that risk of CRA is related to increasing age and increasing cumulative dose of cytotoxic chemotherapy, in particular, alkylating agents (14). A recent study of more than 2,000 pre- and perimenopausal women randomized to docetaxel-doxorubicin versus concurrent docetaxel-doxorubicin-cyclophosphamide or sequential doxorubicin-cyclophosphamide followed by docetaxel found that the women in the non-cyclophosphamide containing group had significantly less likelihood of CRA (15). Younger age was also significantly protective against CRA. Likewise, an earlier prospective longitudinal survey of 595 U.S. women with breast cancer diagnosed at age 25 to 40 undergoing adjuvant chemotherapy confirmed that menstrual cycles were less likely to persist at 1 year among women treated with regimens containing higher cumulative doses of cyclophosphamide (i.e., cyclophosphamide-methotrexate-5-fluorouracil [CMF] or 5-fluorouracil-doxorubicin-cyclophosphamide rather than doxorubicin-cyclophosphamide, doxorubicin-cyclophosphamide-paclitaxel, or doxorubicin-cyclophosphamide-docetaxel) (OR 0.37, 95% CI, 0.37–0.67) (16) (see Fig. 90-2). Rates of menstrual bleeding six months after completion of chemotherapy were also strongly related to patient age, with approximately 85% of women age <35 years having ongoing menses, 61% in women ages 35 to 40, and <25% in those age >40 (see Fig. 90-3). Recent evidence suggests that the addition of the taxanes to anthracycline-based adjuvant chemotherapy confers little or no increased risk of CRA, although data are mixed (17–20). Table 90-1 summarizes the risk of CRA with common adjuvant therapy regimens by age (14).

Even among women who remain premenopausal after cytotoxic therapy, menopause may ensue earlier than would have been expected in the absence of chemotherapy. An analysis of

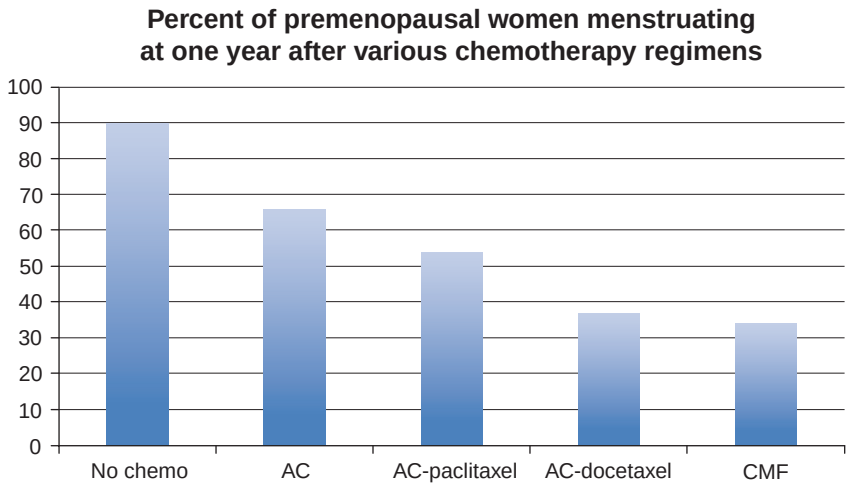

FIGURE 90-2 Menstrual bleeding by chemotherapy regimen received. (Data from Petrek JA, Naughton MJ, Case LD, et al. Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study. *J Clin Oncol* 2006;24:1045–1051.) (Ref. 16)

the International Breast Cancer Study Group (IBCSG) Trials V and VI revealed that 227 women who were menstruating and disease free at 2 years after diagnosis and treatment with 6 to 7 cycles of CMF had earlier menopause compared to controls (21). For a woman who was 30 years old at time of diagnosis and menstruating 24 months after 6 cycles of CMF, there was a 37% risk of menopause only 3 years later (at age 35) and an 84% risk at age 40. Other studies have also shown that ovarian reserve is diminished even in young women who remain premenopausal after chemotherapy for breast cancer (22–24). Hormonal treatments appear to primarily impact fertility due to delayed child-bearing, allowing natural waning of ovarian function (25).

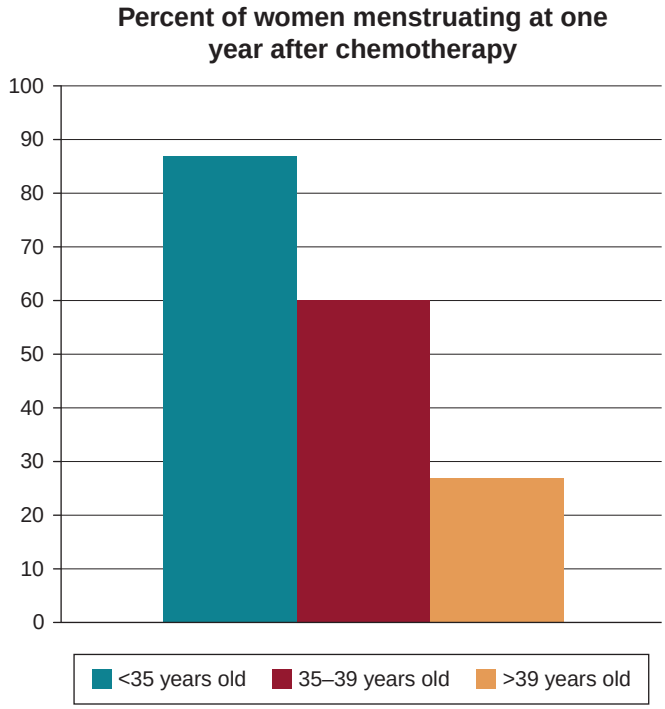

FIGURE 90-3 Menstrual bleeding by patient age at receipt of chemotherapy. (Data from Petrek JA, Naughton MJ, Case LD, et al. Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study. *J Clin Oncol* 2006;24:1045–1051.) (Ref. 16)

CONSIDERATIONS FOR WOMEN WHO DESIRE TO HAVE A FUTURE BIOLOGICAL CHILD

Many young women with breast cancer struggle with the competing interests of optimizing personal survival and wishing to have a future biological child (26). Some choose to modify their expectations regarding future biological children, often considering alternatives such as adoption

TABLE 90-1

Estimated Rates of Chemotherapy-Related Amenorrhea (CRA) with Modern Chemotherapy Regimens by Age

Chemotherapy Regimen	*CRA (%), Age ≤30*[a]	*CRA (%), Age 30–40*[a]	*CRA (%), Age ≥40*[a]
None	~0	<5	20–25
AC × 4	~0	13	57–63
AC × 4 followed by T × 4	15		>38
AC × 4 followed by D × 4	6	12	35–70
CMF × 6	19	31–38	76–96
CAF/CEF × 6	23–47		75–89
FEC × 6	38		73
TAC × 6	51–58		
AT	38%		

[a]Studies varied by inclusion of persons aged 30, 40, or 50 in the younger or older age categories (14–17,25,69–71).
AC × 4, 4 cycles of adriamycin and cyclophosphamide (IV); T × 4, 4 cycles of paclitaxel; D × 4, 4 cycles of docetaxel; CMF × 6, 6 cycles of cyclophosphamide (oral), methotrexate, 5-fluorouracil; CAF/CEF × 6, 6 cycles of cyclophosphamide (oral), adriamycin or epirubicin, 5-fluorouracil; FEC × 6, 6 cycles of 5-fluorouracil, epirubicin, cyclophosphamide (IV); TAC × 6, 4–6 cycles of docetaxel, adriamycin, cyclophosphamide; AT, 4 cycles of doxorubicin-docetaxel.
Adapted from Partridge AH, Ruddy KJ. Fertility and adjuvant treatment in young women with breast cancer. *Breast* 2007; 16(Suppl 2):S175–181. (Ref. 72)

(though adoption can be more difficult when a person has a history of cancer). For others, minimizing treatments or pursuing interventions aimed at fertility preservation, or a combination of these, may be appropriate.

Approach to a Patient Concerned about Fertility

The American Society of Clinical Oncology (ASCO) has published recommendations regarding fertility preservation considerations for cancer patients (27). For women with breast cancer, data regarding the efficacy and safety of strategies for fertility preservation are somewhat limited. These limitations may impede discussions about these issues, referrals to reproductive specialists, and enthusiasm for available techniques (28). Lack of awareness by healthcare providers regarding the importance of fertility issues may also be an obstacle to optimal care (29). The first step in counseling breast cancer patients regarding fertility is to assess each patient's desire for a future biological child (see Fig. 90-4). The second step is to describe the risk of premature menopause and/or infertility associated with various treatment options so that a patient can make informed decisions about treatments and about fertility-sparing strategies. Some women may elect to forego some therapy if the incremental benefit is modest and the risk of subsequent infertility is high (6).

Fertility Preservation Strategies

For those who desire a future biological child and need systemic therapy that will put them at risk for premature menopause, fertility preservation strategies are available. While studied in other cancer populations, there is limited enthusiasm for using oral contraceptives during chemotherapy in young women with newly diagnosed breast cancer due to concerns that exogenous hormones may worsen prognosis (30). Ovarian suppression with gonadotropin-releasing hormone (GnRH) agonists (e.g., leuprolide acetate) is widely available and can be administered during cytotoxic chemotherapy to attempt to reduce the gonadotoxicity of the treatments by halting ovarian cycling. However, the results of several randomized studies have been mixed with regard to the efficacy of this strategy (31–34). Cryopreservation of oocytes and ovarian tissue, the former of which usually entails ovarian stimulation prior to treatment, are also options where available. Oocyte cryopreservation is widely used internationally and recently had its experimental label removed in the United States by the American Society of Reproductive Medicine (35–38). Oocyte cryopreservation by experienced centers is now nearly as effective as embryo cryopreservation in young women and is particularly appealing to patients who do not have a male partner and do not wish to use donor sperm. Ovarian tissue cryopreservation in theory could allow preservation of hundreds of primordial follicles (containing immature eggs) prior to chemotherapy without ovarian stimulation and the associated concerns about high hormone levels, and without treatment delay, other than to remove the ovarian tissue. However, this method suffers from substantial technical limitations (39), and there have been fewer than 20 published reports of live births to date (40,41). This technique is also associated with theoretical concerns about the reintroduction of cancer cells via the reimplanted ovarian tissue though a recent small study showed no metastatic cells in 51 biopsies of cryopreserved ovaries from patients with breast cancer (42). Research to enable *in vitro* maturation and *in vitro* fertilization of oocytes from these ovarian tissue

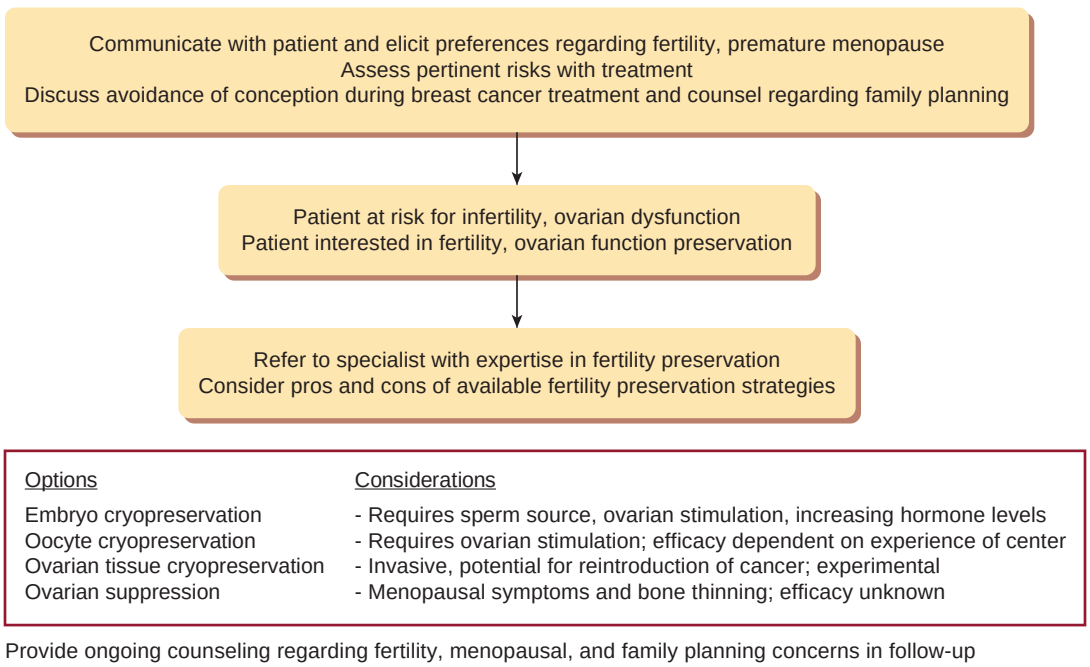

FIGURE 90-4 Management summary for premenopausal women with breast cancer regarding issues. (Adapted from Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006;24:2917–2931.) (Ref. 27)

fragments is ongoing. Cryopreservation of embryos following *in vitro* fertilization (IVF) is a standard procedure with a relatively high success rate in infertile women, with an approximately 20% to 40% live birth rate per transfer of 2 to 3 thawed embryos depending on maternal age, as described at www.sart.org.

Ovarian Stimulation for Egg Retrieval

In women with breast cancer, there has been concern that ovarian stimulation for cryopreservation of oocytes or embryos, with the associated supraphysiologic estradiol and other hormone levels, might increase the risk of cancer recurrence, particularly in the setting of hormone receptor-positive disease. Estradiol levels during traditional stimulated IVF cycles can be greater than 2,000 pg/mL, while levels average less than 300 pg/mL in the normal menstrual cycle. Because natural cycle IVF (not using ovarian stimulation) has much lower oocyte and embryo yield compared to stimulated cycles, alternative stimulation strategies have been investigated. Tamoxifen and letrozole have been used for ovarian stimulation in women with recently diagnosed early breast cancer prior to IVF, and preliminary results are reassuring in that no effect on recurrence is evident (43,44). When letrozole is used during ovarian stimulation, estradiol levels are not substantially higher than in natural menstrual cycles (45). The 2- to 6- week period required for this procedure prior to beginning systemic breast cancer treatment may not be prudent in some disease settings (e.g., inflammatory breast cancer) though this is reasonable for many patients, usually in the interval between surgery and the start of chemotherapy.

ASSESSMENT OF OVARIAN FUNCTION AND FERTILITY AFTER BREAST CANCER

Many survivors are interested in understanding their reproductive potential, but assessment of fertility and even menopausal status after treatment for breast cancer can be complicated and imprecise. Interruptions in menstrual cycles are not sensitive or specific for infertility. Temporary amenorrhea is common after chemotherapy, even in women who later resume menstrual functioning, and hormonal treatments make the presence or absence of menses a less accurate reflection of reproductive potential. In a prospective cohort of 595 premenopausal women age 20 to 40 at the diagnosis of early breast cancer, the proportion experiencing monthly bleeding decreased from 90% to 40% following the first dose of chemotherapy (16). The rates of monthly bleeding rose to 55% over the next 15 months but then slowly declined to 35% at 5 years after diagnosis. Women who were taking tamoxifen were 15% less likely to be menstruating at 1 year after beginning therapy, presumably due to temporary ovarian dysfunction during treatment.

Hormonal biomarkers may clarify how likely a woman is to be able to conceive. Even within the normal ranges of follicle-stimulating hormone (FSH), there may be a correlation between higher levels and poorer chance of conception (46). Women with decreased ovarian reserve often have shorter menstrual cycles due to accelerated follicle development. FSH levels on the third day of menses >10 mIU/mL, resulting in E2 levels >75 pg/mL, cause early ovulation, which is associated with reduced fertility. Inhibin levels and anti-mullerian hormone (AMH) levels may also clarify fertility status. Inhibin A is primarily secreted during the luteal phase, while inhibin B is primarily secreted during the follicular phase. Levels of both decrease during gonadotoxic chemotherapy but may increase to the normal range in those who eventually resume menses (47). AMH levels fall after exposure to chemotherapy for breast cancer (23), and even survivors who resume menses have prolonged reductions in AMH that may herald reduced fertility (48). AMH is produced by early-stage ovarian follicles and, therefore, demonstrates ovarian reserve as reflected by the pool of remaining primordial follicles (49). One recent study showed that AMH >1.2 ng/mL is predictive of more successful egg harvesting in breast cancer patients (50). In addition, vaginal ultrasound can be used to measure the antral follicle count (AFC) on the third day of the menstrual cycle, which is predictive of response to *in vitro* fertilization and potential fertility (51).

However, hormonal manipulation can have a major impact on the values of these biomarkers. Estradiol can be 4 to 5 times higher, and FSH can be markedly suppressed on tamoxifen. Due to the presence of common simple ovarian cysts induced by tamoxifen, AFC while on tamoxifen may not accurately reflect ovarian reserve. AMH is produced in very early follicles and is not influenced by menstrual cycle phase, so it may be the best indicator of ovarian reserve in a woman who has been on tamoxifen although there is only limited research to date in this area (52).

FAMILY PLANNING AND BIRTH CONTROL AFTER BREAST CANCER

Hormonal methods of contraception generally are not recommended for breast cancer survivors because of concerns about a potential effect on breast cancer outcomes, including new primary disease. Barrier methods of contraception or nonhormonal intrauterine devices (IUDs) can be considered to prevent unwanted pregnancy, which can be particularly onerous for young survivors (53).

While there is no clear evidence that ovulation induction or IVF increases the risk of breast cancer (and in fact, the Two Sister Study suggested that women who had received fertility drugs such as clomiphene were at lower future risk of breast cancer) (54), there has been concern that IVF may increase risk of breast cancer in a person with a personal or family history of the disease. IVF has been conducted in cancer survivors, although response to stimulation and subsequent embryo yield have been suboptimal (55).

IMPACT OF PREGNANCY AFTER BREAST CANCER ON ONCOLOGIC OUTCOMES

There has been concern that pregnancy after breast cancer may worsen prognosis, especially among women with hormone receptor-positive disease. To date, the effect of pregnancy after a diagnosis of breast cancer on rates of relapse and survival has not been reported prospectively. Evidence from several retrospective studies on pregnancy following breast cancer suggests no impaired survival or increase in recurrence rate, but these studies are all limited by significant biases (56–60). Table 90-2 presents recent studies evaluating survival among breast cancer survivors who have had a subsequent pregnancy compared to survivors who have not had a pregnancy. Although not all studies reach statistical significance, they all suggest that women who have had a pregnancy

TABLE 90-2

Recent Studies Evaluating Safety of Pregnancy After Breast Cancer

Study	*No. of Breast Cancer Survivors with Subsequent Pregnancy*	*No. of Controls*	*Relative Risk (95% CI) of Recurrence or Death*
Gelber (2001) (56)	94	188	0.44 (0.21–0.46)
Mueller (2003) (57)	438	2,775	0.54 (0.41–0.71)
Blakely (2004) (58)	47	323	0.70 (0.25–1.95)
Ives (2007) (59)	123	2,416	0.59 (0.37–0.95)
Cordoba (2012) (60)	18	97	0.80

Adapted from Partridge AH, Ruddy KJ. Fertility and adjuvant treatment in young women with breast cancer. *Breast* 2007;16(Suppl 2):S175–181.

after breast cancer may actually have a lower risk of recurrence and death. In a recent meta-analysis including data from 14 studies, it was concluded that the 1,244 women who became pregnant after breast cancer had a 41% lower risk of death than the 18,145 young breast cancer patients who did not (61). While these data are reassuring, all studies may be confounded by the "healthy mother" effect (i.e., survivors who are healthier and less likely to develop a recurrence at baseline may be more likely to become pregnant, perhaps in part due to the advice of their physicians) (62). Nonetheless, it is possible that there is a beneficial biological effect from the immunologic changes or high hormonal levels of pregnancy. High-dose estrogen and progestins are effective treatments for breast cancer, and they have demonstrated an antitumor effect in *in vitro* and animal models, possibly due to signaling via the insulin growth factor pathway (63). Ongoing prospective studies may help to elucidate further the risks and benefits of pregnancy after breast cancer.

A common recommendation is for breast cancer survivors to wait at least 2 years after treatment before attempting a pregnancy in an effort to get them beyond the period of highest risk of recurrence. However, the available data have not revealed that an earlier pregnancy impairs disease outcomes. Given that many women with breast cancer are at risk of recurrence long beyond the first few years after diagnosis, and given that fertility wanes with age, some women elect not to wait a substantial period of time to become pregnant after diagnosis. For women with hormone receptor-positive disease, five to ten years of tamoxifen therapy is often recommended, during which time pregnancy is contraindicated. This approach is problematic for many women, given the concerns about declining fertility, and some may elect to forgo completion of a course of tamoxifen to try to become pregnant sooner rather than later.

PRACTICAL ISSUES PERTAINING TO PREGNANCY AND LACTATION AFTER BREAST CANCER

There are a range of medical and psychosocial issues that impact whether a breast cancer survivor who is interested in future fertility ultimately becomes pregnant. There are limited data on fertility and pregnancy outcomes among women with a history of breast cancer. Findings from select populations of young women with breast cancer suggest that approximately 5% to 15% of young breast cancer survivors will become pregnant at least once after their diagnosis (59,64). Three large studies including nearly 4,000 total offspring of childhood cancer survivors, excluding clearly hereditary cancers, revealed no statistically significant increase in cancers or malformations (65). Some BRCA1 or BRCA2 mutation carriers will consider *in vitro* fertilization with embryo biopsy and preimplantation genetic testing or prenatal genetic testing once they are pregnant (66). Women who have been treated with cytotoxic agents in the past may be at increased risk of peripartum complications (e.g., cardiomyopathy due to prior anthracycline and trastuzumab), but data are scarce. Future research in this area is warranted, and women with a history of breast cancer treatment should consider receiving "high risk" obstetrical care during a pregnancy.

Breast cancer survivors who have a baby may be interested in breast-feeding (53). The degree to which local therapy has affected the normal breast anatomy will dictate the ability of that breast to produce milk. Women who have had a mastectomy can lactate from the opposite breast. Milk production may be limited by the lack of the second breast, and substantial asymmetry may result between the engorged, lactating breast and the contralateral chest wall or reconstructed breast during the period of lactation. For women who have undergone breast conserving therapy (BCT), resection of a centrally located tumor, particularly if affecting the nipple-areolar complex, is more likely to impair lactation. Radiation therapy can cause lobular sclerosis and atrophy within breast tissue, which may also limit milk production (67). Asymmetry may be a problem in this situation as well, with the treated breast producing less milk. In a multicenter, retrospective review of 53 women who became pregnant after BCT, one-third had some lactation from the affected breast. Many of these women reported low milk output or the baby preferring the untreated breast, and only 25% of women were able to successfully breast-feed from the treated breast (68). While it is evident that lactation works as primary prevention against breast cancer, there have been no efforts to evaluate the benefits of lactation in breast cancer survivors, in part because so few survivors have successfully breast-fed.

MANAGEMENT SUMMARY

- Young women with early stage breast cancer have a strong desire to not only decrease their risk of recurrence but to continue to live satisfying lives.
- Some feel that the ability to have a biological child in the future is important to their quality of life.
- Discussions about fertility should be tailored to each patient's preferences, taking into account the baseline risk of her disease, risk reduction from recommended therapy, as well as risk of infertility from treatment.
- Because of the time-sensitive nature of treatment initiation as well as of most fertility preservation strategies, early referral to a fertility specialist is prudent for those interested (27).
- For some patients, a combination of fertility preservation strategies may be optimal, while many will elect to forgo any such intervention.
- Regardless, shared and informed decision-making not only about conventional risks of treatment (e.g., nausea, hair loss, fatigue) but also about the possibility of treatment-related infertility is likely to lead to more realistic expectations and better psychosocial outcomes for young breast cancer survivors.
- Healthcare providers should also educate patients about effective and safe contraception during and after their breast cancer treatment.

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CHAPTER 91

Cost and Cost Effectiveness Considerations

Bruce E. Hillner

CHAPTER CONTENTS

Cancer care costs have been growing faster than the overall rates of health care, especially over the last 20 years. The combination of the 2008 worldwide recession and the recent U.S. debate over healthcare reform has focused attention on the rising costs of new cancer therapies. U.S. costs for breast cancer care were estimated to exceed $16 billion in 2010 (1) and are the highest overall of any cancer type.

The spiraling costs of new cancer therapies are increasingly recognized by cancer professional organizations such as ASCO (2)and ACS, but what to do about them is another hurdle without consensus. Since 2008, the greatest source of discussion focusing on breast cancer costs is likely to have been around the FDA. decision to revoke the approval of bevacizumab. Those discussions were usually a mix of concern about the bevacizumab's costs (~$88,000 per year of treatment) and/or an implicit cost-effectiveness analysis ("it's not worth it") given the uncertainties of any overall benefit (3).

In this chapter, I will review the literature published since 2008 that addresses the costs and cost-effectiveness of breast cancer assessment and treatments for the initial care, adjuvant therapies, and advanced/recurrent disease as well as highlight where these reports by inference give guidance to quality of care indicators.

For this review, I searched Medline for publications from January 2008 to late 2012 with the following search characteristics: breast neoplasm/economics, an abstract (except for editorials), English languages, and excluded reports addressing prevention, strategies for high-risk women, and screening (principally mammography). The individual report abstracts were reviewed for relevance to U.S. clinical practice, thereby excluding many reports from limited resource countries. Table 91-1 lists the categories used to structure this review.

COST ANALYSIS VOCABULARY

Before jumping into the review, because most readers of this book are not knowledgeable about the methodology used in these reports, the following brief section discusses the key terms as a platform for the chapter.

There are five common categories of cost studies used in assessing healthcare. The first category, *cost of illness* studies, are studies that describe the financial burden or consequences of illness but do not make any comparison to other conditions. A *cost comparison* report explicitly addresses the relative costs of two (or more) approaches or populations. A comparison report will specify what cost elements and time frame are being compared and defers to the reader to make any inferences.

Cost minimization reports either explicitly or implicitly assume no difference in the benefit (or harm) incurred between two different approaches. By comparing the costs incurred, the lowest cost strategy will be, by definition, preferred as it has the lowest cost. The recent American Board of Internal Medicine Foundation Choosing Wisely® (www.choosingwisely.org) campaign fits the definition of cost minimization. Each specialty was asked to identify five tests or procedures commonly used whose common use and clinical value are not supported by the literature. The ASCO list for cancer included the following breast cancer topic: avoid advanced imaging in staging early breast cancer as well as in the surveillance of asymptomatic individuals' post-initial treatment (4).

Cost-effectiveness analyses (CEA) and *cost-utility analyses* (CUA) estimate the additional cost per unit of benefit associated with the use of a given intervention as compared to the alternative. The intervention of interest can be of any type: prevention, screening, diagnosis, treatment, or symptom control. CEAs consider either a specific health effect

TABLE 91-1

Review Categories of Costs of Breast Cancer Therapy Literature

Diagnostic Procedures
Local-Regional Therapy
Organization
Staging and management of the axilla
Radiation therapy
Lymph edema
Prognostic and Predictive Factors
Imaging
Genomic tests
Adjuvant Therapy
Endocrine
Chemotherapy
Trastuzumab
Colony-stimulating factors
Bisphosphonates
Follow-up Care
Employment/Disability
Metastatic Disease
Chemotherapy
Trastuzumab
Brain metastases
Bisphosphonates
Summary Costs

(e.g., disease free survival) without assigning a specific value to it or use years of life. A CUA is a specific type of cost-effectiveness analysis that combines mortality and morbidity into a single multi-dimensional measure called a quality adjusted life year (QALY).

The result of a CEA is usually expressed as a ratio of the difference in cost between the two competing strategies divided by the difference in benefit. A CEA is of most interest when the new intervention is more effective and more costly than the reasonable alternative strategy. The lower the ratio of the additional cost of the new intervention to gain the additional benefit, the more appealing to society as a whole it is to add the intervention to current medical approaches.

For the interested reader, several sources of standards and checklists for best practice reporting of CEA studies are available (5–7). In this chapter, three recurring concerns will be pointed out: —i) In cost minimization studies, was it appropriate to assume the two strategies are equally effective? ii) Were the data used to guide the efficacy estimates accurate, representative, and credible? and iii) Was the default strategy representative of current patterns of care in a particular location and during those years?

LIFETIME COSTS

Accurate, current estimates of the cost of illness incurred for breast cancer treatment are hard to identify. In the United States data sources have shifted from single centers to claims analyses have been predominantly of three different groups—patients insured by Medicaid (poor and relatively young), patients insured by self-insured employers (wealthier, young) and the elderly (usually with a linkage of Medicare claims with registry data from SEER).

TABLE 91-2

NCI 2010 Estimates of U.S. Costs for Breast Cancer Care

Phase of Illness	*Age <65*	*Age >65*
Initial year	$27,700	$23,100
Continuing care (per year)	$2,200	$2,200
Last year of life	$94,300	$62,900

Modified from Mariotto AB, Yabroff KR, Shao Y, et al: Projections of the cost of cancer care in the United States: 2010–2020. *J Natl Cancer Inst* 2011;103:117–128.

Mariotto and colleagues from the NCI (1) have recently updated their national projection of costs for 2010 and projected to 2020 associated with care for 15 different cancer types including breast cancer (1). Table 91-2 shows their projections for breast cancer. The higher costs for women younger than 65 years were based on studies from integrated managed care organizations (in the 1990s) that showed costs for younger patients (of all cancer types) were 20% higher in the initial year and 50% higher in the last year of life than for Medicare beneficiaries. In my opinion, especially for younger women, the initial management costs are likely a substantial under-estimation as the type and frequency of more-expensive adjuvant chemotherapies are more common in younger women. In either case, their first year costs (local surgical therapy, axillary staging/dissection, and adjuvant therapies) were estimated at $25,000 to $30,000, continuing care after the first year at $2,200, and for those developing recurrent disease, the average costs in the last 12 months of life were $63,000 to $94,000.

The challenges in doing cost-of-illness studies in breast cancer were addressed in two excellent reviews (8,9). The review (n = 29) reports of U.S. costs of illness studies published between 1984 and 2007 covered a broad range ($20,000 to $100,000 per lifetime) (8), were predominantly from an insurer/third party payer perspective, predominantly of early stage disease, and did not include many, or most, of the expensive innovations of the last decade (e.g., IMRT, CSFs, 3rd generation chemotherapy). These limitations, or under-estimations, from either inaccurate or outdated sources have an often important hidden impact when added to most economic evaluations because these need to project the future. Fortunately, there have been recent reports of new, large, detailed analyses of U.S. metastatic disease costs that will be discussed later.

DIAGNOSTIC PROCEDURES

The increased use of stereotaxic core biopsy has reduced the rates of open surgical biopsy throughout the world. Between 2000 and 2005, in the Netherlands, surgical biopsies were reduced from 54% to 10% of the total diagnostic costs associated with screen detected breast cancers (10). A Swedish audit of fine-needle aspiration (FNA) cytology compared to core needle biopsy (CNB) found a difference; FNA had lower rates of definitive diagnosis, more additional needle biopsy, or surgical biopsy prior to definitive surgery (11). An Austrian budget impact audit of CNB compared to open surgical biopsy found a 30% total cost reduction per lesion and obviated the need for open surgical procedure in 60% of women (12).

For these non-palpable lesions, the current standard of wire localization (WL) to guide surgical excision appears to be evolving. WL is unfortunately associated with positive margins due to migration. Radioactive seed localization that permits equal or superior localization and is associated with lower re-excision may be another major cost-reduction tool if the results from experienced centers using it become generalizable (13). To date, no cost consequence studies of radioactive seeds were identified.

Ongoing uncertainty persists concerning the role of breast MRI in the initial staging. The cost of a dedicated breast MRI is high and the downstream costs of pursuing false-positives are well known. Changes in primary surgical treatment were noted in 8% to 33% of women in a recent meta-analysis, yet without randomized, prospective assessments the benefit value cannot be determined (14).

STAGING THE AXILLA

The rapid acceptance of the use of axillary sentinel lymph node detection to guide managing axillary lymphadenectomy was reinforced by several cost-minimization reports from around the world. The French reported a prospective national, multi-institutional, cost comparative analysis found an ~12% reduction in costs (15) while a large, single center, Italian series found cost savings of 10% to 26%. The potential role of axillary ultrasound in obviating the need for SLN for patients with bulky enlarged nodes has intuitive appeal but prospective, comparative studies are needed (see Chapter 38) (16).

RADIATION THERAPY

Alternatives to the traditional 6-week course of whole breast radiation following breast-conserving surgery have obvious cost of care implications with uncertain relative cost-effectiveness. The first alternative is more expensive with uncertain reductions in local control. Intensity-modulated radiation therapy (IMRT) has been rapidly adopted in the United States, increasing from <1% of women in 2001 to 11.2% in 2005 among the U.S. elderly, with a doubling of costs compared to whole breast radiation (Medicare payments $15,230 for IMRT vs. $7,180 for whole breast) (17).

Shorter courses using hypo-fractionation, accelerated partial breast, or targeted intra-operative radiotherapy are all less costly. Hypo-fractionated whole-breast radiotherapy (WBR) (over 3 weeks) in Australia was estimated to reduce total treatment costs by 24% (18). The major uncertainty is whether these shorter courses lead to inferior outcomes in terms of local recurrences. Another factor is whether patient selection is appropriate. The economic consequences of accelerated partial-breast irradiation (PBI) as an alternative to WBR or IMRT are still uncertain, especially in light of a recent report stating that about one-half of Medicare patients receiving PBI did not receive the level of care recommended by the American Society for Radiation Oncology consensus guidelines (19).

PROGNOSTIC AND PREDICTIVE FACTORS

The challenges associated with obtaining Medicare coverage for innovative diagnostics (e.g., molecular imaging, genomic profiling, circulating tumor cells) are well illustrated by the many year battle prior to recent Medicare coverage of Oncotype Dx and Mammaprint. Fifteen reports were found addressing the cost consequences of genomic predictions. As reviewed in detail in Chapter 48, the current patient subgroups for which these tests should be used are cancer that are ER+ with axillary node negative and possibly one-three node positive women eligible for chemotherapy. Pricing in 2012 for Oncotype Dx and Mammaprint are almost identical at $4,200.

The economic consequences have been assessed by hypothetical decision models using Markov chains to estimate projected costs from the societal perspective in Canada, Europe, Israel, Japan, and the United States Hornberger et al compared and summarized these economic assessments in a 2012 review (20). In sum, each gene profiler is superior to authoritative guidelines, Adjuvant!, or current practice. We are unaware of any direct comparisons of Oncotype Dx to Mammaprint. The incremental cost-effectiveness ratios, or cost-savings results, varied with the pre-test recurrence risk (node-negative, positive, or both), the costs of chemotherapy used (especially dose-dense), time horizon, and comparator (Adjuvant! was the second best). For example, in a U.S. managed care setting, Oncotype showed costs savings and the incremental costs were <$30,000/QALY. These assays are the first of their kind and suggest that the best care is less care.

ADJUVANT THERAPY—ENDOCRINE THERAPY

Several reports addressed the question of adherence to hormonal aromatase inhibitors (AI) in U.S. women using administrative pharmacy benefit claims. Neuget et al. assessed mail order prescription records from January 1, 2007, to December 31, 2008 for women older than 50 years (21). They used two distinct, useful definitions—"non-persistence" was defined as a prescription supply gap of more than 45 days without subsequent refill and "non-adherence" was a medication possession ratio of less than 80% of eligible days. This study of 8,100 women age 50 to 64 years and 14,000 age >65 found non-persistence in 21% and 24% and non-adherence in 11% and 9% by age group, respectively. As expected, higher co-payment amounts were associated with both types of gaps. A similar type of analysis that assessed the first year following an initial claim for an AI found non-adherence (using the same definition as Neuget) was 23% over the year in 13,600 commercially insured women. Co-payments >$30 per prescription, younger age, and higher co-morbidity was associated with non-adherence (22). In a one-state Medicaid cohort (n = 1,538) adherence was even lower (58% at one year) and more troubling was that hormonal therapy of any kind was not promptly initiated within one-year (68%) in an analysis of linked pharmacy claims and state cancer registry (23).

Numerous cost-effectiveness assessments of different AIs and schedules were reviewed in the previous edition of this book!. A unique analysis reviewed economic analyses of AIs in breast cancer published between 1999 to 2008 (n = 32) and categorized the conclusions of the reports and pharmaceutical company sponsorship (n = 26). Only one of the 26 (4%) pharmaceutical company-sponsored studies reported unfavorable cost-effectiveness of an AI, which was a competitor's product, whereas two of four (50%) non-pharmaceutical company-sponsored studies concluded AIs are not cost-effective in certain clinical scenarios (p < .05). Seven pharmaceutical company-sponsored studies conducted a comparison among several AIs; all 7 studies reported favorable conclusions for the sponsoring company's products (24).

ADJUVANT THERAPY—CHEMOTHERAPIES

Twelve different cost-effectiveness analyses were reported that all addressed the use of docetaxel in node-positive disease and used either the BCIRG001 (TAC vs. FAC) or the PACS 01 trial (FEC-D vs. FEC) as the efficacy source for their projected CE ratios. For more detailed discussion of these findings see Chapter 44. What is most notable is that these analyses were from such a divergent group of countries (Canada, Korea, Spain, U.K., China, France, Japan, and Iran). With the exception of Iran, where the toxicities may have been overweighted, all reports using modeling of future anticipated benefits, found that the docetaxel regimens were "cost-effective." For example, the British assessment, using a 10-year timeframe, projected that TAC with growth factor support had an incremental cost/QALY of 20,400 pounds (25) and the French assessment of FEC-D found an incremental cost/QALY of 9,700 euro (26). Relatively low, favorable incremental cost-effectiveness ratios were associated with pharmaceutical support of the study. One noteworthy, indirect economic analysis for four regional Ontario cancer centers noted that FEC-D, in routine practice, was associated with febrile neutropenia in 23% of women. The costs of FEC-D should assume primary prophylaxis with growth factors for all women (27). These economic analyses, given the febrile neutropenia concerns, support the apparently worldwide adoption of these combinations.

Growth Factors

In most Western countries in 2013, the most expensive element of more aggressive third generation adjuvant therapies, or dose-dense therapies, is granulocyte colony-stimulating factors (CSFs). Several industry supported cost-effectiveness models were reported showing benefits from primary prophylaxis with peg-filagrastim in support of a highly myelo-suppressive regimen (28,29). These models inherently hinge upon superior efficacy of the new therapy. Hershman has recently reported that U.S. oncologists were early adopters of dose-dense therapy leading to an explosion in the use of CSFs in Medicare recipients since 2003 (30). However, with longer follow-up and subsequent trials, the benefits of dose-dense treatment in estrogen receptor positive disease are now more uncertain (31,32). It is now thought that substantial savings could occur if dose-dense therapy were restricted to women with ER-negative, luminal B-type cancers.

Trastuzumab

Several results of ongoing follow-up of the pivotal adjuvant trials of trastuzumab have economic consequences—the benefits are durable well beyond the initial follow-up years, treatment for two years versus one year provides no additional benefit (33), and the late development of congestive heart failure is uncommon (34). The drug is very effective and the concerns about the dire financial consequences of this expensive drug have not come to pass. While the price paid per unit of trastuzumab varies from country to country, adjuvant trastuzumab has been widely adopted in most economically advanced countries. It is also reassuring that the favorable incremental cost-effectiveness ratios reported by numerous independent teams were found in a 2011 review to be of high methodological quality (35). One noteworthy report suggested that by 2016 the use of adjuvant trastuzumab in the United States would yield a ratio of adjuvant vs. metastatic trastuzumab of 3:1 due to it's efficacy in preventing metastatic recurrences (36). A new concern, at least in the United States, is that women of color and/or low education were found in a NCCN database to less often complete full duration (>9 months) of therapy (37).

EMPLOYMENT CONSEQUENCES

The adverse impact of the initial, and adjuvant treatment of, early stage breast cancer on employment is generally recognized. In general, the impact is greater in blue-collar, self-employed, lower-wage, and non-Caucasian women (38). Even in Canada, a study of 962 women from eight hospitals found they lost an average of 27% (median) of their projected annual wages in the first year of treatment (39). Two similar studies of commercially insured women addressed short-term disability. Each study had >800 patients. The first observed an average of 35 days of absenteeism and 51 days of short-term disability and the second 60 days of disability (40,41). In the latter report, however, there was no difference between years 2 and 4 and breast cancer survivors stayed with their employer longer.

PAYING FOR QUALITY CARE

One unique 2004 report from Los Angeles examined the use of financial incentives related to performance on quality measures reported by medical or radiation oncologists and surgeons associated with a population-based cohort of patients with breast cancer (42). In this survey of 350 providers, about 20% reported financial incentives based on patient satisfaction and 15% based on guideline adherence, predominantly for services through a network-model HMO.

SECOND AND THIRD LINE METASTATIC THERAPY

The few cost-effectiveness reports of second or third line therapies all found relatively high CE ratios. The Swiss addressed continuing or stopping trastuzumab (and adding capecitabine) at the time of progression when treating *HER2*+ metastatic disease and found a gain of ~0.3 QALY at ~100,000 euros/QALYs (43). The alternative of switching to lapatinib (plus capecitabine) was projected to have a gain of only 0.12 QALYs at $166,000 per QALY (44). A third report of an economic companion study including quality of life estimates of the licensing trials comparing ixabepilone plus capecitabine vs. capecitabine for metastatic disease progressive after anthracyline and taxane treatments adds about $31,000 in cost and is associated with about one-month of quality adjusted survival (45). We had the opportunity to write the accompanying editorial highlighting that efficacy does not necessarily translate into cost-effectiveness (46).

Brain Metastases

The direct medical care costs for brain metastases were addressed in two reports. A U.S. commercial insurer database from 2002 to 2004 identified 779 incident brain metastases patients whose costs of care and/or utilization indicators compared to non-brain metastatic breast cancer were about double—mean twelve-month payment of ~$100,000 vs. $47,900 (47). A French national database analysis of all patients admitted in 2008 for brain metastases and who previously had received target anti-*HER2* therapy found 2,100

TABLE 91-3

Direct Medical and Pharmacy Costs (U.S. $) per Month for Commercially Insured Women with Metastatic Disease

	All	*Endocrine*	*HER2*	*Cytotoxic Therapy*	*No active systemic therapy*
Patients, n	7,698	3,187	711	2,278	1,522
Total Cost, $	**9,800**	**5,300**	**10,100**	**13,200**	**13,900**
95% CI	(9,400–10,100)	(5,100–5,500)	(6,700–10,100)	(12,700–13,800)	(12,300–15,500)
Inpatient, $	**3,100**	**1,000**	**1,500**	**4,100**	**6,600**
Outpatient, $	**6,300**	**4,100**	**8,200**	**8,500**	**6,700**
Anti-cancer therapy	1,930	1,100	4,900	3,300	200
Diagnostics	930	620	880	1,200	1,200
Radiation therapy	740	650	750	840	790
Out-patient surgery	600	350	370	560	1,300
Other	2,100	1,400	2,900	2,500	3,200
Average time from first to last systemic therapy, yrs.	1.7	2.4	2.1	0.6	0.0

Noted:
Revise footnote to "Costs in 2010$".
95% confidence intervals calculated by author.
Mean age 51.6 years. Average follow-up 2.2 years.
Modified from Montero AJ, Eapen S, Gorin B, et al: The economic burden of metastatic breast cancer: a U.S. managed care perspective. *Breast Cancer Res Treat* 2012;134:815–822.

women whose annual hospital treatment costs were 22,500 euros (48).

Metastatic Disease

Three European reports tracked deaths from metastatic cancer using either a region (Uppsala, Sweden) or single centers (Great Britain and France) (49,50,51). While these reports provide summary estimates for costs by site of care (inpatient vs. outpatient), they do not provide the units consumed (e.g., hospital days, chemotherapy days, radiation days). The Swedish audit of 53 patients—ER+ 60%, *HER2*+ 25%, mean 26 months and median survival 19 months—suggest a representative disease severity distribution. Totals costs were estimated at 93,700 euros (95% CI 78,500–109,600) in 2006 currency. The British estimate included 30% local recurrences and little trastuzumab use; therefore, their estimates are artificially low at 25,200 pounds per patient. The French report of 290 women from 2005 to 2008 is more detailed. This cohort's survival from diagnosis of metastatic disease was an average of 25 months and a median survival of 18 months. They stratified costs into the following categorizes –50% for outpatient chemotherapy, 38% for inpatient care, 15% for palliative care, and only 4% for radiotherapy. Total costs were 36,500 euros in 2008 currency.

Several large multi-year detailed analyses of American insurer data of employed women with claims-inferred metastatic breast cancer provide a much-needed cost-of-illness summary (52–54). These reports all used a similar approach—a HIPPA compliant, de-identified administrative claims payment record for women with employee-sponsored health insurance. The index date for presence of metastatic disease was defined by the first one or two dates of claims with a diagnosis of secondary malignant neoplasm (ICD 196.xx) plus breast cancer (ICD 174.xx). Each used total payments including patient deductibles, copays, and/or coinsurance. One analysis stratified therapies by drug-inferred type (hormonal, *HER2*, cytotoxic, and no systemic therapy), a second on payments from the first chemotherapy claim without concurrent hormonal therapy or trastuzumab claims, and the last on inferred hormone receptor positive disease based on hormonal therapy (oral or infusion) without concurrent chemotherapy.

Table 91-3 shows the results from 7,700 women (with an average age at index of 52 years, and average follow up of 2.2 years) meeting the above definition of metastatic cancer between 2003 and 2009. Stratified by inferred treatment types the cohort included 41% hormonal only therapy, 9% *HER2* treatment with trastuzumab, 29% with at least three months of cytotoxic chemotherapy claims, and 20% with none or less than three months of these cancer-directed therapies (53). Costs were reported as payments per patient per month (PPPM). The average PPPM was $9,800 and, at the average 2.2 years of claims, equates to a lifetime cost of $250,000 per woman! For the three active therapy categories, inpatient hospital costs accounted for 20% to 33% of costs versus about 50% in women receiving no active therapy. Anti-cancer therapy, including anti-emetics, bisphosphonates, and red or white cell growth factors accounted for about 20% in the hormonal only therapy group, 25% in the chemotherapy group, and 49% in the *HER2* group. The average size of the expenditures for all forms of outpatient diagnostics (blood and imaging) of >$20,000 per woman and radiation therapy (for presumed bone or brain metastases) of ~$9,000 were surprisingly high.

Table 91-4 shows the results from the analysis of 1,444 women from their first chemotherapy claim without hormonal or *HER2* therapy (52). This report of care between 2000 and 2006 is useful as it gives resource use averages separate from aggregated payments. During these years, hospitalization became an infrequent event and is likely even lower in 2012—1.7 lifetime admissions for an average of 10.7 days (including end of life) and accounted for only 25% of overall payments. The volume of outpatient unique

TABLE 91-4

Payments for 1,444 Women with Metastatic Disease Receiving Chemotherapy

Category		*Costs, 2006 fl $*
Total Payments		128,600 (95% CI, 118,400–137,600)
Hospitalizations—n, days	1.7, 10.7	**25,400«**
Outpatient Services, total		**37,900**
Office Visits, n	59	2,900
Diagnostic Radiology	*	7,200
Therapeutic Radiology	*	5,000
Other Outpatient Service		17,500
Medications, Total		**65,300**
Chemotherapy		31,600
G-CSF		5,000
ESAs		5,600
Anti-emetics		2,700
Bisphosphonates		2,800
Other meds		17,550

Costs rounded to nearest 100.
«Professional charges for inpatients were not separately reported
*An additional 25 days for hospital outpatient services (such as therapeutic radiology).
Modified from Vera-Llonch M, Weycker D, Glass A, et al. Healthcare costs in women with metastatic breast cancer receiving chemotherapy as their principal treatment modality. *BMC Cancer* 2011;11:250.

visits is the real news—an average of 59 lifetime outpatient visits plus an additional 25 days to hospital outpatient services as well as 6 days of home health or hospice. Overall, medication costs accounted for about 50% of overall care ($65,300 per woman) costs of which about one-half was for cytotoxic chemotherapy. The last report estimated costs incurred for women only receiving hormonal therapy as well as after they transitioned to receiving chemotherapy (54). In this cohort, the combined drug costs after starting chemotherapy accounted for about 2/3 of overall costs.

PALLIATIVE AND END OF LIFE CARE

No reports were found that specifically assessed breast cancer patient patterns or costs of their end of life care. The reader is directed to an analysis of end-of-life care in the U.S. elderly of beneficiaries with cancer from 2003–2007 involving about 215,000 cancer decedents of whom 5.6% had breast cancer (55). Key findings were a commonly high intensity of care in the last month of life (e.g., 30% death in hospital, 64% hospitalized) and late hospice used (median 8 days before death). The intensity for younger women who have been through all available effective therapies is likely even higher.

How to address the societal problem of patients (and their families) having unrealistic expectations and the failure of physicians to be more forthright in their prognosis and resistance to giving futile cancer-directed therapy are beyond the scope of this chapter. The reader is directed to the further discussion of this in Chapter 73 by Jennifer Cheng and Thomas Smith as well as their recent commentary (56).

SUMMARY

Oncology practitioners and their professional organizations are increasingly aware of the need to address the spiraling escalation of cancer care costs. As a broad generalization, most attention has focused on routine measurement and improvement in quality of care metrics without attending to the associated costs. Targets for substantial cost savings need to stratify between initial therapies versus recurrent disease. Obvious targets are for shorter, simpler radiotherapy of the primary site, less (or more targeted) use of adjuvant chemotherapy requiring colony-stimulating factors, sequential monotherapies for advanced disease, and in all situations less imaging. The breast cancer scientific community has been the leader in innovative basic and translational science. The breast cancer practitioner community needs to be leaders in a new dimension of competency—stewardship of financial resources and for practicing in a cost-conscious fashion (57). Stewardship of resources or for practicing in a cost-conscious fashion (57). If not, further erosions of our professional independence, patient choice, access to care, and fewer new therapeutic options will prevail.

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