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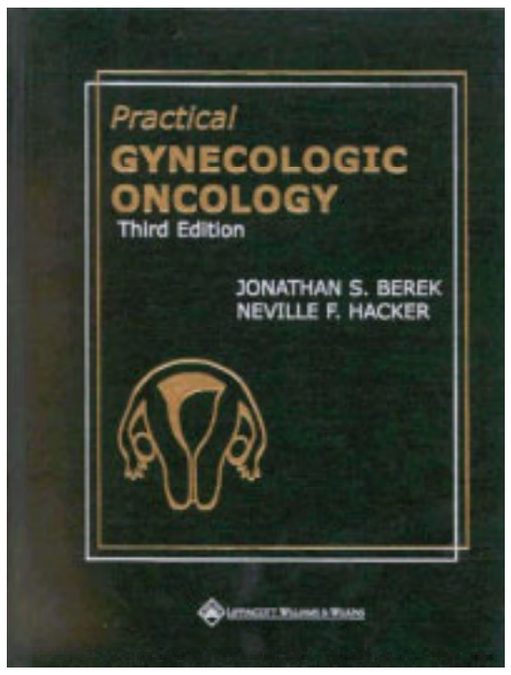

Practical Gynecologic Oncology

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Foreword to the First Edition

Close to the beginning of this century, William Osler observed that “The practice of medicine is an art, based on science.” That brief characterization of our profession rings true even as we approach the next century in the midst of brilliant, accelerating scientific discovery.

Some aspects of the art—including compassion and the basic skills of history taking and physical examination—are, or should be, common to all physicians and remain largely unchanged by a century of research. In other ways the “art,” which can also be translated as “craft” from the original Greek word “techne,” has been greatly enlarged and diversified by science and technology. Thus the special skills required by a gynecologic oncologist derive not only from experience and practice, but also from the proliferation of knowledge in many branches of science. Indeed, it is mainly the developments of science in obstetrics and gynecology—and in some other disciplines—that have evolved the clinical subspecialty of gynecologic oncology.

The art and the science are connected not only by ancestry, however. Their relationship continues to be an interdependent one. One of the ever-expanding glories of medicine is that what is learned in the laboratory can enhance learning at the bedside and what is learned from experience with patients helps to shape and direct scientific inquiry.

Doctors who remain lifelong students are exhilarated by these interconnections and make the best teachers of clinical medicine. It is in this scholarly tradition that Jonathan S. Berek and Neville F. Hacker, with contributions from distinguished colleagues in their own discipline and in fields that bear upon it, have brought together the salient information required to develop the acumen and skills that enable clinicians to understand and to care for women suffering from tumors.

Practical Gynecologic Oncology reflects the indivisibility of art and science in medicine. The two editors—one in Los Angeles and one in Sydney—worked and studied together for 7 years in the same hospital and laboratories and remain mutually helpful intellectual allies on opposite shores of the Pacific Ocean.

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Preface

In many countries over the past quarter of a century gynecologic oncology has achieved recognition as a subspecialty of obstetrics and gynecology. The development and expansion of our professional societies and fellowship programs has been noteworthy. Progress in the basic and clinical sciences, especially in genetics and molecular biology, has led to improvements in the diagnosis and treatment of gynecologic cancers. New discoveries have enhanced the ability of physicians and other health care professionals to care for women with these diseases, giving them improved quality of life and longer survival.

Our Third Edition of *Practical Gynecologic Oncology* incorporates the most recent information while preserving the basic format and style of the previous editions. The book is now divided into four sections: general principles, disease sites, medical and surgical topics, and quality of life. We have written new chapters on biology and genetics, tumor markers and screening, immunology and biologic therapy, pathology, preinvasive disease, cervical cancer, laparoscopy, pelvic exenteration, and communication skills. All other chapters have been thoroughly revised and updated.

The recent literature has been critically reviewed and the most important references have been included in the chapter bibliographies. As we stated in the preface to our First Edition, “This book was written to provide a practical guide to current evaluation and treatment strategies for patients with preinvasive and invasive malignancies of the female genital tract.... We undoubtedly have interjected some personal biases but have tried to justify our points of view with adequate reference to the literature.... The bibliography is not intended to be exhaustive but rather is sufficiently comprehensive to allow each subject to be adequately reviewed.”

This book would not have been possible without the important input from our coauthors, all of whom are internationally acknowledged experts in the field. We are most grateful to Tim Hengst for his outstanding illustrations and drawings. We appreciate the important contribution of our publishers and their staff, especially Lisa McAllister, Ray Reter, and Elaine Verriest. At UCLA, we wish to acknowledge the generosity of our benefactors, especially Nicole Kidman, Tom Cruise, and Jennifer Jones Simon. At the Royal Hospital for Women, we acknowledge the support of our GO Committee, especially Brian McGuigan and Vivian Greig, and the support of Denis Lidis and Steven Eckowitz. At both institutions, the wonderful support of our benefactors has been critical to our gynecologic oncology research and clinical programs.

Our purpose remains unchanged, “the text has been written primarily for fellows undertaking postgraduate training in gynecologic oncology, but it also should be of interest to gynecology residents, consultant gynecologists, and physicians in allied fields whose practice involves a significant component of gynecologic oncology.”

We offer this book to those who strive to improve the care for women with gynecologic malignancies.

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Illustrations by Timothy C. Hengst, CMI, FAMI

Dedication *To our wives, Deborah and Estelle, without whose love and understanding our continued work would not be possible.*

1 Biology and Genetics

G. Larry Maxwell and Andrew Berchuck

Cancer is a complex disease that arises because of genetic alterations that disrupt numerous cellular functions, including proliferation, programmed cell death, and senescence, that ultimately control the number of cells in a population (Fig. 1.1). **The genetic damage that underlies the development of cancers has a diverse etiology, and loss of DNA repair mechanisms may play a role in allowing mutations to accumulate. Cancers also are characterized by the ability to invade surrounding tissues and to metastasize; many of the molecular alterations involved in this process have been elucidated.** The initial sections of this chapter outline what is known about the basic molecular mechanisms involved in the development of cancers and evolution of the malignant phenotype. The molecular alterations characteristic of gynecologic cancers are outlined in the latter sections.

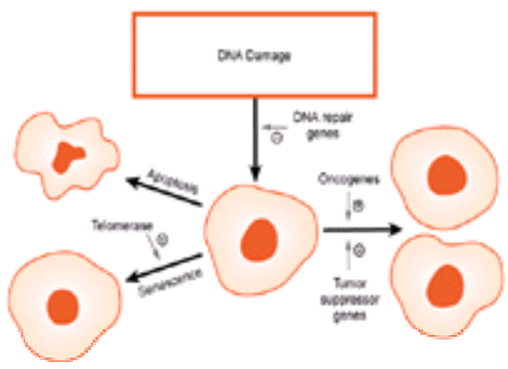

Figure 1.1 Role of proliferation, apoptosis, senescence, and DNA damage in cancer development.

Regulation of Proliferation

The rate of proliferation is a major determinant of the number of cells in a population. To prevent excessive proliferation, DNA synthesis and cell division ordinarily are restrained. When proliferation is appropriate, these inhibitory mechanisms are turned off and growth-stimulatory signals are generated. In some tissues—such as bone marrow—continuous proliferation is required, whereas in other tissues—such as the brain—proliferation rarely occurs.

Malignant tumors are characterized by alterations in genes that control proliferation. There is increased activity of genes involved in stimulating proliferation *(oncogenes)* and loss of growth-inhibitory *(tumor suppressor)* genes. In the past, it was thought that cancer might arise entirely because of more rapid proliferation and/or a higher fraction of cells proliferating. It is now clear that this was an overly simplistic view. Although increased proliferation is a characteristic of many cancers, the fraction of cancer cells actively dividing and the time required to transit the cell cycle are not strikingly different than those seen in some normal cells. Increased proliferation is only one of several factors that contribute to cancerous growth.

Cell Death

Cells are capable of activating a suicide pathway, referred to as *apoptosis.* The term *apoptosis* derives from Greek and alludes to a process akin to leaves dying and falling off a tree. Apoptosis is an active, energy-dependent process that involves cleavage of DNA by endonucleases and proteins by proteases. Morphologically, apoptosis is characterized by condensation of chromatin and cellular shrinkage. This is in contrast to the process of necrosis, which is characterized by loss of osmoregulation and cellular fragmentation. The molecular events that effect cell death in response to various stimuli have been only partially elucidated, but it appears that a family of genes encoding proteins that reside in the mitochondrial membrane are directly involved (1). The *bcl-2* gene was first identified at a translocation breakpoint in B-cell lymphomas, and expression of this gene inhibits apoptosis (2). The *bcl-*X_L gene also inhibits apoptosis, whereas others, such as bax and *bcl-*X_S, have proapoptotic activity. It remains unclear exactly how these mitochondrial proteins act to regulate apoptosis, but those that increase membrane permeability stimulate apoptosis, whereas those that decrease permeability prevent it. Activation of a family of cytosolic proteolytic enzymes called *caspases* also occurs during apoptosis, leading to breakdown of cellular proteins.

Because the size of a population of cells is normally static owing to a balance between the birth and death rates, growth of a neoplasm theoretically could result from either increased proliferation or decreased apoptosis. In addition to restraining the number of cells in a population, apoptosis serves an important role in preventing malignant transformation by specifically eliminating cells that have undergone mutations. After exposure of cells to mutagenic stimuli, including radiation and carcinogenic drugs, the cell cycle is arrested so that DNA damage may be repaired (3). If DNA repair is not sufficient, apoptosis occurs so that cells that have undergone significant damage do not survive (Fig. 1.1). This serves as an anticancer surveillance mechanism by which mutated cells are eliminated before they become fully transformed. **The *p53 tumor suppressor gene* is a critical regulator of cell cycle arrest and apoptosis in response to DNA damage, but apoptosis also may be triggered through other pathways under different circumstances.**

Cellular Senescence

It has long been appreciated that normal cells are capable of undergoing division only a finite number of times before becoming senescent. More recently, it has been shown that cellular senescence is due to a shortening of repetitive DNA sequences (TTAGGG) called *telomeres* that cap the ends of each chromosome. ***Telomeres* are thought to be involved in chromosome stabilization and in preventing recombination during mitosis.** At birth, chromosomes have long telomeric sequences that become progressively shorter each time a cell divides. **Malignant cells appear to avoid senescence by turning on expression of *telomerase* activity, which acts to lengthen the telomeres** (4,5). Telomerase is a ribonucleoprotein complex, and both the protein and RNA subunits have been identified. The RNA component serves as a template for telomere extension and the protein subunit acts to catalyze the synthesis of new telomeric repeats.

Because telomerase is expressed in many tissues primarily during development, it has been suggested that detection of telomerase might be useful for early diagnosis of cancer. ***Telomerase activity* is detectable in a high fraction of many cancers, including ovarian** (6,7 and 8), **cervical** (9,10 and 11), **and endometrial cancers** (12). The utility of telomerase detection as a cancer diagnostic test remains unproven, however. Lack of specificity may be a more significant issue in some organs than in others. In this regard, endometrium is one of the adult tissues in which telomerase expression is most common (13). Perhaps this relates to the need for a large number of lifetime cell divisions because of rapid growth and shedding of this tissue each month during the reproductive years.

Origins of Genetic Damage

Essentially, all human cancers are thought to arise because of a series of genetic alterations that lead to disruption of normal mechanisms governing cell growth, death, and senescence. The origins of genetic damage are diverse. Mutations may be inherited or arise after birth owing to exposure to exogenous carcinogens, or because of endogenous mutagenic processes within the cell (14) (Table 1.1). **In general, the incidence of both hereditary and sporadic cancers increases with aging, because the longer a person is alive, the higher the likelihood of a cell acquiring sufficient genetic damage to become fully transformed. It is thought that at least three to six alterations are required fully to transform a cell.**

Type of Genetic Damage	*Examples*
Hereditary	
Germline mutations in high-penetrance cancer susceptibility genes	*BRCA1* and *BRCA2* DNA repair genes
Exogenous carcinogens	
Ultraviolet radiation	*p53* and other genes in skin cancer
Tobacco	*ras*, *p53*, and others in aerodigestive cancers
Endogenous carcinogens	
Methylation and deamination	*p53* gene in ovarian, breast, and colon cancers
Spontaneous errors in DNA synthesis	Various genes

Table 1.1 Origins of Genetic Damage in Human Cancers

Although most cancers arise sporadically in the population because of acquired genetic damage, inherited mutations in cancer susceptibility genes are responsible for some cancers (15,16 and 17). Families that carry these mutations exhibit a high incidence of specific types of cancers. The age of cancer onset is younger in these families and it is not unusual for some individuals to be affected with multiple primary cancers. Many of the genes involved in hereditary cancer syndromes have been identified (Table 1.2). ***Tumor suppressor genes* have been implicated most frequently in hereditary cancer syndromes, followed by DNA repair genes. In only a few instances are *germline mutations* in *oncogenes* responsible for hereditary cancers.** Although affected individuals carry the germline alteration in every cell of their bodies, cancer susceptibility genes are characterized by a limited repertoire of cancers. Surprisingly, there is no relationship between expression patterns of these genes in various organs and the development of specific types of cancers. For example, *BRCA1* expression is high in the testis, but men who inherit mutations in this gene are not predisposed to development of testicular cancer. In addition, the *penetrance* of these cancer susceptibility genes is incomplete because all individuals who inherit a mutation do not develop cancer. The emergence of cancers in carriers appears to depend on the occurrence of additional genetic alterations.

Syndrome	Gene	Chromosome	Predominant Cancers
Familial breast/ovarian cancer	*BRCA1* *BRCA2*	17q21 13q12	Breast, ovary Breast, ovary
Ataxia-telangiectasia	*AT*	11q22	Breast
Hereditary nonpolyposis colon cancer	*MSH2* *MLH1* *PMS1* *PMS2*	2p16 3p21 2q31 7p22	Colon, endometrium, ovary, and others
Familial polyposis coli	*APC*	5q21	Colonic polyps and cancers
Li-Fraumeni syndrome	*p53*	17p13	Sarcomas, leukemias, breast, brain, and others
Wilms' tumor	*WT1*	11p13	Kidney
von Hippel-Lindau disease	*VHL*	3p25	Kidney and others
Neurofibromatosis	*NF1* *NF2*	17q11 22q12	Neurofibromas Neurofibromas
Retinoblastoma	*Rb*	13q14	Retinoblastoma, sarcomas
Familial melanoma	*p16*	9p21	Melanoma
Multiple endocrine neoplasia type 2	*ret**	10q11	Thyroid, adrenal, parathyroid
Hereditary papillary renal carcinoma	*met**	7q31	Papillary kidney

*Oncogenes.

Table 1.2 Hereditary Cancer Syndromes

The etiology of acquired genetic damage also has been elucidated to some extent. For example, a strong causal link exists between cigarette smoke and cancers of the aerodigestive tract and between ultraviolet radiation and skin cancer. For many common forms of cancer (e.g., colon, breast, endometrium, ovary), however, a strong association with specific carcinogens does not exist. It is thought that the genetic alterations responsible for these cancers may arise from endogenous mutagenic processes such as *methylation, deamination*, and *hydrolysis* of DNA (18). In addition, spontaneous errors in DNA synthesis may occur during the process of DNA replication associated with normal proliferation (19,20). Although DNA is synthesized with a high level of fidelity, it is estimated that errors occur approximately once every million base pairs. Several families of DNA repair genes exist, but some types of mutations more readily elude detection and repair. In addition, the efficiency of these DNA repair systems may vary between individuals because of inherited differences in activity of various alleles of DNA repair genes.

Oncogenes

It has been convincingly demonstrated that alterations in genes that stimulate cellular growth *(oncogenes)* can cause malignant transformation. Oncogenes can be activated through several mechanisms. In some cancers, amplification of oncogenes with resultant overexpression of the corresponding protein has been noted. Instead of two copies of one of these genes, there may be as many as 40 copies. Some oncogenes may become overactive when affected by *point mutations*. Finally, oncogenes may be *translocated* from one chromosomal location to another and then come under the influence of promoter sequences that cause overexpression of the gene. This mechanism frequently occurs in leukemias and lymphomas, but has not been demonstrated in gynecologic cancers or other solid tumors. In cell culture systems in the laboratory, many genes that are involved in normal growth-regulatory pathways can elicit transformation when altered to overactive forms by amplification, mutation, or translocation. On this basis, a large number of genes have been classified as oncogenes (Fig. 1.2, Table 1.3). Studies in human cancers have suggested that the actual spectrum of genes altered in the development of human cancers may be more limited, however. A number of genes that elicit transformation when activated *in vitro* have not been documented to undergo alterations in human cancers. In this section, the various classes of oncogenes are summarized and particular attention is paid to those that are altered in gynecologic cancers.

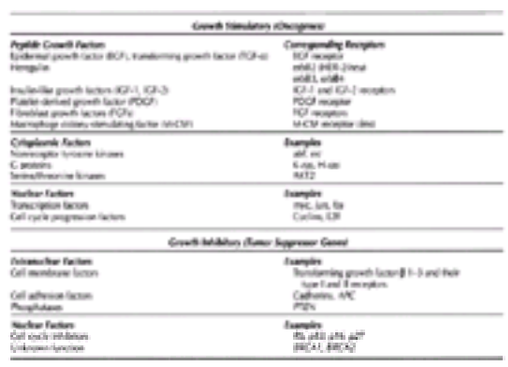

Table 1.3 Classes of Genes Involved in Growth-Regulatory Pathways and Malignant Transformation

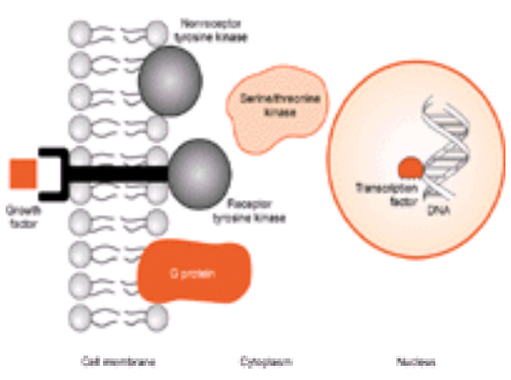

Figure 1.2 Potential sites of action of oncogenes.

Peptide Growth Factors and Their Receptors

By binding to cell membrane receptors, peptide growth factors in the extracellular space can stimulate a cascade of molecular events that leads to proliferation. Unlike endocrine hormones, which are secreted into the bloodstream to act on distant target organs, peptide growth factors usually act in the local environment where they have been secreted. The concept that *autocrine growth stimulation* might be a key strategy by which cancer cell proliferation becomes autonomous is intellectually appealing and has received considerable attention. In this model, it is postulated that cancers secrete stimulatory growth factors that then interact with receptors on the same cell. Although increased production of stimulatory growth factors may play a role in enhancing proliferation associated with malignant transformation, these factors also are involved in development, stromal-epithelial communication, tissue regeneration, and wound healing.

Cell membrane receptors that bind peptide growth factors are composed of an *extracellular ligand binding domain*, a membrane-spanning region, and a cytoplasmic *tyrosine kinase domain*. Binding of a growth factor to the extracellular domain results in aggregation and conformational shifts in the receptor and activation of the inner tyrosine kinase (21,22). This kinase phosphorylates tyrosine residues on both the growth factor receptor *(autophosphorylation)* and targets in the cell interior, leading to activation of secondary signals. For example, phosphorylation of phospholipase C leads to breakdown of cell membrane phospholipids and generation of diacylglycerol and inositol triphosphate, both of which play a role in propagation of the mitogenic signal.

More than a dozen receptor tyrosine kinases have been identified that bind peptide growth factors (Table 1.3). Although peptide growth factors accelerate cellular proliferation and likely are requisite for growth, there is little evidence to suggest that overproduction of growth factors is a precipitating event in the development of gynecologic cancers. Peptide growth factors may function as necessary cofactors rather than as the driving force behind malignant transformation. On the other hand, there is clear evidence that overexpression of growth factor receptors occurs in some cancers.

Extranuclear Signal Transduction

After peptide growth factors and their receptors interact, secondary molecular signals are generated to transmit the mitogenic stimulus toward the nucleus. This function is served by a multitude of complex and overlapping signal transduction pathways that occur in the inner cell membrane and cytoplasm. Many of these signals involve phosphorylation of proteins by enzymes known as *kinases* (23). Cellular processes other than growth also are regulated by kinases, but one family of kinases appears to have evolved specifically for the purpose of transmitting growth-stimulatory signals. These tyrosine kinases transfer a phosphate group from adenosine triphosphate to tyrosine residues of target proteins (Fig. 1.3). Some kinases that phosphorylate proteins on serine and/or threonine residues also are involved in stimulating proliferation. The activity of kinases is regulated by phosphatases, which act in opposition to the kinases by removing phosphates from the target proteins (24). Although several families of intracellular kinases have been identified that can elicit transformation when activated *in vitro*, it remains uncertain whether structural alterations in these molecules play a key role in the development of human cancers.

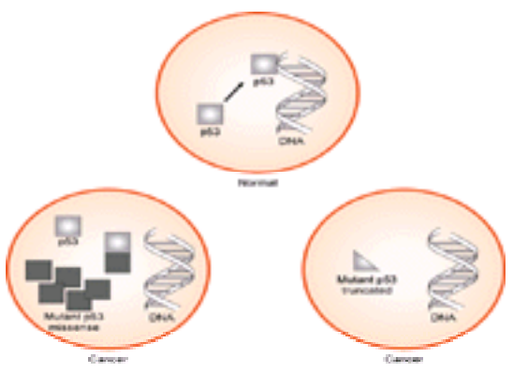

Figure 1.3 Inactivation of the *p53* tumor suppressor gene by "dominant negative" missense mutation or by truncation mutation and deletion.

G proteins represent another class of molecules involved in transmission of growth-stimulatory signals toward the nucleus (25,26). They are located on the inner aspect of the cell membrane and have intrinsic guanosine triphosphatase (GTPase) activity that catalyzes the exchange of GTP for guanosine diphosphate (GDP). In their active, GTP-bound form, G proteins interact with kinases that are involved in relaying the mitogenic signal. Conversely, hydrolysis of GTP to GDP, which is stimulated by GTPase activating proteins, leads to inactivation of G proteins. G protein genes of the *ras* family are among the most frequently mutated oncogenes in human cancers (e.g., gastrointestinal and endometrial cancers). Activation of ras genes usually involves point mutations in codons 12, 13, or 61 that result in constitutively activated molecules.

Nuclear Factors

If proliferation is to occur in response to signals generated in the cytoplasm, these events must lead to activation of nuclear factors responsible for DNA replication and cell division. Expression of several genes that encode nuclear proteins increases dramatically within minutes of treatment of normal cells with peptide growth factors. Once induced, the products of these genes bind to specific DNA regulatory elements and induce transcription of genes involved in DNA synthesis and cell division. When inappropriately overexpressed, however, these transcription factors can act as oncogenes. Among the nuclear transcription factors involved in stimulating proliferation, amplification of members of the *myc* gene family has most often been implicated in the development of human cancers (27).

Tumor Suppressor Genes

Loss of tumor suppressor gene function also plays a role in the development of most cancers. This usually involves a two-step process in which both copies of a tumor suppressor gene are inactivated. In most cases, there is mutation of one copy of a tumor suppressor gene and loss of the other copy because of deletion of a large segment of the chromosome where the gene resides. There is also evidence that some tumor suppressor genes may be inactivated by methylation of the promoter region of the gene (28). The promoter is an area proximal to the coding sequence that regulates whether the gene is transcribed from DNA into RNA. When the promoter is methylated, it is resistant to activation and the gene is essentially silenced despite remaining structurally intact. Like oncogenes, tumor suppressor gene products are found throughout the cell. In this section, the various classes of tumor suppressor gene products are reviewed, with particular attention paid to those involved in gynecologic cancers.

Nuclear Tumor Suppressor Genes

The *retinoblastoma gene (Rb)* was the first tumor suppressor gene discovered (29,30). In the G_1 phase of the cell cycle, Rb protein binds to the *E2F transcription factor* and prevents it from activating transcription of other genes involved in cell cycle progression. When Rb is phosphorylated, E2F is released and stimulates entry into the DNA synthesis phase of the cell cycle. The phosphorylation of Rb is regulated by a complex series of events that involves *cyclins, cyclin-dependent kinases (cdks)*, and *cdk inhibitors* such as *p16* (28). Other cyclins and related pathways are involved in regulating progression from G_2 to mitosis. Mutations in the *Rb* gene have been noted primarily in retinoblastomas and sarcomas, but rarely in other types of cancers. Inactivation of the *p16 tumor suppressor gene* by deletions or promoter methylation also occurs in some cancers, and it is thought that this may preclude the need for direct mutation of *Rb* (28).

Mutation of the *p53 tumor suppressor gene* is the most frequent genetic event described thus far in human cancers (31,32 and 33) (Fig. 1.3). The *p53* gene encodes a 393–amino-acid protein that appears to play a central role in the regulation of both proliferation and apoptosis (34,35 and 36). In normal cells, p53 protein resides in the nucleus and exerts its tumor suppressor activity by binding to transcriptional regulatory elements of genes, such as the *cdk inhibitor p21*, that act to arrest cells in G_1. Beyond simply inhibiting proliferation, normal p53 is thought to play a role in preventing cancer by stimulating apoptosis of cells that have undergone excessive genetic damage (37). In this regard, p53 has been described as the "guardian of the genome" because it delays entry into S phase until the genome has been cleansed of mutations. If DNA repair is inadequate, p53 may initiate apoptosis, thereby eliminating cells with genetic damage.

Many cancers have *missense mutations* in one copy of the *p53* gene that result in substitution of a single amino acid in exons 5 through 8, which encode the DNA binding domains. Although these mutant *p53* genes encode full-length proteins, they are unable to bind to DNA and regulate transcription of other genes. Mutation of one copy of the *p53* gene often is accompanied by deletion of the other copy, leaving the cancer cell with only mutant p53 protein. If the cancer cell retains one normal copy of the *p53* gene, mutant p53 protein can complex with wild-type p53 protein and prevent it from interacting with DNA. Because inactivation of both *p53* alleles is not required for loss of p53 function, mutant *p53* is said to act in a "dominant negative" fashion. Although normal cells have low levels of p53 protein because it is rapidly degraded, missense mutations encode protein products that are resistant to degradation and overaccumulate in the nucleus, and overexpression of mutant p53 protein can be detected immunohistochemically. A smaller fraction of cancers have mutations in the *p53* gene that encode truncated protein products (38). In these cases, loss of the other allele occurs as the second event, as is seen with other tumor suppressor genes.

Extranuclear Tumor Suppressor Genes

Although most tumor suppressor gene products are nuclear proteins, some extranuclear tumor suppressors have been identified. Theoretically, any protein that normally is involved in inhibition of proliferation could conceivably act as a tumor suppressor. In this regard, phosphatases that normally oppose the action of the tyrosine kinases by dephosphorylating tyrosine residues are appealing candidates (24). Analysis of deletions on chromosome 10q23 in human cancers led to the discovery of the *PTEN gene* (39,40 and 41). In addition to its phosphatase activity, it is homologous to the cytoskeleton proteins *tensin* and *auxin*, and it has been postulated that PTEN might act to inhibit invasion and metastasis through modulation of the cytoskeleton (39). The *APC* gene product is involved in cellular adhesion rather than directly in regulating growth, but has also been classified as a tumor suppressor gene because loss of this gene facilitates malignant transformation.

Invasion and Metastasis

Although alterations in growth-regulatory genes are responsible for the development of cancers, most are fatal because of metastatic spread rather than local growth. This process is characterized by several steps, including loss of adhesion, degradation of the surrounding stroma, migration, and neovascularization (42,43). Many of the molecular events involved in invasion and metastasis have been elucidated and are described in the following sections (Fig. 1.4).

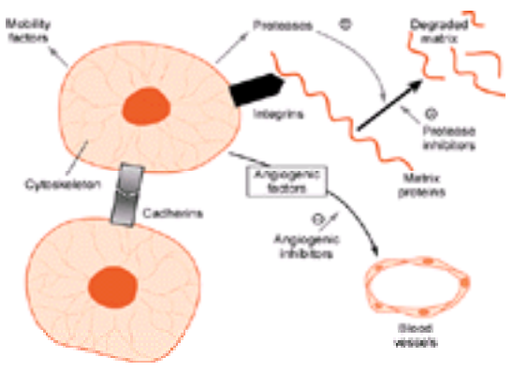

Figure 1.4 Molecular pathways involved in invasion and metastasis.

Loss of Adhesion

The orderly arrangement of cells in normal tissues is due to the interaction of cell–cell and cell–stroma adhesion molecules. In cancers, expression of these adhesion molecules is altered, resulting in breakdown of this normal homeostatic mechanism. *Integrins* are a family of heterodimeric transmembrane adhesion receptors that include two covalently bound subunits (44,45). Approximately 15 b subunits and 9 a subunits have been identified, and at least 21 receptor combinations exist. The extracellular domain of integrins binds to matrix proteins such as *collagens, laminin, vitonectin*, and *fibronectin* that express a specific three–amino-acid sequence (arginine-glycine-aspartic acid). The intracellular domains of integrins interact with cytoskeletal components and are actively involved in generating intracellular signals. **Changes in the pattern of integrin expression are seen in cancers and likely facilitate invasion and metastasis.**

Cadherins are a superfamily of cell surface glycoproteins sharing a common extracellular 110–amino-acid "cadherin" domain. *E-cadherins* are the subgroup predominantly found in epithelial cells (46). These transmembrane proteins mediate cell–cell adhesion: cadherins on neighboring cells preferentially bind to the same types of cadherins on adjacent cells. Cadherin dysfunction is associated with loss of cell–cell cohesion, altered cellular motility, and increased invasiveness and metastatic potential. E-cadherin mutations occur only rarely (47), but cadherin expression may also be downregulated in the absence of mutations. The cytoplasmic tails of cadherins exist as a macromolecular complex with b-catenin, which is involved in signaling pathways that result in transcriptional activation (48). Regulation of b-catenin activity also is dependent on the adenomatous polyposis coli (APC) gene product. Mutations in the *APC* gene that abrogate its ability to inhibit b-catenin activity are common in both the hereditary APC syndrome and sporadic colon cancers (49). Mutations in the b-*catenin* gene that result in constitutively activated molecules also have been observed in some cancers, including endometrial cancers (50).

Invasion

Lysis of the basement membrane and matrix proteins such as collagen, laminin, and fibronectin is required for tumor cell invasion and migration (42,43). Breakdown of the extracellular matrix is mediated by a family of *metalloproteinases (MMPs)* that are characterized by a zinc atom at their active site (51). These proteins are involved in tissue modeling during development as well as in implantation of the placenta and other normal physiologic processes. At least 15 different MMPs have been identified, as have a family of *metalloproteinase antagonists (TIMPs 1 through 4)* that inhibit MMP activity. Increased MMP activity has been associated with a number of cancers, implicating loss of MMP regulation as a mechanism associated with the invasive phenotype. Elevated levels of MMPs have been detected in endometrial, cervical, and ovarian cancer cell lines (52). Preclinical trials using the TIMPs *batimastat* and *marimastat* to inhibit tumor cell invasion have been promising (53).

In addition to degradation of the extracellular matrix, cancer cell motility is an important component of the invasion process (42,43). A number of autocrine motility factors such as *insulin-like growth factor (IGF-2)* and *autotaxin* have been identified that are secreted by cancer cells. In addition, paracrine chemotactic factors such as *histamine* and *IGF-1* may be secreted by surrounding normal cells. Finally, matrix proteins aid cancer cell motility by their interaction with cell surface integrins.

Angiogenesis

The growth of cancer cells depends on diffusion of nutrients from the surrounding stroma. **Expansion of a solid tumor beyond 1 mm^3 requires neovascularization** (42,43,54,55). **These new blood vessels also provide a route by which cancer cells can metastasize, and a correlation has been observed between high vessel density and poor survival in gynecologic cancers** (56,57). Tumor angiogenesis requires proliferation and migration of endothelial cells and is stimulated by several cytokines, including the *fibroblast growth factor (FGF)* family, *angiogenein, endothelial cell growth factor*, and *vascular endothelial growth factor (VEGF).* A number of inhibitors of angiogenesis, including angiostatin, also have been described. Several groups are exploring the potential clinical utility of antiangiogenic cancer therapy. Strategies under investigation include antibodies that neutralize proangiogenic factors like VEGF, or administration of antiangiogenic compounds. Even if inhibition of angiogenesis does not dramatically shrink cancers, it might be useful for maintenance therapy after most of the cancer is eradicated using conventional modalities such as chemotherapy.

Gynecologic Malignancies

Cancer is a heterogeneous disease with respect to clinical features such as tumor grade, histology, stage, response to treatment, and survival. It is now appreciated that there also is a great deal of heterogeneity with respect to the genetic basis of cancers. Some cancers arise in the setting of an inherited mutation in a cancer susceptibility gene such as *BRCA1*, but most occur sporadically in the absence of a strong hereditary predisposition. The spectrum of genes that are mutated varies strikingly between various types of cancers. There also is significant variety with respect to the spectrum of genetic changes in a given type of cancer. Cancers with an identical microscopic appearance may share little in common at a genetic level. In some instances, however, it appears that molecular features may be predictive of clinical features such as stage, histologic type, and survival. As we gain a more complete understanding of the clinical implications of various genetic alterations in gynecologic cancers, the molecular profile may prove valuable in predicting clinical behavior and response to treatment.

Endometrial Cancer

Epidemiologic studies have demonstrated that unopposed estrogen is the strongest risk factor for the development of endometrial cancer. The mechanism by which estrogen acts as a carcinogen is not completely clear. It has long been believed that estrogens may contribute to the development of endometrial cancer by virtue of their mitogenic effect on the endometrium. A higher rate of proliferation in the endometrium in response to estrogens may lead to an increased frequency of spontaneous mutations. In addition, when genetic damage occurs, regardless of the cause, the presence of estrogens may facilitate clonal expansion. It also has been postulated that estrogens may act as "complete carcinogens" in the sense that they may act both as initiation factors, because of the carcinogenic effect of certain estrogenic metabolites, and as tumor promoters because of their ability to enhance proliferation.

The first evidence that genetic alterations occur during the process of endometrial carcinogenesis came from studies of total cellular DNA content *(ploidy)* and cytogenetic analyses. Approximately 20% of endometrial adenocarcinomas have an increased DNA content *(aneuploidy)* relative to normal cells (58). Aneuploidy is associated with advanced stage, adverse histologic features, and poor survival. In addition, cytogenetic studies have described gross chromosomal alterations in endometrial cancers, including changes in the number of copies of specific chromosomes (59). Alterations in specific cancer-causing genes have been described. Some of these genetic alterations are characteristic of *"type I" estrogen-dependent endometrial cancers*, whereas others are associated with the more virulent *"type II" endometrial cancers* (Table 1.4).

	Class	Activation	Approximate Frequency	Type I/II*
Hereditary				
hMSH2	DNA repair	Mutation	Rare	I
hMLH1	DNA repair	Mutation	Rare	I
Sporadic Oncogenes				
HER-2/neu	Tyrosine kinase	Amplification/overexpression	10%	II
c-fms	Tyrosine kinase	Overexpression	?	II
K-ras	G protein	Mutation	10%–30%	II
c-myc	Transcription factor	Amplification/overexpression	20%–30%	I
Tumor Suppressor Genes				
p53	Transcription factor	Mutation/overexpression	20%	II
PTEN	Tyrosine phosphatase	Mutation	40%	I

*Type I: well-differentiated, endometrioid, estrogen-associated cancers; type II: poorly differentiated, non-endometrioid cancers.

Table 1.4 Genetic Alterations in Endometrial Adenocarcinomas

Oncogenes

Alterations in several oncogenes have been demonstrated in endometrial cancers. **Overexpression of HER-2/*neu* receptor tyrosine kinase has been noted in 10% to 15% of endometrial cancers** (58,60,61,62,63,64 and 65) **and is associated with advanced stage and poor outcome.** In one of the largest studies to date, the group at the Mayo Clinic performed a study of HER-2/*neu* expression in 247 endometrial cancers (61). Expression was scored as high in 15% of cases, mild in 58%, and absent in 27%; 5-year progression-free survival rates were 56%, 83%, and 95% in these groups, respectively. Among stage I cases, 13% had high expression of HER-2/*neu* and the 5-year progression-free survival rate was 62%, compared with 97% in cases with lesser expression. The incidence of overexpression was higher in advanced-stage cases (25%). Multivariate analysis revealed that high expression was an independent variable associated with poor survival.

The *fms* oncogene encodes a tyrosine kinase that serves as a receptor for *macrophage colony-stimulating factor (M-CSF).* Expression of *fms* in endometrial cancers was found to correlate with advanced stage, poor grade, and deep myometrial invasion (66,67). Subsequently, it was shown that *fms* and its ligand (M-CSF) usually were coexpressed in endometrial cancers, and it was proposed that this receptor–ligand pair might mediate an autocrine growth-stimulatory pathway (68). In support of this hypothesis, M-CSF serum levels are increased in patients with endometrial cancer. In addition, M-CSF increases the invasiveness of cancer cell lines that express significant levels of *fms*, but has no effect on cell lines with low levels of the receptor (69).

The K-*ras* oncogene undergoes point mutations in codons 12, 13, or 61 that result in constitutively activated molecules in many types of cancers. Boyd et al. (70) examined codons 12, 13, and 61 of the K-*ras*, H-*ras*, and N-*ras* genes in 11 immortalized endometrial cancer cell lines. Mutations in codon 12 of K-*ras* were seen in four cell lines, whereas three had mutations in codon 61 of H-*ras.* Similarly, they also examined codons 12, 13, and 61 of the three *ras* genes in ten primary endometrial cancers (71). A mutation in codon 12 of K-*ras* was found in one case, whereas the other *ras* genes were not mutated. Subsequent studies of primary endometrial adenocarcinomas have confirmed that codon 12 of K-*ras* is mutated in 10% to 20% of cases (71,72,73,74,75,76,77 and 78). There does not appear to be a strong relationship between K-*ras* mutation and clinical behavior of endometrial cancers. K-*ras* mutations also have been identified in some endometrial hyperplasias (73,76,78), however, which suggests that this may be a relatively early event in the development of some endometrial cancers.

Among the nuclear transcription factors involved in stimulating proliferation, amplification of members of the *myc* family has most often been implicated in the development of human cancers. It has been shown that c-*myc* is expressed in normal endometrium (79) and endometriosis (80), with higher expression in the proliferative phase relative to the secretory phase. Several studies have suggested that c-*myc* may be amplified in a fraction of endometrial cancers (62,81).

Tumor Suppressor Genes

Loss of *p53* tumor suppressor gene function is among the most frequent genetic events described thus far in human cancers, and alterations in this gene are common in endometrial cancers (31). In an initial study, we found that mutant p53 protein was overexpressed in 20% of primary endometrial adenocarcinomas, including 9% of stage I/II and 41% of stage III/IV cancers (82). p53 overexpression was associated with several known prognostic factors, including advanced stage, poor grade, and nonendometrioid histologic type (58,82). In addition, **survival of patients whose cancers overexpressed p53 was worse than that of patients whose cancers did not overexpress p53.** Numerous other studies have confirmed the strong association between p53 overexpression and high-risk pathologic features and poor survival (65,83,84,85,86,87 and 88). In more recent studies, p53 overexpression has been demonstrated to be associated with worse survival even after controlling for stage (89,90). This suggests that loss of p53 tumor suppressor function confers a particularly virulent phenotype. Although little is known regarding molecular alterations in uterine sarcomas, we found that overexpression of mutant p53 frequently occurs in mixed mesodermal sarcomas of the uterus (74%) (91).

Endometrial cancers that overexpress p53 protein have been shown to harbor *missense mutations* in conserved regions of exons 5 through 8 of the gene that result in amino acid substitutions in the protein (74,82,92,93 and 94). These mutations lead to loss of DNA binding activity. Because *p53* mutations rarely, if ever, occur in endometrial hyperplasias (74,95), this may represent a relatively late event in the development of endometrioid endometrial cancers. Alternatively, it is possible that acquisition of a *p53* mutation leads to development of a virulent, poorly differentiated and/or serous endometrial cancer that does not pass through a phase of hyperplasia and is associated with rapid spread of disease. Tashiro et al. (96) found that both papillary serous carcinoma and its putative endometrial surface precursor demonstrated p53 overexpression in 90% and 78% of cases, respectively.

Mutations in the *PTEN tumor suppressor gene* on chromosome 10q occur in approximately 30% to 50% of endometrial cancers (97,98 and 99), **and this represents the most frequent genetic alteration described thus far in these cancers.** Most of these mutations are deletions, insertions, and nonsense mutations that lead to truncated protein products, whereas only approximately 15% are missense mutations that change a single amino acid in the critical phosphatase domain. Mutations in the *PTEN* gene are associated with endometrioid histologic type, early stage, and favorable clinical behavior (100). In addition, *PTEN* mutations have been observed in 20% of endometrial hyperplasias, suggesting that this is an early event in the development of some endometrioid endometrial cancers (101). Because *PTEN* mutations are frequent in endometrial cancers with mircosatellite instability, it is thought that some mutations in *PTEN* may arise due to loss of DNA repair activity.

DNA Repair Genes

***Microsatellite DNA sequences* consist of repetitive tracts that are widely dispersed throughout the genome.** Some microsatellites are within the coding sequence of genes, but most are located in the noncoding DNA between genes. These nucleotide repeats may be mono (e.g., AAAAA), di (e.g., CACACA), tri (e.g., CCGCCGCCG), tetra (CAAACAAACAAA), or higher-order repeats. Because of their repetitive structure, microsatellites are particularly susceptible to mutation during DNA replication. Approximately 20% of endometrial cancers have been found to contain mutant microsatellite alleles that do not correspond in size to either inherited allele (102,103 and 104). **Endometrial cancers that exhibit these microsatellite mutations, also called *microsatellite instability*, are usually type I cancers and have a favorable prognosis.**

Microsatellite instability initially was noted in colorectal cancers of patients with *hereditary nonpolyposis colorectal cancer (HNPCC)*, also known as *Lynch syndrome type II* (105,106). Endometrial cancer is the second most common malignancy observed in these families, but ovarian, gastrointestinal, and upper urinary tract malignancies also occur. Subsequently, it was shown that affected members of HNPCC families carry germline mutations in one of a family of DNA repair genes. The *MSH2* gene on chromosome 2p and the *MLH1* gene on chromosome 3p account for most HNPCC families, but at least two other DNA repair genes (*PMS1* and *PMS2*) also have been implicated (107,108 and 109). In bacteria and yeast, mutations in these DNA repair enzymes also lead to microsatellite instability, confirming the cause-and-effect relationship between these events.

In families in which early-onset colon cancer occurs along with other cancers, including endometrial cancer, genetic testing for mutations in DNA repair genes is appropriate. In one study of several kindreds in which *MSH2* or *MLH1* mutations had been identified, the lifetime risk in women of endometrial cancer (42%) exceeded the risk of colon cancer (30%) (109). In contrast, the lifetime risk of colorectal cancer in men was 74%. Early diagnosis and prevention of colon, endometrial, and other associated cancers is an important issue in families with germline mutations in DNA repair genes. The role of colonoscopy versus prophylactic colectomy remains controversial. Screening endometrial biopsies have been advocated and a hysterectomy should be performed in female carriers in whom colectomy is undertaken.

Because microsatellite instability has been noted in some sporadic endometrial cancers in women who do not carry germline DNA repair gene mutations (102), several groups have attempted to identify acquired mutations in these genes. Although sporadic DNA repair gene mutations have been found in some endometrial cancers with microsatellite instability, in most cases mutations have not been found (110,111 and 112). It is possible, however, that additional DNA repair genes that have not yet been identified may underlie microsatellite instability in some cases.

In addition to causing harmless damage to microsatellite sequences in noncoding regions of the genome, inherited or acquired loss of DNA repair mechanisms may lead to accumulation of genetic damage in growth-regulatory genes that have microsatellite sequences in their coding regions. In this regard, mutations in several growth-regulatory genes, including K-*ras* (103), *PTEN* (97), and the gene for the IGF-2 receptor (113), are more frequent in endometrial cancers with microsatellite instability. Thus, loss of DNA repair efficiency may be an initial event that increases the likelihood of malignant progression due to alterations in oncogenes and tumor suppressor genes.

Ovarian Cancer

Epidemiologic and molecular studies have shed some light on the etiology of ovarian cancer. **Approximately 10% of ovarian cancers arise in women who carry mutations in cancer susceptibility genes. A series of genetic alterations appears to be requisite for the development of both sporadic and hereditary ovarian cancers, however.** The causes of acquired genetic damage in the ovarian epithelium remain uncertain, but exogenous carcinogens have not been strongly implicated. Some mutations may arise spontaneously because of increased epithelial proliferation required to repair ovulatory defects. In this regard, epidemiologic studies have shown that reproductive events that decrease lifetime ovulatory cycles (e.g., pregnancy and birth control pills) are protective against ovarian cancer (114). The protective effect of these factors is greater in magnitude than would be predicted based on the extent that ovulation is interrupted. Five years of oral contraceptive use decreases risk by approximately 50%, but decreases total years of ovulation by only approximately 10% to 20%. There is evidence to suggest that the progestagenic milieu of pregnancy and the pill might also protect against ovarian cancer by increasing apoptosis of ovarian epithelial cells, thereby cleansing the ovary of cells that have acquired genetic damage (115). The action of other reproductive hormones such as estrogens and gonadotropins also may contribute to the development of ovarian cancers.

Hereditary Ovarian Cancer

Most hereditary ovarian cancers appear to be due to inherited mutations in the *BRCA1* breast/ovarian cancer susceptibility gene (16,17,116) (Fig. 1.5). The *BRCA1* gene, identified on chromosome 17q in 1994, encodes a protein of 1,863 amino acids whose cellular function remains poorly understood. The finding that the *BRCA1* gene complexes with the Rad51 protein suggests that it might play a role in DNA repair (117). ***BRCA1* has been classified as a tumor suppressor gene** because the normal copy of *BRCA1* is invariably deleted in breast and ovarian cancers that arise in women who inherit a mutant *BRCA1* gene (118).

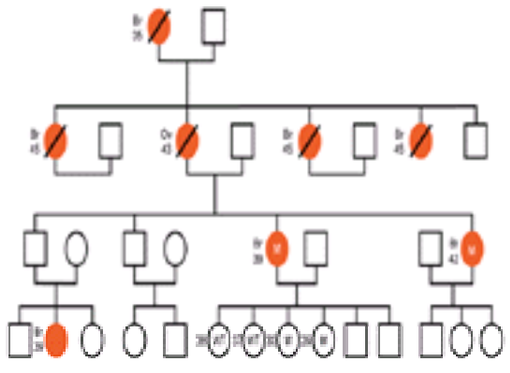

Figure 1.5 Familial ovarian cancer pedigree with *BRCA1* mutation. The age of family members at diagnosis and type of cancers are noted. *Solid circles* represent individuals affected with cancer, and slashes denote those who have died of cancer. Individuals denoted *M* have the 5382 insert C mutation in *BRCA1*, whereas those denoted *WT* have normal *BRCA1.*

The histologic features of ovarian cancers in *BRCA1* carriers do not differ strikingly from sporadic cancers. Most cases are advanced-stage, moderate to poorly differentiated, serous cancers (118,119,120 and 121). In one initial study, survival of *BRCA1* carriers with ovarian cancer was better than that of a control group of sporadic cases that was matched for age, stage, and other prognostic factors (122). Some subsequent studies have not confirmed the association with favorable prognosis (123), but none of the studies performed to date is adequate to allow for definitive conclusions.

The most recent population-based studies have suggested that the lifetime risk of ovarian cancer is approximately 20% to 30% in *BRCA1* carriers, but this increased risk is not manifest until approximately 40 years of age (124). It is unclear why ovarian cancer develops in only a fraction of women who carry *BRCA1* mutations. It has been postulated that incomplete penetrance may be due to the effect of modifying genes or gene–environment interactions (e.g., birth control pill use) (125). In some series, mutations in the carboxy terminus of *BRCA1* have been associated with a higher frequency of breast cancer relative to ovarian cancer (126). Conversely, mutations in the proximal amino terminal of the gene resulted in a higher likelihood of development of ovarian cancer. This observation has not been confirmed by the group at Myriad Genetic Laboratories, however (127). They identified 102 *BRCA1* mutations in 798 high-risk families, but there was no relationship between proximal mutations and a higher risk of ovarian cancer. Further studies are needed to examine whether a genotype–phenotype correlation exists.

The second breast/ovarian cancer susceptibility gene *(BRCA2)* was identified on chromosome 13q in 1995. *BRCA2* is a large gene that is not closely related structurally to other known genes, and its role in normal breast and ovarian epithelium remains unclear. Both male and female *BRCA2* carriers have a high risk of early-onset breast cancer (128,129). **Ovarian cancer initially appeared to be a much less prominent feature of *BRCA2* families, but it is now thought that as much as 35% of hereditary ovarian cancer may be attributable to *BRCA2*** (130). Some studies have suggested that ovarian cancer may occur more often in families with truncation mutations in exon 11 (131). Because ovarian cancer is less frequent in *BRCA2* families than in *BRCA1* families, large series that examine the clinicopathologic features of *BRCA2*-associated ovarian cancers have not yet been reported.

A report from the Breast Cancer Linkage Consortium included 94 families with ovarian cancer (132). *BRCA1* mutations were identified in 81% of families, whereas *BRCA2* mutations were found in 14%. The risk of ovarian cancer in *BRCA2* carriers was only 0.4% by 50 years of age, but rose to 27% by 70 years of age. At Myriad Genetic Laboratories, both the *BRCA1* and *BRCA2* genes were sequenced in 38 probands from high-risk families that included at least one ovarian cancer and one early-onset breast cancer in first-or second-degree relatives (130). Mutations were found in *BRCA1* in 16 cases and in *BRCA2* in 8 cases. Although in 14 families no clearly deleterious mutation was detected, some had

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Mutations have been observed throughout the entire *BRCA1* and *BRCA2* genes, and approximately 80% to 90% predict truncated protein products (127,130). Missense mutations that encode a full-length protein product in which only a single amino acid is altered occur in approximately 10% to 15% of hereditary cases. In some families it may be unclear whether a missense change represents a disease-causing mutation or an insignificant polymorphism. Segregation of a missense alteration with breast and ovarian cancer in a family suggests, but does not prove, its significance. In small families and families in which some individuals decline testing, segregation analysis may not be possible, however.

Because mutations in *BRCA1* and *BRCA2* occur throughout the entire coding sequence, the most reliable method of detecting mutations is complete gene sequencing. The effort and cost involved in sequencing these large genes is relatively high, however, and it remains impractical to perform mutational analysis in low-risk individuals. **The probability of finding a *BRCA1* or *BRCA2* mutation in a woman older than 50 years of age who is the only person in her family with ovarian or breast cancer is less than 3%. At the other extreme, in families with two cases of breast cancer and two cases of ovarian cancer, the probability of finding a mutation may be as high as 80%** (127,130) (Table 1.5). **Those who believe that it is reasonable to test "high-risk" individuals usually advocate testing when the family history suggests at least a 10% probability of finding a mutation. In practical terms, this translates into two first- or second-degree relatives with either ovarian cancer at any age or breast cancer before 50 years of age** (see Chapter 11). It is preferable to begin by testing individuals in a high-risk family who already have been affected by cancer, because a negative test in an unaffected individual may reflect failure to inherit the mutant allele even though others in the family carry a mutation. When a specific mutation is identified in an affected individual, others in the family can be tested much more rapidly and inexpensively.

Two or more first- or second-degree relatives with breast or ovarian cancer
Early onset of breast cancer (20–40 years of age)
Early onset of ovarian cancer (30–50 years of age)
Male breast cancer (*BRCA2* only)
Ashkenazi Jewish heritage

Table 1.5 Clinical Characteristics of *BRCA1* and *BRCA2* Carriers

Although the frequency of mutations in the general population is estimated to be approximately 1 in 800 for *BRCA1* and somewhat less for *BRCA2*, it is apparent that this frequency varies significantly between ethnic groups. In addition, "founder mutations" that presumably arose in a single ancestor have been identified repeatedly in many ethnic groups. The most common founder mutations described thus far are the *BRCA1* 185delAG and *BRCA2* 6174delT mutations, which occur in approximately 1.0% and 1.4% of Ashkenazi Jews, respectively (133,134 and 135). A third, less common founder mutation (*BRCA1* 5382insC) also has been noted in the Ashkenazi population. The high frequency of these three mutations implies that they likely arose approximately 100 generations ago.

Women should receive educational material and counseling explaining the postulated risks and benefits before deciding to undergo testing (136). In addition, posttest counseling and follow-up are crucial to help women work through various issues, including decisions regarding prophylactic surgery and other interventions designed to decrease cancer mortality. Failure to identify a *BRCA1* or *BRCA2* mutation in a family may be reassuring, but must be tempered by the realization that *BRCA* mutational analysis may miss some mutations, and other undiscovered hereditary ovarian cancer genes may exist.

With the discovery of *BRCA1* and *BRCA2*, only a minority of cases of familial ovarian cancer should have to be managed as we have in the past, by simply recommending prophylactic oophorectomy on the basis of a strong family history. Although the penetrance of various mutations is still somewhat uncertain, it is clear that carriers have a strikingly increased relative risk of ovarian cancer relative to the general population. The value of screening for early-stage ovarian cancer with CA125 and/or ultrasound is unproven, but seems reasonable until controlled studies are available. Fortunately, the incidence of ovarian cancer in carriers does not begin to rise appreciably until approximately 40 years of age, when most women have completed their family. In view of this, prophylactic oophorectomy represents a reasonable approach to decreasing ovarian cancer mortality in mutation carriers. Use of birth control pills as a chemopreventive has been suggested as an alternative because this is strongly protective against ovarian cancer in the general population. Oral contraceptives are a particularly attractive option for young women who have not yet completed childbearing, and one study found a strong protective effect in *BRCA1* carriers (125).

Sporadic Ovarian Cancer

Ovarian carcinoma usually is a monoclonal disease that originates in the ovary (137). **There is some evidence, however, that some papillary serous cancers that arise in the peritoneum of patients with *BRCA1* mutations may be polyclonal** (138). Most ovarian cancers are characterized by a high degree of genetic damage that is manifest both at the karyotypic and molecular levels. It is unclear whether the severity of these alterations reflects the need to inactivate multiple genes or is the result of widespread loss of genomic stability. Specific genes that are altered during the development of ovarian cancers are discussed later (Table 1.6).

	Class	Activation	Approximate Frequency
Hereditary			
BRCA1	Tumor suppressor	Mutation/deletion	5%
BRCA2	Tumor suppressor	Mutation/deletion	3%
MSH2	DNA repair	Mutation	1%
Sporadic			
HER-2/neu	Tyrosine kinase	Amplification/overexpression	20%–30%
K-ras	G protein	Mutation	5%
AKT2	Serine/threonine kinase	Amplification	10%
c-myc	Transcription factor	Overexpression	20%–30%
p53	Tumor suppressor, transcription factor	Mutation/deletion, overexpression	60%
p16	Tumor suppressor, cyclin-dependent kinase inhibitor	Homozygous deletion	15%

Table 1.6 Genetic Alterations in Epithelial Ovarian Cancers

It has been shown that ovarian cancers produce and/or are capable of responding to various peptide growth factors. For example, *epidermal growth factor (EGF)* (139) and *transforming growth factor*-a (*TGF*-a) (140) are produced by some ovarian cancers that also express the receptor that binds these peptides (EGF receptor) (141,142). Some cancers produce *IGF-1* and *IGF-1 binding protein*, and express *type 1 IGF receptor* (143). *Platelet-derived growth factor (PDGF)* also is expressed by many types of epithelial cells, including human ovarian cancer cell lines, but these cells usually are not responsive to PDGF (144,145 and 146). In addition, ovarian cancers produce basic *FGF* and its receptor, and basic FGF acts as a mitogen in some ovarian cancers (147). Ovarian cancers produce *M-CSF* (148), and serum levels of M-CSF are elevated in some patients (149). Because the *M-CSF receptor (fms)* is expressed by many ovarian cancers (150), it may comprise an autocrine growth-stimulatory pathway in some cancers. In addition, M-CSF could act in a paracrine fashion to stimulate recruitment and activation of macrophages. Because macrophage products such as *interleukin-1 (IL-1), IL-6*, and *tumor necrosis factor*-a have been shown to stimulate proliferation of some ovarian cancer cell lines (151,152 and 153), the potential for paracrine stimulation of the cancer by macrophages also exists (see Chapter 3). In addition to expression of peptide growth factors and their receptors, ascites of patients with ovarian cancer contains phospholipid factors that stimulate proliferation of ovarian cancer cells (154).

Several groups also have demonstrated that normal ovarian epithelial cells produce, and are responsive to, many of the same peptide growth factors as malignant ovarian epithelial cells (142,155,156 and 157). Thus, despite circumstantial evidence demonstrating the potential for autocrine and paracrine growth regulation of ovarian cancer cells by peptide growth factors, it remains unclear whether alterations in expression of growth factors are critical in either the development of ovarian cancer or regulation of cell growth after malignant transformation.

The HER-2/*neu* (erbB2) tyrosine kinase is a member of a family of related transmembrane receptors that includes the *EGF receptor* (erbB1) as well as erbB3 and erbB4 (158). Although a ligand that binds to HER-2/*neu* has been identified, activation of this receptor requires aggregation with other members of the erbB family. Approximately 30% of breast cancers express increased levels of the HER-2/*neu* (159), which often is due to amplification of this gene. Overexpression of HER-2/*neu* in breast cancer has been associated with poor survival. **The HER-2/*neu* oncogene also is overexpressed in approximately 20% of ovarian cancers, and overexpression has been associated with poor survival in some** (159,160), **but not all** (161,162), **studies.** Actual amplification of the gene with high-level overexpression is less common in ovarian cancers, however. Monoclonal antibodies that interact with HER-2/*neu* can decrease growth of breast and ovarian cancer cell lines that overexpress this receptor (163,164). An *anti-HER-2*/neu *antibody* that induces breast cancer regression has been approved for clinical use by the Food and Drug Administration (165). It is possible that this approach might also benefit some women whose ovarian cancers overexpress HER-2/*neu.*

Cytoplasmic serine/threonine kinases appear to relay mitogenic signals from tyrosine kinases and G proteins on the cell membrane toward the nucleus (166,167). Several of these kinases, which phosphorylate cellular proteins on serine and threonine residues, can be oncogenically activated under certain experimental conditions. The *AKT2 serine/threonine kinase* has been shown to be amplified and overexpressed in 2 of 8 ovarian cancer cell lines and 2 of 15 primary epithelial ovarian cancers (168). Further studies are needed to delineate the functional significance of AKT2 overexpression in ovarian cancers.

Mutations in the *ras* genes do not appear to be a common feature of invasive serous epithelial ovarian cancers (72,169,170). K-*ras* mutations have been noted more frequently in mucinous ovarian cancers, but these tumors comprise only a small fraction of epithelial ovarian cancers. In contrast, K-*ras* mutations are common in borderline epithelial ovarian tumors, occurring in 20% to 50% of cases (171,172). Thus, studies of the K-*ras* oncogene suggest that the molecular pathology of borderline tumors differs from that of invasive epithelial ovarian cancers.

Amplification of the c-*myc* oncogene occurs in some epithelial ovarian cancers. In five small studies, c-*myc* was reported to be amplified in a total of 24 of 77 cases (31%) (173,174,175,176 and 177). In a more recent study in which 51 epithelial ovarian cancers were analyzed, a similar incidence of c-*myc* overexpression was observed (37%) (178). In this study, c-*myc* overexpression was more frequently observed in advanced-stage serous cancers. Preliminary evidence exists suggestive that *cyclin E* may also be amplified in some ovarian cancers, but large studies are needed to confirm this observation (179).

The *TGF*-b family of growth factors inhibit proliferation of normal epithelial cells (180). It is thought that TGF-b causes cell cycle arrest in G_1 by triggering pathways that result in inhibition of cdks. Three closely related forms of TGF-b have been discovered that are encoded by separate genes *(TGF*-b*1*, *TGF*-a*2*, *TGF*-a*3)*. All three forms of TGF-b are 25-kd homodimers in which the subunits are bound together by disulfide bonds. TGF-b is secreted from cells in an inactive form bound to a portion of its precursor molecule, from which it must be cleaved to release biologically active TGF-b . Active TGF-b interacts with type I and II cell surface TGF-b receptors and initiates serine/threonine kinase activity (181). Prominent intracellular targets include a class of molecules called *Smads* that translocate to the nucleus and act as signal transcriptional regulators (182). Although mutations in the TGF-b receptors and Smads have been reported in some cancers, this does not appear to be a feature of ovarian cancers.

Normal ovarian epithelial cells produce, activate, and are growth inhibited by TGF-b (183), although most immortalized ovarian cancer cell lines have lost the ability to produce, activate, or respond to TGF-b (145,183,184,185,186 and 187). This suggested that TGF-b might normally act as an autocrine growth inhibitory factor in normal ovarian epithelium, and that loss of this pathway might play a role in the development of some ovarian cancers. Although convenient to work with, immortalized cell lines frequently have undergone profound genetic alterations in tissue culture. Examination of primary ovarian cancers obtained directly from patients revealed that in almost all cases cancers were sensitive to the growth-inhibitory effect of TGF-b (188). Thus, it remains unclear whether alterations in the TGF-b pathway play a role in the development of ovarian cancers.

Alteration of the *p53* tumor suppressor gene is the most frequent genetic event described thus far in ovarian cancers (38,189,190,191,192,193,194 and 195). **The frequency of overexpression of mutant *p53* is significantly higher in advanced stage III/IV disease (40% to 60%) than in stage I cases (10% to 20%).** In addition, *p53* inactivation is uncommon in borderline tumors (196). The higher frequency of p53 overexpression in advanced stage cases may indicate that this is a “late event” in ovarian carcinogenesis. Alternatively, it is possible that loss of p53 may confer an aggressive phenotype associated with more rapid dissemination of disease. In advanced-stage ovarian cancer, there is a suggestion that overexpression of p53 may be associated with somewhat worse survival (189,191,192,193,194 and 195). The literature is not entirely consistent, and most studies have not been large enough or optimally designed to yield reliable prognostic information. Finally, although there is a high concordance between *p53* missense mutations and protein overexpression, approximately 20% of advanced ovarian cancers contain mutations that result in truncated protein products that usually are not overexpressed (38). Overall, approximately 70% of advanced ovarian cancers have either missense or truncation mutations in the *p53* gene.

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It has been suggested that loss of functional p53 might confer a chemoresistant phenotype because p53 plays a role in chemotherapy-induced apoptosis. In this regard, several studies have examined the correlation between chemosensitivity and *p53* mutation in ovarian cancers *in vitro* (197,198,199,200 and 201). Some have suggested a relationship between *p53* mutation and loss of chemosensitivity, but in other, equally valid studies, such a relationship has not been observed. It is likely that the status of the *p53* gene is one of a number of factors that determine sensitivity to chemotherapy.

Several other known tumor suppressor genes, including *Rb, WT1*, and *PTEN*, have been examined in ovarian cancers, but do not appear to be altered frequently in these cancers. The *p16* tumor suppressor gene, which is an inhibitor of cdks, undergoes homozygous deletions in approximately 15% of ovarian cancers, however (202). It is likely that other, as yet undiscovered, tumor suppressor genes play a role in the development of ovarian cancers.

Cervical Cancer

Cervical cancer is the most common gynecologic malignancy worldwide and accounts for over 400,000 cases annually (203). Molecular and epidemiologic studies have demonstrated that most cervical dysplasias and cancers are attributable to sexually transmitted *human papillomavirus (HPV)* infection (203,204,205 and 206). The peak incidence of HPV infection is in the third and fourth decades, and the incidence of cervical cancer increases from the third decade to a plateau between 40 and 50 years of age. Although HPV plays a major role in the development of most cervical cancers, invasive cervical cancer develops in only a small minority of women who are infected. This suggests that other genetic and/or environmental factors are involved in cervical carcinogenesis. For example, individuals who are immunosuppressed, such as those with human immunodeficiency virus infection (207), invasive cervical cancer is more likely to develop after HPV infection.

Human Papillomavirus

The HPV DNA sequence consists of 7,800 nucleotides divided into “early” and “late” open reading frames (ORFs). Early ORFs fall within the first 4,200 nucleotides of the genome and encode proteins (E1 to E8) important in viral replication and cellular transformation. Late ORFs (L1 and L2) are found within the latter half of the sequence and encode structural proteins of the virion. In oncogenic subtypes like HPV 16 and 18, transformation may be accompanied by integration of episomal HPV DNA into the host genome. Opening of the episomal viral genome usually occurs in the *E1/E2* region, resulting in a linear fragment for insertion. The location of the opening may be significant because E2 acts as a repressor of the *E6/E7 promotor* and disruption of E2 can lead to unregulated expression of the *E6/E7 transforming genes.* HPV 16 DNA may be found in its episomal form in some cervical cancers, however, and unregulated E6/E7 transcription may occur independent of viral DNA integration into the cellular genome.

There are over 70 HPV subtypes, but only approximately a dozen affect the lower genital tract, and types 6, 11, 16, 18, 31, and 33 are most frequently observed. Types 6 and 11 rarely are oncogenic and usually are associated with low-grade dysplasia or condyloma, whereas types 16 and 18 account for 80% to 90% of cancers. Examination of the biologic effects of HPV-encoded proteins has shed light on the mechanisms of HPV-associated transformation. Expression of the *E4 transcript* results in the production of intermediate filaments that colocalize with *cytokeratins.* E4 proteins of oncogenic subtypes disrupt the cytoplasmic *cytokeratin matrix*, whereas those of nononcogenic strains do not. It has been suggested that this may facilitate the release of HPV particles in oncogenic subtypes such as HPV 16. The *E5 oncogene* encodes a 44–amino-acid protein that usually forms dimers within the cellular membrane. The transforming properties of E5 appear to involve potentiation of membrane-bound EGF receptors or PDGF receptors.

The E6 and E7 oncoproteins are the main transforming genes of oncogenic strains of HPV (208) (Fig. 1.6). Transfection of these genes *in vitro* results in immortalization and transformation of some cell lines. **The HPV E7 protein acts primarily by binding to and inactivating the retinoblastoma (Rb) tumor suppressor gene product.** E7 contains two domains, one of which mediates binding to Rb, whereas the other serves as a substrate for casein kinase II phosphorylation. Variations in oncogenic potential between HPV subtypes may be related to differences in the binding efficacy of E7 to Rb. High-risk HPV types contain E7 oncoproteins that bind Rb with more affinity than E7 from low-risk types. The transforming activity of E7 may be increased by casein kinase II mutation, implying a role for this binding site in the development of HPV-mediated neoplasms. **The E6 proteins of oncogenic HPV subtypes bind to and inactivate the p53 tumor suppressor gene product** (209,210). There also is a correlation between oncogenicity of various HPV strains and the ability of their E6 oncoproteins to inactivate p53. Inactivation of Rb and p53 by E6/E7 circumvents the need for mutational inactivation of these key growth regulatory genes.

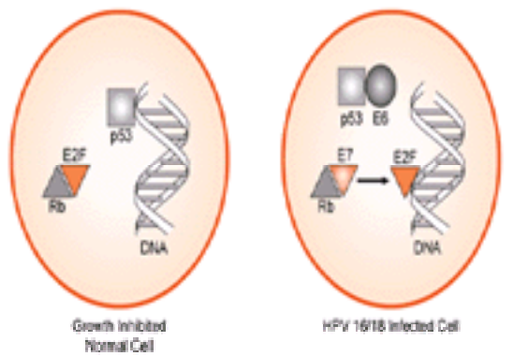

Figure 1.6 Neutralization of p53 and Rb by human papillomavirus subtypes 16 and 18 in cervical cancer.

Acquired Genetic Alterations

Only a small fraction of HPV-infected women develop cervical cancer. This suggests that additional genetic alterations are requisite for progression to high-grade dysplasia and cancer, but little is known about these events. Allele loss suggestive of involvement of tumor suppressor genes has been noted at loci on chromosomes 3p, 11p, and others, but alterations in specific genes have not yet been identified. In addition, alterations have not been found in a number of tumor suppressor genes that are involved in other types of cancers.

The role of several oncogenes has been examined in cervical carcinomas, including, most prominently, the *ras* and *myc* genes. Mutant *ras* genes are capable of cooperating with HPV in transforming cells *in vitro.* There is some evidence that mutations in either K-*ras* or H-*ras* may play a role in a subset of cervical cancers (211,212,213 and 214). Alterations in *ras* genes have not been seen in cervical intraepithelial neoplasia, suggesting that mutation of *ras* is a late event in the pathogenesis of some cervical cancers. In contrast, c-*myc* amplification and overexpression may be an early event in the development of some cervical cancers (215). Overexpression of c-*myc* has been demonstrated in one third of early invasive carcinomas and some *cervical intraepithelial neoplasia, grade 3 (CIN 3)* lesions, but not in normal cervical epithelium or lower-grade dysplasia. It has been reported that overexpression of the c-*myc* gene may be due to amplification of the gene (4- to 20-fold) in some cases. In some studies, amplification correlated with poor prognosis in early-stage cases (216). Other studies have not confirmed the finding of amplification of c-*myc* in cervical cancers, however. Integration of the HPV genome near c-*myc* on chromosome 8q may lead to increased expression because of enhanced transcription of the gene rather than amplification. Further studies are needed to clarify the role of *ras* genes, c-*myc*, and other oncogenes in cervical carcinogenesis.

Gestational Trophoblastic Disease

The genetic alterations that underlie gestational trophoblastic disease have been elucidated to a great extent. The most prominent feature of these tumors is an imbalance of parental chromosomes. In the case of partial moles, this involves an extra haploid copy of one set of paternal chromosomes, whereas complete moles usually are characterized by two complete haploid sets of paternal chromosomes and an absence of maternal chromosomes. Although the risk of repeat molar pregnancy is only approximately 1%, women who have had two molar pregnancies have approximately a 25% risk for development of another mole. Although this suggests a hereditary defect that affects gametogenesis, this remains speculative. There is no evidence that damage to specific tumor suppressor genes or oncogenes contributes to the development of gestational trophoblastic disease.

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2 Tumor Markers and Screening

Usha Menon and Ian J. Jacobs

One of the established strategies for combating cancer is screening the asymptomatic population for premalignant conditions and early-stage disease. These screening strategies are based on criteria laid down by the World Health Organization (1) (Table 2.1). Mass screening for cervical cancer fulfills most of these tenets, and organized screening programs in numerous countries have led to a significant reduction in cervical cancer mortality (2,3 and 4). Ovarian cancer is the other gynecologic malignancy that may meet the criteria of a disease for which population screening is justified (5). The disease is usually diagnosed in advanced stages when chances for long-term survival are poor. Effective treatment is available for early-stage disease and there is preliminary evidence that early detection may be beneficial (6). Mass screening for endometrial cancer is unlikely to be of benefit because women present in early stages with symptomatic disease. However, screening of “high-risk” populations may be useful. Vaginal and vulvar cancers are too rare to justify screening, although it is important to raise the awareness of these conditions among the elderly population.

1. The condition sought should be an important health problem.
2. There should be accepted treatment for patients with recognized disease.
3. Facilities for diagnosis and treatment should be available.
4. There should be a recognizable latent or early symptomatic stage.
5. There should be a suitable test or examination.
6. The test should be acceptable to the population.
7. The natural history of the condition, including development from latent to declared disease should be adequately understood.
8. There should be an agreed policy on whom to screen.
9. The cost of case-finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10. Case-finding should be a continuing process, and not a “once and for all” project.

From Wilson J, Junger G. *WHO principles and practice of screening for disease*. Geneva: World Health Organization, [1968]:6-17.

Table 2.1 World Health Organization Criteria for a Screening Program

Screening of cancers is based on detection of tumor markers. The term “tumor marker” is poorly defined and can be used to denote any change that indicates the presence of cancer. Markers may be biochemical substances produced by or in response to the tumor; cytologic, molecular or cytogenetic events detected in exfoliated cells; architectural abnormalities detected by ultrasound and other imaging modalities; or vascular changes detected by colposcopy or color-flow Doppler. The rapid growth of imaging technology, molecular biology, and cytogenetics continually adds to this ever-expanding armamentarium. Ideally, tumor markers should be tumor specific, allow detection of minimal disease, and quantitatively reflect tumor burden.

For screening protocols, the value of the marker depends heavily on its *sensitivity (proportion of cancers detected by a positive test)* and *specificity (proportion of those without cancer identified by a negative test)*, which must be well established before the protocol is adopted into routine practice (see Chapter 7).

Biochemical tumor markers can be broadly classified into *tumor-specific* and *tumor-associated antigens* (see Chapter 3). The former are rare, a typical example being idiotypes of immunoglobulins of B-cell tumors. Tumor-associated antigens comprise most of the serum markers in clinical use. Most of them were initially thought to be highly tumor specific, but subsequently they have been found to be produced in normal physiologic states as well as in benign and other malignant diseases. The most useful among those described are the macromolecular tumor antigens, which include enzymes, hormones, receptors, growth factors, biologic response modifiers, and glycoconjugates (7).

Evaluation of exfoliated cells has been in use for many decades. In gynecology, the entire cervical screening program is based on nuclear-cytoplasmic changes detected on microscopy of Papanicolaou-stained cells obtained from cervical sampling (Pap smear). These changes do not entirely fulfill the criteria for true tumor markers because their presence usually denotes an underlying premalignant condition [i.e., cervical intraepithelial neoplasia (CIN)] rather than a frank malignancy. A large number of sophisticated molecular techniques are now available for examining exfoliated cells for key events associated with carcinogenesis, including the presence of “high-risk” human papillomavirus (HPV) DNA, telomerase activity, and K-*ras* mutation.

Cancers possess some morphologic characteristics that, although not highly specific, are very sensitive markers for screening. A variety of imaging modalities have been used to identify these features. In gynecology, real-time ultrasound is most commonly used because it has minimal side effects and provides a detailed picture of tumor morphology that can be quantified using a variety of scoring systems. Identification of morphologic changes on transvaginal scanning is the basis of both ovarian and endometrial cancer screening.

Neovascularization associated with malignancy is another marker that has been exploited in screening for genital cancers. Color-flow Doppler is used to detect altered patterns of blood flow and to demonstrate decreased resistance in the thin-walled new vessels in ovarian and endometrial cancers. Colposcopy exploits the same phenomenon in an entirely different manner, i.e., the abnormal new vessels are directly visualized as patterns of mosaicism and punctation.

An important aspect of screening is defining the risk groups to target for screening. Even for cervical cancer, where mass screening is the norm, age may be used to define the population. For example, in the United Kingdom, screening is limited to women between the ages of 20 and 64 years. Risk groups for sporadic ovarian cancer are defined by postmenopausal status and age (50 years or older), whereas for hereditary ovarian malignancy, they are defined by family history criteria and presence of *BRCA1* and *BRCA2* mutations. Increased risk based on family history is also the basis of defining a target population for endometrial cancer screening.

Ovarian and Fallopian Tube Cancer

Deficiencies in our knowledge of the molecular and biologic events in ovarian carcinogenesis have hampered our ability to screen for this disease. A true precursor lesion for ovarian cancer has not been identified, limiting the goal of screening to detection of asymptomatic, early-stage disease. Biochemical, morphologic, vascular, and cytologic tumor markers have all been explored with varying success. There is as yet only preliminary evidence that ovarian cancer screening might reduce mortality (6), and the most appropriate option for women in the general population is participation in ongoing trials.

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Biochemical Markers

Circulating antigens released by the tumor predominate in this group, the best known being CA125. **CA125 is an antigen expressed by fetal amniotic and celomic epithelium. In the adult, it is found in tissue derived from celomic epithelium (mesothelial cells of the pleura, pericardium, and peritoneum) and mullerian epithelium (tubal, endometrial, and endocervical).** The surface epithelium of normal fetal and adult ovaries does not express the determinant, except in inclusion cysts, areas of metaplasia, and papillary excrescences (8).

CA125 was initially detected using a murine monoclonal antibody, OC125, raised in response to immunologic challenge with an ovarian cancer cell line (9). It is now known that CA125 carries two major antigenic domains classified as A, the domain binding monoclonal antibody OC125, and B, a domain binding monoclonal antibody M11 (10). Current immunoassays for the quantitation of serum CA125 levels are based on a heterologous assay (CA125 II) using both monoclonal antibodies (M11, OC125) in place of the original homologous assay with monoclonal antibody OC125 alone.

A serum CA125 of 35 U/mL, initially measured using the homologous assay and representing 1% of healthy female blood donors, is usually accepted as the upper limit of normal (11). This cutoff value is fully retained by the CA125 II assay (12), which is now preferred because of reduced interassay variation (13). **An upper limit of normal of 35 U/mL is an arbitrary cutoff and may not be ideal for certain applications of CA125. For example, in postmenopausal women or in patients after hysterectomy, CA125 levels tend to be lower than in the general population, and lower cutoffs may be more appropriate; 20 and 26 U/mL, respectively, have been suggested** (14,15).

Interest in CA125 as a screening test was initiated by the fact that approximately 83% of patients with epithelial ovarian cancer had CA125 levels ³35 U/mL (11,16). Elevated levels were found in 50% of patients with stage I disease and in more than 90% of women with more advanced stages (17) (see Chapter 11). In addition, it became apparent that CA125 could be elevated in the preclinical asymptomatic phase of the disease because elevated levels were found in 25% of 59 stored serum samples collected 5 years before the diagnosis of ovarian cancer (18). A summary of prospective screening studies performed in the general population is presented in Table 2.2. In a prospective ovarian cancer screening study of Swedish women, a specificity of 97% and positive predictive value of 4.6% were achieved using CA125 (³30 U/mL) in 4,290 volunteers aged 50 years and older (19). Similar specificity (96.6%) and positive predictive value (4.2%) were obtained more recently on screening 2,550 volunteers in New Zealand (20). **The low specificity and positive predictive value of CA125 used as the sole screening test for ovarian cancer is in part due to the marker being elevated in other cancers (pancreatic, breast, bladder, liver, lung), as well as in benign disease (diverticulitis, uterine fibroids, endometriosis) and physiologic conditions (pregnancy and menstruation)** (5).

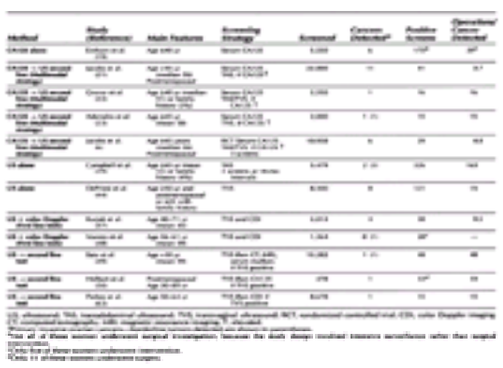


Table 2.2 Prospective Ovarian Cancer Screening Studies in the General Population

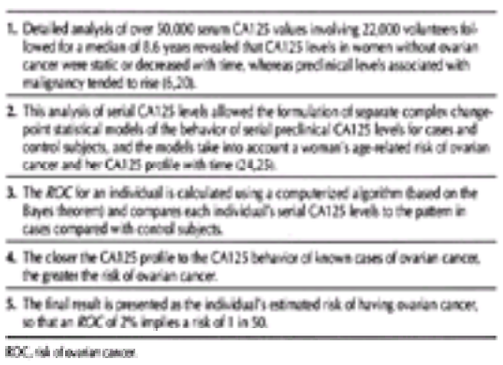
Improving Specificity of Ovarian Cancer Screening

Specificity of screening with CA125 was improved by limiting its use to postmenopausal women who were at increased risk of ovarian cancer and in whom many of the nonmalignant conditions mentioned previously do not occur. A CA125 of 30 U/mL or more in an asymptomatic postmenopausal woman is associated with a 36-fold increased risk of ovarian cancer in the subsequent year (21).

Specificity for screening can be further improved by the addition of pelvic ultrasound as a second-line test to assess ovarian volume and morphology. Using multimodal screening tests that incorporated sequential CA125 and pelvic ultrasound, a specificity of 99.9% and positive predictive value of 26.8% (approximately four operations for each cancer detected) for detection of ovarian and fallopian tube cancer was achieved in 22,000 postmenopausal women (21). Other studies (22,23), using a similar multimodal approach, have reported lower positive predictive values.

Risk of Ovarian Cancer Algorithm

Further improvements to the strategy have been made by a more sophisticated approach to interpretation of CA125 results. **It has been observed that elevated CA125 levels in women without ovarian cancer are static or decrease with time, whereas levels associated with malignancy tend to rise. This finding has been incorporated into an algorithm that uses age, rate of change of CA125, and absolute levels of CA125 to calculate an individual's *risk of ovarian cancer (ROC)*** (24,25) (Table 2.3). Transvaginal ultrasound and refined interpretation of scan findings in women with elevated CA125 levels may further improve the specificity of multimodal screening and decrease the number of women without ovarian cancer who have a positive screening result. The sensitivity of CA125 using multimodal screening has been reported as 78.6% to 100% at 1 year (22,23). **The ROC algorithm increases the sensitivity of CA125 compared with a single cutoff value, because women with normal but rising levels are identified as being at increased risk.**



1. Detailed analysis of over 50,000 serum CA125 values involving 22,000 volunteers followed for a median of 8.6 years revealed that CA125 levels in women without ovarian cancer were static or decreased with time, whereas preclinical levels associated with malignancy tended to rise (6,20).
2. This analysis of serial CA125 levels allowed the formulation of separate complex change-point statistical models of the behavior of serial preclinical CA125 levels for cases and control subjects, and the models take into account a woman's age-related risk of ovarian cancer and her CA125 profile with time (24,25).
3. The *ROC* for an individual is calculated using a computerized algorithm (based on the Bayes theorem) and compares each individual's serial CA125 levels to the pattern in cases compared with control subjects.
4. The closer the CA125 profile to the CA125 behavior of known cases of ovarian cancer, the greater the risk of ovarian cancer.
5. The final result is presented as the individual's estimated risk of having ovarian cancer, so that an *ROC* of 2% implies a risk of 1 in 50.

ROC, risk of ovarian cancer.

Table 2.3 Risk of Ovarian Cancer

Complementary Markers

The second approach to improving sensitivity is use of other serum markers in addition to CA125. Certain tumors (e.g., invasive and borderline mucinous tumors and borderline serous tumors) are less likely to be associated with elevated CA125 levels than invasive serous cancers (17,26). Numerous markers have been evaluated for complementarity with CA125, and those for which preliminary studies suggest complementarity are detailed in Table 2.4. Most of these studies used serum samples from women with clinically diagnosed ovarian cancer (i.e., in the differential diagnosis of ovarian cancer) as opposed to asymptomatic preclinical disease (i.e., early detection of ovarian cancer).

Tumor Marker	*Description*
CA72-4 or TAG 72	***Cancer antigen 72, or Tumor-associated glycoprotein 72,*** **a glycoprotein surface antigen found in colon, gastric, and ovarian cancer, is more frequently elevated in mucinous tumors.** There are conflicting reports regarding additional sensitivity for detection of ovarian cancer when combined with CA125 compared to CA125 alone (27–31).
M-CSF	**Serum *macrophage colony-stimulating factor* is a cytokine produced constitutively by normal as well as neoplastic ovarian epithelium.** Levels are elevated in 68% of patients with ovarian cancer compared with 2.5% of apparently healthy control subjects (32). Elevated levels have been found in ovarian cancer patients with normal levels of CA125 (32). Whereas CA125 alone was elevated in 67% of 46 patients with stage I ovarian cancer, CA125 or M-CSF was elevated in 91% (33).
OVX1	**Monoclonal antibody OVX1 recognizes an antigenic determinant present in ovarian and breast cancer cells** (34). In 31 patients with stage I epithelial ovarian cancer, using a panel of CA125, OVX1, and M-CSF, at least one marker was elevated in all cases (33). Of a panel of 18 tumor markers, OVX1 in combination with CA125 had the highest sensitivity and specificity for early detection of ovarian cancer (35).

[a]Others undergoing preliminary evaluation are bladder related peptides (e.g., pro-alpha C inhibin), cytokeratin 19 fragments (CYFRA 21-1), galactosyltransferase associated with tumor (GAT), and immunosuppressive acidic protein (IAP).

Table 2.4 Tumor Markers that May Be Useful in Screening for Ovarian Carcinoma[a]

Prospective Ovarian Cancer Screening Trials

There are currently two large randomized, controlled ovarian cancer screening trials recruiting postmenopausal women from the general population that incorporate CA125 measurement. The United Kingdom Collaborative Trial of Ovarian Cancer Sreening (36) (Fig. 2.1) and the National Institutes of Health Prostatic, Lung, Colorectal, and Ovarian cancer study (NIH-PLCO) (37) in the United States (Fig. 2.2) are designed to measure the impact of screening on ovarian cancer mortality in the general population.

Figure 2.1 The United Kingdom Collaborative Trial of Ovarian Cancer Screening (36). After a normal risk of ovarian cancer (ROC) (<1 in 2,000), a repeat CA125 is done in 1 year; after an intermediate risk ROC (>1 in 2,000 to <1 in 500), a repeat CA125 is done in 1 to 6 months; and after an elevated ROC (>1 in 500), a transvaginal ultrasound and CA125 is done in 6 to 8 weeks. The primary outcome measure is mortality from ovarian or fallopian tube cancer. Follow-up is by postal questionnaires and a cancer registry. The study duration is 7 years.

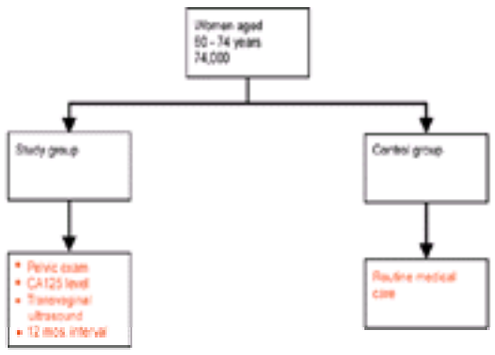


Figure 2.2 The National Institutes of Health Prostatic, Lung, Colorectal, and Ovarian cancer study (NIH-PLCO) (37). Ovarian screening is part of this study and the primary outcome measure is mortality from ovarian or fallopian tube cancer. The follow-up is 10 years.

Morphologic Markers

Real-time ultrasound screening is aimed at detecting the earliest possible architectural changes in the ovary that accompany carcinogenesis. Both ovarian volume and morphology are assessed, with cutoffs for volume ranging from 10 (38) to 20 mL (39), depending on menopausal status. Persistence of ultrasonic features on a repeat scan 4 to 6 weeks after detection of abnormalities on the initial screening scan can help to reduce the false-positive rate. The lack of physiologic changes in ovarian volume in postmenopausal women improves the specificity in this group compared with premenopausal women.

Most screening protocols use a weighted scoring system or morphologic index based on ovarian volume, outline, presence of papillary projections, and cyst complexity (i.e., number of loculations, wall structure, thickness of septa, and echogenicity of fluid). There is no standardized index and systems vary as to the number and type of variables evaluated (40,41). Based on gross anatomic changes at the time of surgery, papillary projections have the highest correlation and simple cysts and septal thickness the lowest correlation with a diagnosis of ovarian malignancy (42).

Initially, transabdominal ultrasound was used (39), and a specificity of 97.7% and positive predictive value of 1.5% was achieved. The transvaginal route is now preferred because more detailed pictures can be obtained. In the general population, 12 prospective ultrasonic screening trials for the detection of ovarian cancer have been reported (43). Most of these studies reported a sensitivity of 100% at 1 year, although few have provided details of follow-up of those patients with negative screening. Only one ultrasonic study reported detection of a case of primary ovarian carcinoma 12 months after a negative screen (44). The disadvantage of this strategy is the high false-positive rate, ranging from 1.2% (45) to 2.1% of women undergoing screening (46). Applied to a population with an annual incidence of ovarian cancer of 40 per 100,000, such false-positive rates imply 30 to 60 diagnostic surgical procedures for each case of cancer detected, which would not be acceptable in clinical practice. Lower false-positive rates of 0.7% and 0.3%, respectively, were obtained by combining ultrasound with color-flow Doppler (47,48). Other strategies have explored computed tomography and magnetic resonance imaging (49), as well as CA125 (50) and multiple serum tumor markers (51), as second-line tests after ultrasound. In Europe, there is an ongoing multicenter, prospective, randomized trial of ovarian cancer screening using transvaginal ultrasound that is aiming to recruit 120,000 women 50 years of age and older (52) (Fig. 2.3).

Figure 2.3 European randomized trial of ovarian cancer screening: protocol design (52). The primary outcome measure is mortality from ovarian or fallopian tube cancer. Follow-up is through a cancer registry. (*Assessment scan is performed 3 weeks after the screening scan and assesses the volume and morphology changes of the ovary relative to the screening scan.)

Screening for High-Risk Ovarian Cancer

In women with strong evidence of a hereditary predisposition for ovarian cancer, screening has been frequently advocated, although the efficacy of such surveillance or other measures to reduce risk in these individuals or even in those who carry cancer-predisposing mutations (e.g., *BRCA1, BRCA2*, or DNA mismatch-repair gene) is unknown (53). Screening can be problematic because this high-risk population often includes premenopausal women who have a higher incidence of false-positive CA125 elevations and ultrasound abnormalities. In these high-risk populations, initial screening trials used ultrasound alone (54,55) or with color-flow Doppler (56), and were associated with high false-positive rates (2.5% to 4.9%). The current trend is to combine ultrasound with CA125 screening.

There are now five prospective studies ongoing in which combined screening has been undertaken in high-risk populations (43). **In three screening programs involving a total of 1,228 women with a family history of ovarian cancer, no invasive ovarian cancer was detected, and false-positive rates have ranged from 0.4% to 3.9%** (57,58 and 59). In the remaining two studies, one case of ovarian cancer was detected on screening 137 high-risk women, with a false-positive rate of 0.7% (60), and 9 cases were detected on screening 180 women, with a false-positive rate of 3.9% (61).

Women in the high-risk population who request screening should be counseled about the current lack of evidence for the efficacy of both CA125 and ultrasonic screening and the associated false-positive rates. Many still opt for screening despite understanding the risks and limitations.

Vascular Markers

***Neovascularization* is an obligate early event in tumor growth and neoplasia** (62). Fast-growing tumors contain many new vessels that have less smooth muscle in their walls and therefore provide less resistance to blood flow than vessels in benign ovarian tumors. *Color-flow Doppler* imaging uses these altered malignant blood flow patterns as markers to differentiate malignant from physiologic and benign lesions. It has been used as a first-line screening test in combination with transvaginal ultrasound (47,49,55), as well as a second-line test after an abnormal ultrasound (40,63) in both general and high-risk population screening.

The initial promise of retrospective analysis of color-flow Doppler to differentiate between malignant and benign ovarian masses and therefore improve the specificity of ultrasound (40,63) has not been confirmed in prospective studies (38,52,57). This may in part be due to lack of uniformity of Doppler examinations and differing sensitivities of the various machines. The optimal parameters and cutoff level (pulsatility index <1.0, resistance index <0.4, 0.6, 0.8, or peak flow velocity) with the highest predictive value for malignancy are still unresolved. The European Randomized Trial of Ovarian Cancer Screening study has now dropped color-flow Doppler from its protocol because it did not alter the false-positive rate for ultrasound in the pilot phase of their randomized, controlled trial (52). The Royal London/St. Bartholomew's Hospital trial (36) is gathering data on color-flow Doppler after an abnormal ultrasound, although this result is not being used in the decision-making process. Analysis of these data will probably help resolve the contribution of color-flow Doppler to screening performance.

Endometrial Cancer

The prevalence of endometrial cancer in asymptomatic women is low and the overall prognosis is good because women present in early stages with abnormal bleeding. Therefore, screening may be recommended only for women at high risk, such as those from families with hereditary nonpolyposis colorectal cancer (64). These families have inherited germline mutations of DNA mismatch-repair genes, and the cumulative incidence of endometrial carcinoma in these women is 20% by 70 years of age, compared with 3% in the general population (65). The efficacy of screening measures is unknown, so screening is best carried out within the context of research protocols designed to evaluate clinical outcomes.

The other group of women who are often considered for screening are those with breast cancer on long-term adjuvant therapy with *tamoxifen*. However, although the risk of endometrial cancer in these women is approximately twofold greater than in the general population, these patients tend to present with vaginal bleeding. Also, the association between *tamoxifen* use in patients with breast carcinoma and the subsequent development of endometrial malignancy reported in some studies (66,67) has not been substantiated in others (68,69 and 70).

There is no need to screen asymptomatic women before initiating hormone replacement therapy (71). However, women taking unopposed estrogen replacement therapy should certainly be screened.

Morphologic Markers

The most commonly used tumor marker is endometrial thickness measured using transvaginal ultrasound, defined as the distance from the proximal to the distal interface of the hypoechoic halo that surrounds the more echogenic endometrium. In symptomatic patients with postmenopausal bleeding who are not on hormone replacement therapy, a cutoff for endometrial thickness of more than 4.0 mm has a sensitivity for detection of endometrial cancer of 98% and a negative predictive value of 99% (72). Although this cutoff effectively excludes endometrial atrophy, it fails to differentiate between hyperplasia and carcinoma (73). As a tumor marker in asymptomatic postmenopausal women, the same poor positive predictive value but high negative predictive value for detecting serious endometrial disease exists for endometrial thickness (74). Screening studies using conventional and color-flow Doppler ultrasound in apparently healthy postmenopausal women have established that endometrial carcinomas can be detected at a preclinical stage (47,51,75,76 and 77) and that transvaginal ultrasound is more sensitive than blind endometrial biopsy (78). **However, in the absence of symptoms, repeat endometrial sampling is not warranted in patients with a thickened endometrium and negative findings at initial biopsy** (79). Endometrial fluid accumulation is detected in 12% of asymptomatic elderly postmenopausal women and is rarely a sign of malignancy (80). Newer techniques under investigation include three-dimensional ultrasonography for the measurement of endometrial volume (81) and sonohysterography (82).

In asymptomatic women on long-term *tamoxifen*, abnormal ultrasonographic findings are common in the absence of underlying endometrial disease. The apparent increase in thickness observed on ultrasound is probably due to *tamoxifen*-induced changes in endometrial stroma and myometrium (83,84). The sensitivity of endometrial ultrasonography is poor and prompt investigation of abnormal vaginal bleeding rather than screening is probably the best option in this group (84). It has been reported that women on *tamoxifen* who are at risk for severe atypical hyperplasia can be identified on the basis of hyperplastic lesions detected on endometrial biopsy before starting the drug (85).

Cytologic Markers

Although the Pap smear was designed to detect cervical cancers, it can detect the presence of malignancy in women with endometrial malignancy. The presence of normal- as well as abnormal-looking endometrial cells in cervical smears in the second half of the menstrual cycle or in postmenopausal women should alert the clinician to the possibility of underlying endometrial disease. In 13.5% of postmenopausal women with normal endometrial cells on routine smear, 23% of those with atypical cells and 77% of those with suspicious cells had either endometrial hyperplasia or carcinoma on retrospective analysis. Among premenopausal women, 3 of 57 with normal endometrial cells in the secretory phase of the menstrual cycle had endometrial hyperplasia, whereas 1 of 2 with atypical cells had endometrial polyps, and both with cells suspicious for carcinoma had endometrial carcinoma (86). A similar positive predictive value of 64% for later diagnosis of endometrial malignancy was obtained on follow-up of 359 women who received a cytologic report of endometrial malignancy from the Victorian Cytology Service during 1982 to 1987 (87). In a more recent series, 13.5% of women with endometrial cells of some type on a Pap smear had endometrial carcinoma (88). The presence of glandular abnormalities and high-grade squamous intraepithelial lesions on smear is also associated with an increased risk of endometrial carcinoma (88,89,90 and 91). The sensitivity of cervical cytology performed within 2 years before the diagnosis of endometrial malignancy is 28% (87).

The low sensitivity of cytology using conventional Pap smears that indirectly sample the endometrium can be improved by directly sampling the endometrial cavity using a variety of commercially available sampling devices. Although these techniques are simple, with low risk and good yield, they are associated with technical difficulties because of cervical stenosis, and with varying degrees of patient discomfort. Their use in screening asymptomatic women is probably best limited to those with a positive result on first-line ultrasonic screening (92). Diagnostic outpatient hysteroscopy, another modality increasingly used in evaluating symptomatic patients, is also not as sensitive or acceptable as transvaginal ultrasonography in screening asymptomatic women (93).

Molecular Markers

Polymerase chain reaction (PCR)-based technology has made possible the detection of mutations and other key events in small numbers of cancer cells scattered among large numbers of normal cells. Al-Jehani et al. (94) found that six of seven cervical smears taken immediately before surgery for endometrial cancer contained K-*ras* mutations identical to those in the seven primary tumors. There were no false-positive cases in smears from 35 cancers with no mutations. Interestingly, three smears taken up to 5 months before the diagnosis of endometrial carcinoma had K-*ras* mutations, despite having normal cytologic appearances. Although K-*ras* mutations are found only in 10% to 30% of tumors, this model indicates the possibility of using mutations in oncogenes and tumor suppressor genes as molecular markers to detect endometrial carcinoma from cervical smears. Markers that may be suitable include microsatellite instability present in 15% of endometrial carcinomas, *p53* mutations in 20%, and *PTEN*/*MMAC1* gene mutations in 34% (95,96). Some of these are late events in endometrial carcinogenesis and may not be suitable for screening purposes.

Telomerase, a ribonucleoprotein complex associated with synthesis of telomeric DNA, is preferentially expressed in most malignant tissues, including endometrial carcinoma (97). It is expressed by normal cycling endometrium (98,99), but activity is absent or weak in postmenopausal atrophic endometrium (98,100,101), raising the possibility of its use as a marker for endometrial hyperplasia and carcinoma in postmenopausal women (102).

Until the ideal tumor marker for endometrial cancer is described, screening tests will continue to be characterized by low false-negative but high false-positive rates. Although screening is inappropriate for the general population, a strategy of early evaluation of postmenopausal bleeding with judicious use of hysteroscopy and endometrial biopsy is important for the early detection of endometrial cancer.

Cervical Cancer

Screening for cervical cancer is one of the most prevalent and successful public health measures for the prevention of cancer. Primary screening is based on detection of established cytologic markers on a Pap smear, with colposcopy as a second-line test (see Chapter 8). Although Pap smear screening remains the best available method of reducing the incidence and mortality rate of invasive cervical cancer (103), cytologic screening alone will not eradicate the disease. An audit of smear histories in women younger than 70 years of age with cervical cancer revealed that 49% of cancers occurred despite adequate cytologic screening and follow-up in the 5 years before diagnosis (104). Numerous strategies such as neural network–based automated slide reading systems and thin-layer slide preparations are being investigated to decrease the false-negative rate of cervical cytology. Immunostaining with antibodies against the DNA regulation proteins, Cdc6 and Mcm5, have been described to improve the detection efficiency for dysplastic cells in Pap smears (105).

Human Papillomavirus

There is a well established causal link between HPV and all grades of CIN and invasive cervical cancer (106). The association is type specific. HPV types 6, 11, 42, 43, and 44 are associated with low-grade cervical intraepithelial lesions (CIN 1) and HPV types 16, 18, 31, 33, 35, 45, 51, 52, 56, and 58 are associated with high-grade cervical intraepithelial lesions (CIN 2 and 3) and cervical carcinoma (107). The development of persistent infection with the latter oncogenic HPV types is thought to be an early event in cervical carcinogenesis. This has led to the investigation of HPV detection as a secondary test in patients with smears indicating atypical squamous cells of unknown significance and low-grade squamous intraepithelial lesions, as well as in primary screening. Although some studies have shown that the detection rate of CIN 2 and 3 can be improved by HPV testing (108,109,110 and 111), others have failed to establish a definite advantage over cytologic screening (112,113,114 and 115). Some of these differences are due to variations in HPV assays. The technology for HPV detection is still evolving, with continuing optimization of type spectrum, sensitivity, specificity, and ease of use. The value of HPV typing may be further increased by subtyping because some variants of HPV 16 confer a 6.5-fold increase in risk of CIN 2 and 3 compared with other HPV 16 variants (116). Data regarding these factors as well as a clear cost–benefit analysis are sparse or pending in several large trials. Until such data are available, caution in clinical implementation of HPV testing is warranted (106).

Telomerase

The enzyme *telomerase* is a ribonucleoprotein complex consisting of three major components—human telomerase RNA (hTR), telomerase-associated protein (TP1/ TLP1), and human telomerase catalytic subunit (hTRT/hEST2). It facilitates unlimited proliferation of cells by adding telomeric repeats to the ends of chromosomes and thereby compensates for the progressive loss of telomeric DNA that normally accompanies cell division. There is increasing evidence that telomerase expression may be a marker of premalignant and malignant squamous cell lesions of the cervix.

Using the *telomere repeat amplification protocol*, telomerase activity was detected in 100% of squamous cell carcinomas, 62% to 96% of CIN 2 and 3 lesions, 33% to 56% of CIN 1 lesions, and only 0% to 18% of normal cervical tissue (102,117,118). Assessment of cytologic specimens revealed a similar distribution of telomerase activity, with 88% to 100% of samples from cervical cancers, 40% to 59% from CIN, and 7% to 9% from normal cervices showing telomerase activity (119,120 and 121). Interest in the role of telomerase in cervical screening was further stimulated by the finding that five cases of CIN with no cytologic abnormality had telomerase activity (120). However, other studies have found telomerase assay of cervical cytologic samples to have poor sensitivity (4.5% to 25%) for detection of CIN 2 and 3 (117,122). Poor correlation has been reported between telomerase activity in paired cervical cytologic samples and frozen sections (122). In addition, telomerase activity has been detected in 46% to 56% of benign cervical lesions (102,123). It has been suggested that the detection of hTRT messenger RNA using reverse transcription-PCR analysis of exfoliated cells may be useful in cervical screening (124).

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3 Immunology and Biologic Therapy

Otoniel Martínez-Maza and Jonathan S. Berek

Cancer is caused by the accumulation of successive molecular changes that result in an altered cellular phenotype refractory to normal growth control mechanisms. The molecular changes can include the overexpression, amplification, or mutation of oncogenes; the failure of tumor suppressor gene function because of mutation or deletion or the subversion of tumor suppressor molecules by viral infection; and the inappropriate expression of growth factors and cytokines or the cellular receptors for these molecules. These molecular events interact to result in the generation of tumor cells. In addition to these molecular lesions, the subversion of host antitumor immune responses may play a role in the development of cancer. It is clear that the human immune system, as well as playing a central role in host defense against infection, participates in the maintenance of organismal integrity, including host responses to neoplasia. The immune system can interact with tumor cells, including solid tumors, and immune responses, whether natural or induced, can lead to tumor regression. As more is learned about the interactions between cancer and the immune system, opportunities for new immunotherapeutic or immunodiagnostic approaches arise. This chapter presents a brief overview of immunology and biologic therapies relevant to gynecologic cancers.

Components of the Immune System Involved in Antitumor Responses

Various types of human immune responses can target tumor cells. Immune responses historically have been categorized as humoral or cellular, a distinction based on the observation in experimental systems that some immune responses could be transferred by serum (humoral) and others by cells (cellular). **In general, *humoral responses* refer to antibody responses; antibodies are antigen-reactive, soluble, bifunctional molecules composed of specific antigen-binding sites associated with a constant region that directs the biologic activities of the antibody molecule, such as binding to effector cells, or complement activation** (Fig. 3.1). ***Cellular immune responses* are mediated directly by activated immune cells, rather than by the production of antibodies** (Fig. 3.2).

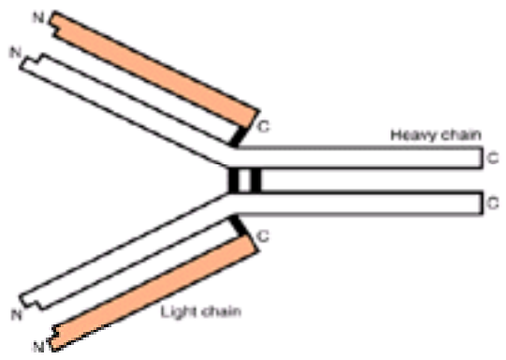

Figure 3.1 The basic immunoglobulin structure. The unit consists of two identical light polypeptide chains and two identical heavy polypeptide chains linked together by disulfide bonds (red). Note the position of the amino (N) and carboxyl (C) terminal ends of the peptide chains. (Redrawn from Roitt I, Brostoff J, Male D. *Immunology.* St. Louis: CV Mosby, 1985:5.1, with permission.)

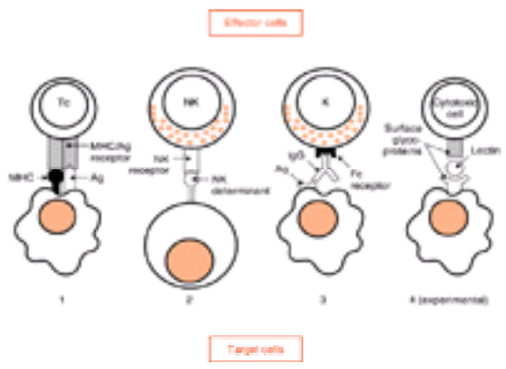

Figure 3.2 Cell-mediated cytotoxicity: four different types of cell binding in cell-mediated cytotoxicity. (1) Cytotoxic T cells (Tc) bind their target while recognizing antigen (Ag) and major histocompatibility complex (MHC) determinants. (2) Natural killer (NK) cells recognize determinants expressed on neoplastic cells. (3) Killer (K) cells recognize the Fc (crystallizable fragment) of immunoglobulin G (IgG) antibody bound to antigen on the target cell surface. (4) Experimentally, glycoproteins on the surface of effector and target can be cross-linked by lectins. (Redrawn from Roitt I, Brostoff J, Male D. *Immunology.* St. Louis: CV Mosby, 1985:11.5, with permission.)

It has become apparent, however, **that nearly all immune responses involve both humoral and cellular components: specific immune responses involve the coordinated activities of populations of lymphocytes, operating in concert with each other and with antigen-presenting cells, resulting in some effector function** (Fig. 3.3). Cellular interactions involved in immune responses include direct cell–cell contact, as well as cellular interactions mediated by the secretion of, and response to, cytokines. ***Cytokines* are biologic messenger molecules that play important roles in the genesis, amplification, and effector functions of immune responses.** Both innate and adaptive immune responses can exert potent antitumor activity. *Adaptive immunity* is the response of antigen-specific cells to antigens, including the evolution of *immunologic memory*; innate responses involve a variety of non–antigen-specific mechanisms, which are present at all times, and which do not increase with repeated exposure to a given

and with antigen-presenting cells, resulting in some effector function (Fig. 3.3). Cellular interactions involved in immune responses include direct cell–cell contact, as well as cellular interactions mediated by the secretion of, and response to, cytokines. ***Cytokines*** **are biologic messenger molecules that play important roles in the genesis, amplification, and effector functions of immune responses.** Both innate and adaptive immune responses can exert potent antitumor activity. *Adaptive immunity* is the response of antigen-specific cells to antigens, including the evolution of *immunologic memory*; innate responses involve a variety of non–antigen-specific mechanisms, which are present at all times, and which do not increase with repeated exposure to a given antigen (1). An example of an *adaptive immune response* would be the generation of specific cytolytic T cells directed to a tumor-associated antigen. An *innate antitumor response* would be the killing of tumor cells by exposure to natural killer (NK) cells.

Figure 3.3 Scope of cell-mediated immunity: cellular communication in the immune response through interleukins. IFNg, gamma interferon; TCR, T-cell receptor; IL, interleukin; Ig, immunoglobulin.

Although many effective antitumor immune responses have been described, it does not appear that antitumor immune responses commonly detect and destroy tumor cells, at least as was envisioned originally, when the concept of immune surveillance was first defined (2). Cancer is a common disease, and immune deficiency certainly is not necessary for its development. In fact, there is little difference in the incidence of common cancers in humans or experimental animals that are severely immunosuppressed compared with immunocompetent individuals. Although profoundly immunodeficient patients do display a higher incidence of cancer, the tumors that are seen in these patients tend to be distinct from those seen in the general population. For example, a greatly increased incidence of some types of cancers is seen in people with acquired immunodeficiency syndrome, who have a severe defect in T-cell–mediated immunity. However, most of these cancers are relatively rare in immunocompetent patients, and for the most part are tumors associated with viral infections, such as lymphoproliferative tumors (non-Hodgkin's lymphoma), many of which are associated with Epstein-Barr virus; Kaposi's sarcoma, which was shown to be associated with a newly recognized g-herpesvirus, human herpesvirus type 8 (HHV-8); and cervical dysplasia and cervical cancer, which are associated with infection of cervical epithelial cells with human papillomavirus (HPV) (3,4). Therefore, the role of adaptive immune responses in preventing cancer may be limited to certain types of neoplasia. However, **innate immune mechanisms may be of great importance in the host response to cancer, and it certainly is possible to modify and direct adaptive immune responses in a manner that results in antitumor responses.**

T Lymphocytes and Antitumor Immunity

T lymphocytes play a pivotal role in the generation of immune responses by acting as helper cells in the generation of humoral and cellular immune responses, and by acting as effector cells in cellular responses. T lymphocyte precursors, which originate in the bone marrow, mature into functional T lymphocytes in the thymus, where they learn to recognize antigen in the context of the *major histocompatibility complex (MHC) molecules* of the individual. Most T lymphocytes with the capability of responding to self-antigens are removed during thymic development. T cells also are selected for the ability to interact with self-MHC molecules during thymic differentiation.

T lymphocytes are distinguished from other types of lymphocytes by their biologic activities and by the expression of distinctive cell surface molecules, including the *T-cell antigen receptor* and *CD3 molecular complex.* The expression of lymphocyte cell surface molecules can be quantified by flow cytometry, using fluorochrome-labeled monoclonal antibodies that can specifically bind these molecules. T lymphocytes recognize specific antigens by interactions that involve the T-cell antigen receptor (5), which is similar, in terms of its general structure and molecular organization, to the antibody molecule, which is the antigen receptor for B lymphocytes (Fig. 3.1). However, there are important differences between the antigen receptor molecules on B lymphocytes and T lymphocytes. For example, the T-cell receptor is not secreted. Also, the T-cell antigen receptor can bind to antigen only in the form of a processed antigen peptide fragment associated with self-MHC molecules expressed on the surface of an antigen-presenting cell. The B-cell antigen receptor (Fig. 3.1) can bind to antigen directly, and therefore is not restricted in this way.

There are two major subsets of T lymphocytes: *T helper/inducer cells*, which express the CD4 cell surface marker, and *T suppressor/cytotoxic cells*, which express the CD8 marker (Fig. 3.3). CD4 T lymphocytes can provide help to B lymphocytes, resulting in antibody production, and also can act as helper cells for other T lymphocytes. Much of the helper activity of T lymphocytes is effected by the production of cytokines, such as interleukin-2 (IL-2). The CD8 T-lymphocyte subset includes cells that are cytotoxic and that can directly kill target cells. A major biologic role of such cytotoxic T lymphocytes is the lysis of virus-infected cells. However, cytotoxic T lymphocytes can directly mediate the lysis of tumor cells, presumably by recognizing antigens presented by tumor cells, leading to a series of events that culminates in tumor cell lysis. Cytotoxic T lymphocytes can kill tumor cells by signaling the induction of apoptosis in the target cells, and by the secretion of perforin, a pore-forming protein (6). T cells also can contribute to antitumor immune responses by producing cytokines, such as tumor necrosis factor (TNF), that induce tumor cell lysis and can enhance other antitumor cell effector responses.

B Lymphocytes and Antibodies

B lymphocytes are the cells that produce and secrete antibodies, which are antigen-binding molecules (Fig. 3.1). B lymphocytes develop from pre-B cells and, after exposure to antigen and appropriate activation signals, differentiate to become plasma cells, terminally differentiated cells that produce large quantities of antibodies. Pre-B cells originate from progenitor stem cells after the rearrangement of immunoglobulin genes from their germ cell configuration to the configuration that results in a functional antibody molecule. Mature B lymphocytes use cell surface immunoglobulin molecules as antigen receptors. In addition to producing antibodies, B lymphocytes play another important role: they can serve as efficient antigen-presenting cells for T lymphocytes.

Although the production of antitumor cell antibodies does not appear to play a central role in host antitumor immune responses, *monoclonal antibodies* reactive with *tumor-associated antigens* have proved useful in antitumor therapy, as well as in the detection of tumors or of tumor-associated molecules. For instance, immunotoxin-conjugated monoclonal antibodies directed to antigens expressed by human ovarian adenocarcinoma have been shown to effect tumor cell killing in experimental animal systems (7). However, many obstacles need to be overcome before monoclonal antibodies become clinically useful, including cross-reactivity of normal cell and tumor-associated antigens, heterogeneity/modulation of tumor cell antigens, and direction of host immune responses to monoclonal antibodies of murine origin. **Unfortunately, no truly unique tumor-specific antigens have been identified, and most tumor-related antigens are expressed to some extent on nonmalignant tissues.** Also, because most monoclonal antibodies are of murine and not human origin, the host's immune system can recognize and respond to murine monoclonal antibodies. This has led to many attempts to develop “humanized” murine monoclonal antibodies (genetically engineered monoclonal antibodies composed of human constant regions with specific antigen-reactive murine variable regions) or to generate human monoclonal antibodies, with the aim of avoiding many of the problems associated with the administration of murine monoclonal antibodies.

Macrophages and Monocytes

Monocytes and macrophages play important roles in immune responses. ***Macrophages*****, which can take part in innate immune responses, also play a key role in the generation of adaptive, lymphocyte-mediated immune responses because they can act as antigen-presenting cells** (Fig. 3.3). Helper/inducer (CD4) T lymphocytes, bearing a T-cell receptor of appropriate antigen and self specificity, can be activated by antigen-presenting macrophages that display processed antigen combined with self-MHC molecules (Fig. 3.1). Antigen-presenting cells also provide costimulatory signals that are important for the induction of T-lymphocyte activation. In addition to serving as antigen-presenting cells, macrophages can ingest and kill microorganisms and can act as cytotoxic antitumor killer cells. In addition, macrophages and monocytes produce various cytokines, including IL-1, IL-6, chemokines [regulated upon activation normal T-cell–expressed and secreted (RANTES), macrophage inflammatory protein 1 (MIP-1) a/b, IL-8], IL-10, and TNF, which can be involved in many immune responses. These monocyte-produced cytokines can have direct effects on tumor cell growth and development, both as growth-inducing and growth-inhibiting factors.

Natural Killer Cells and Antibody-Dependent Cellular Cytotoxicity

***Natural killer cells*, which have a characteristic large granular lymphocytic morphology, are an important component of innate immune responses.** NK cells do not express the CD3 T-cell receptor complex, but they can express some markers that are shared with T lymphocytes or with other types of lymphocytes, as well as other NK-associated markers. NK cells can lyse target cells, including tumor cells, unrestricted by the expression of antigen or self-MHC molecules on the target cell (6). Therefore, NK cells are effector cells in an innate (non–antigen-restricted) type of immune response, and may play a vital role in the nonspecific killing of tumor cells and/or virus-infected cells. Although NK cells represent an innate form of immunity that does not require an adaptive memory response for biologic function, NK responses can be augmented by cytokines, such as IL-2 and interferon-g (IFN-g) (Fig. 3.4). The cells that can effect antibody-dependent cellular cytotoxicity (ADCC) are NK-like cells. ADCC can result in the lysis of tumor cell targets in vitro. Although the mechanisms of tumor cell killing in ADCC are not clearly understood, close cellular contact between the ADCC effector cell and the target cell appears to be required.

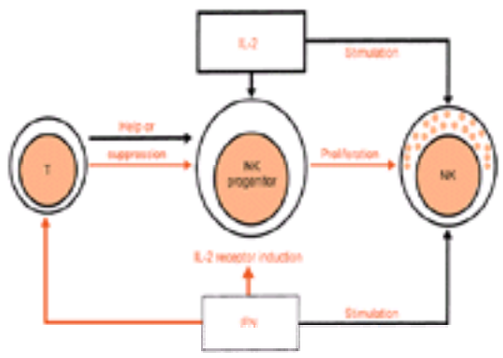

Figure 3.4 Schematic representation of interleukin-2 (IL-2), interferon (IFN), and T-cell regulatory mechanisms influencing natural killer (NK) cell activity. The proliferation of NK cells is under T-cell control. IL-2 also may induce proliferation and stimulate the NK activity of proliferating NK cells. IFN induces expression of IL-2 receptors on the NK progenitor, enhancing proliferation; however, IFN also feeds back on T cells to reduce their activity. (Redrawn from Roitt I, Brostoff J, Male D. *Immunology.* St. Louis: CV Mosby, 1985:18.5, with permission.)

Cytokines

***Cytokines* are soluble mediator molecules that induce, enhance, or effect immune responses** (Table 3.1). Cytokines are pleiotropic: they have multiple and redundant biologic actions. Also, cytokines are heterogeneous, and share little structural or amino acid homology, although some cytokines appear to have evolved from a common ancestral precursor, and are members of a cytokine "family." Cytokine families include the *hematopoietins* (*IL-2, IL-4, IL-6*, and related cytokines), the *TNF family* (*TNF*-a, *lymphotoxin*, and related molecules), *chemokines* (*IL-8, RANTES*, and related cytokines), the *IL-1 family* (*IL-1*a, *IL-1*b, *IL-1RA*), and the *IFNs*. There are three types of IFNs: *IFN*-a, *IFN*-b, and *IFN*-g. IFNs are cytokines that can interfere with viral production in infected cells, as well as have various effects on the immune system. For instance, *IFN*-g, a T-lymphocyte–produced cytokine, can affect immune function by enhancing the induction of MHC molecule expression, enhancing the activity of antigen-presenting cells, and thereby enhancing T-lymphocyte activation.

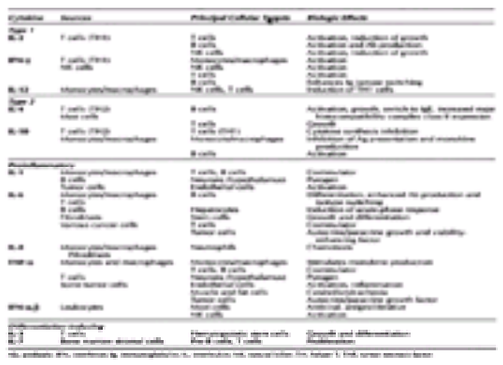

Table 3.1 Cytokines—Cellular Sources, Targets, and Biologic Activities

Cytokines are produced by various types of cells and play critical roles not only in immune responses, but in biologic responses outside of the immune response, such as hematopoiesis or the acute-phase response. Although cytokines are a heterogeneous group of molecules, they share some general properties; cytokines are small to medium-sized secreted proteins, are produced transiently and locally, are potent, and interact with specific cellular receptors, resulting in signal transduction, followed by changes in cellular proliferation and/or differentiation in the target cell.

There are two subpopulations of CD4-positive helper T cells, *type 1 (TH1) cells* and *type 2 (TH2) cells*, which control the nature of an immune response by secreting characteristic and mutually antagonistic sets of cytokines (8,9 and 10). **TH1 clones produce IL-2 and IFN-g, whereas TH2 clones produce IL-4, IL-5, IL-6, and IL-10. TH1 cytokines promote cell-mediated and inflammatory responses, whereas TH2 cytokines enhance antibody production.** Most immune responses involve both TH1 and TH2 components. There is cross-regulation of TH1 and TH2 responses: TH2 cytokines can inhibit the production of IFN-g and other TH1 cytokines by human peripheral blood mononuclear cells, as well as suppress the release of cytokines (IL-1, IL-6, IL-8 and TNF-a) by activated monocytes (8,10). Conversely, TH1 cytokines, such as IL-2 and IFN-g, can downregulate TH2 responses.

As research has provided new information on the activities of cytokines, they have appeared to be extraordinarily pleiotropic, with a bewildering array of biologic activities, including some outside of the immune system. Because some cytokines have direct or indirect antitumor and/or immune-enhancing effects, several of them have been used in the experimental treatment of cancer.

Cytokines: Multiple Potential Roles in the Pathogenesis of Cancer

The potential of cytokines to enhance antitumor immune responses has been exploited in various strategies for the experimental treatment of cancer. These include:

1. *The enhancement of host cytokine production* induced nonspecifically by exposure to biologic response modifiers
2. *Direct treatment with recombinant cytokines*
3. *Adoptive immunotherapy*, in which patient peripheral blood cells or tumor-infiltrating lymphocytes (TIL) are exposed to cytokines such as IL-2 and activated *ex vivo*, generating activated cells with antitumor effects that can then be readministered to the patient
4. *Gene therapy–based approaches*, in which tumor cells are transduced with a cytokine gene, the expression of which will presumably enhance antitumor immune responses
5. *The modulation of local cytokine production* by drug treatment

Even though cytokines have been used, directly or indirectly, in antitumor treatment, the overall effect of cytokines on tumor cell growth and in antitumor immune responses is not fully understood. For example, **in addition to their potential to induce antitumor responses, some cytokines can act as autocrine and/or paracrine growth factors for human tumor cells,** including tumor cells of nonlymphoid origin. For example, IL-6, which is produced by various other types of human tumor cells (11,12,13 and 14), can act as an autocrine growth factor for human myeloma (12), Kaposi's sarcoma (13), and renal carcinoma (14), and vIL-6, a viral homologue of human IL-6 encoded by HHV-8, may act as a paracrine growth factor for multiple myeloma (15) and Castleman's disease (16), as well as for Kaposi's sarcoma, in both human immunodeficiency virus–positive and –negative people (17).

It has been proposed that epithelial ovarian cancer may be a cytokine-propelled disease (18,19,20 and 21). Cytokines, including IL-1 and IL-6, have been shown to enhance the proliferation of ovarian cancer cells (22,23), and various cytokines are known to be produced by ovarian cancer cells, including macrophage colony-stimulating factor (M-CSF), granulocyte–macrophage colony-stimulating factor (GM-CSF), IL-1, TNF-a, and IL-6 (24,25 and 26).

Many ovarian cancer cells produce both M-CSF and *fms*, the M-CSF receptor (20,24,25,27,28). Also, elevated plasma levels of M-CSF were seen in most patients with ovarian cancer (20,25,27). Because M-CSF–stimulated macrophages might produce other cytokines, such as IL-1 or IL-6, that can further stimulate tumor cell growth (25), M-CSF could potentially act as both an autocrine/paracrine tumor stimulatory factor and as a factor that can modify the host environment, resulting in enhanced tumor cell growth.

Ovarian cancer cells also produce IL-6 (11), **as do primary cultures of normal human ovarian epithelium** (29), **and elevated levels of IL-6 were seen *in vivo* in women with ovarian cancer and correlated with the presence of more extensive disease** (30). Serum levels of various cytokines, including IL-6, were examined in people with ovarian cancer: serum levels of IL-1a, IL-1b, IL-6, TNF-a, sIL-2R, and C-reactive protein (CRP) were significantly increased in patients, consistent with the previously reported hypothesis that high IL-6 and/or CRP serum levels may represent an important and independent prognostic factor for outcome in patients with cancer (31). In addition to being produced by tumor cells, IL-6 also may act as a paracrine growth factor for ovarian cancer cells: anti–IL-6 serum inhibited monocyte-produced growth-supporting activity for ovarian cancer cells (22), and inhibition of endogenous IL-6 production resulted in decreased growth of ovarian cancer cells (32).

Also, it has been suggested that the growth of ovarian cancer might be enhanced by a local deficiency of antitumor immune effector mechanisms (33). Therefore, the local production of immune-inhibitory cytokines, such as IL-10, could contribute to tumor growth in the peritoneal environment. Because peritoneal immunosuppression is characteristically seen in ovarian cancer, and IL-10 is a potent immunoinhibitory cytokine, it is possible that the high levels of IL-10 seen in ovarian cancer (32,34) could result in a peritoneal environment characterized by immune unresponsiveness and the promotion of tumor growth.

Although various cytokines can act as autocrine/paracrine growth factors for human tumor cells, cytokines also can play important roles in the generation and expansion of the host immune response to cancer, thereby resulting in the inhibition of tumor cell growth. Certainly, various cytokines, including IL-6, have the potential to modulate antitumor immune responses, and may inhibit tumor cell growth in this way (35). Cytokines clearly are of great potential value in cancer treatment. However, because of their multiple, even conflicting, biologic effects, a thorough understanding of cytokine biology will be essential for the successful use of these molecules in cancer treatment.

Biologic Therapy in Gynecologic Oncology

There is great interest in developing useful biologic therapies for gynecologic malignancies. For example, patients with small-volume, residual peritoneal ovarian cancer are attractive candidates for immunotherapy or biologic therapy, especially approaches based on regional peritoneal immunotherapy or biotherapy (36,37). Also, many patients with advanced disease are significantly immunocompromised (38), suggesting a role for immune-enhancing therapeutic approaches. Dysplastic cervical epithelial cells infected with HPV also present an attractive target for immune enhancement-based therapeutic strategies. Advances in molecular biology, biotechnology, immunology, and cytokine biology have resulted in the availability of many new, promising immunotherapeutic approaches for gynecologic cancers. Increased experience has been gained in immunotherapy for cancer, with various experimental immunotherapeutic approaches having been examined (26).

Monoclonal Antibodies and Antibody-Based Immunotherapy

Monoclonal antibodies have played an important role in the development of tumor markers: OC125, a monoclonal antibody reactive with a molecule produced by epithelial ovarian carcinoma cells is used widely to monitor blood CA125 antigen levels (see Chapter 2 and Chapter 11). Monoclonal antibodies also have been used for radioimmunodetection (39,40).

Monoclonal antibodies can potentially induce antitumor responses in various ways: by complement activation and tumor cell lysis, by directly inducing antiproliferative effects, perhaps by interaction with tumor cell surface signaling molecules, by enhancing the activity of phagocytic cells, or by mediating ADCC (26). However, most monoclonal antibodies (murine) are not directly cytotoxic and fail to activate human immune effector systems.

Monoclonal antibody-directed radiation therapy has been used for the experimental treatment of cancer, although studies evaluating the efficacy of this approach in gynecologic malignancies are limited. Radionuclide-conjugated monoclonal antibodies, given intraperitoneally (I.P.), have been used in patients with advanced chemotherapy-resistant ovarian cancer (39,40,41,42,43 and 44). This approach has the potential to reduce exposure of the monoclonal antibody to normal body tissue antigens. Because advanced chemotherapy-resistant ovarian cancer has a poor prognosis, the investigation of such novel experimental therapeutic approaches is warranted. Phase I therapeutic trials, using I.P. administration of ^{131} *I-labeled OC125 monoclonal antibody*, led to the conclusion that such treatment could be administered safely (41,42). In a phase I study, such patients were treated I.P. with a murine monoclonal antibody targeted to TAG-72, an antigen expressed in epithelial ovarian carcinomas, and labeled with ^{177}Lu(44). Also, a case report has documented a complete clinical remission in a patient with advanced ovarian cancer refractory to *paclitaxel (Taxol)* therapy, after two cycles of ^{131}*I-labeled murine MN-14 anti– carcinoembryonic antigen monoclonal antibody*, given intravenously (I.V.) (43). Another approach has been to link monoclonal antibodies to toxins, such as ricin A or *Pseudomonas* exotoxin (45), or detoxified *Salmonella* endotoxin (46,47).

Monoclonal antibody–based therapeutic strategies also can target the biologic function of cell surface signaling molecules (37). The HER-2/*neu* oncogene may play an important role in the pathogenesis of ovarian cancer; elevated levels of this oncogene were seen in approximately 20% to 30% of ovarian cancers (48). Because HER-2/*neu* is overexpressed in many cancers, the HER-2/*neu* antigen, a transmembrane protein tyrosine kinase that is homologous to the human epidermal growth factor receptor, is an attractive target for immunotherapy (49). Monoclonal antibody directed to HER-2/*neu* has been shown to enhance human tumor cell susceptibility to *TNF* and to *cisplatin* in an experimental animal model system (50), and to block DNA repair after *cisplatin* administration to human breast and ovarian cancer cells (51), confirming the potential value of *anti-HER-2/neu monoclonal antibodies* in the immunotherapy of HER-2/*neu*-expressing gynecologic cancers. One report documented the results of a phase II study of receptor-enhanced chemosensitivity in metastatic breast cancer refractory to chemotherapy, using treatment with recombinant *humanized anti-p185HER-2/neu monoclonal antibody* plus *cisplatin*, in patients with HER-2/*neu*-overexpressing tumors (52). The use of *anti-HER-2 monoclonal antibody* in combination with *cisplatin* resulted in clinical response rates higher than those reported previously for either agent alone, with no apparent increase in toxicity.

Biologic Response Modifier Therapy

Most early experimental biologic therapies for metastatic ovarian cancer involved biologic response modifiers, such as *Corynebacterium parvum* (a heat-killed, gram-negative anaerobic bacillus), bacillus *Calmette-Guerin* (BCG), Freund's complete adjuvant, or modifications of these agents (53). Exposure to *C. parvum* results in the nonspecific enhancement of host immune responses, including the induction of an acute inflammatory response characterized by the infiltration of neutrophils, macrophage attraction, activation, and cytotoxicity, and enhanced NK cell and T-lymphocyte cytotoxicity (54). In animal studies, *C. parvum* was shown to be active in inducing antitumor responses, with tumor rejection temporally associated with a cellular immune response (55,56). Biologic response modifier therapy for ovarian cancer, including treatment with *C. parvum* and BCG, was examined in several studies (57,58,59,60,61 and 62). For the most part, addition of I.V. *C. parvum* or BCG to chemotherapy did not result in any difference in response rates, disease progression-free intervals, or survival.

Malignancies that tend predominantly to grow in the peritoneal cavity, such as residual ovarian cancer, have been treated in many experimental trials with I.P. drugs, most frequently with cytotoxic chemotherapy (63,64). The rationale for this approach is that I.P. administration allows residual tumor cells to be exposed to a higher concentration of the drug than would be the case with systemic administration. This approach has been used as second-line treatment for minimal residual ovarian cancer (see also Chapter 11) (63,64). I.P. biologic response modifier therapy, immunotherapy with cytokines, or gene therapy has been proposed and used for similar reasons. However, these approaches have the additional advantage of potentially inducing the activation of regional immune effector mechanisms in the peritoneal cavity (37,45,65,66,67 and 68). Thus, such forms of therapy could prove to be effective even when a treatment with a similar biologic or gene therapeutic action has been ineffective when administered systemically. This might be particularly true for cytokine-based treatment strategies or for adoptive immunotherapies, because activated immune effector cells may require direct contact with the malignant target cells for most effective antitumor activity (26,46,56,58,69,70).

In an early study, patients with minimal residual epithelial ovarian carcinoma were treated with I.P. *C. parvum* after treatment with combination cytotoxic chemotherapy (46,58). Of the 19 evaluable patients, there were 6 responders, including 2 complete responses. ADCC and NK cytotoxicity were significantly augmented during therapy (56,58,65). However, I.P. treatment with *C. parvum* induced a profound local reaction, including peritoneal fibrosis, and its toxicity precluded more widespread testing.

Cytokine Therapy

The widespread use of recombinant DNA technology has made it possible to produce large quantities of cytokines. Several of these agents have been examined in phase I and II clinical trials, including recombinant human *IFN*-a, *IFN*-g, *TNF*-a, and *IL-2.*

Interferons

In several studies, purified or recombinant *IFN* was administered systemically to patients with ovarian cancer (68,69,70,71,72,73,74 and 75). IFN-a, which is capable of augmenting cytotoxicity of autologous peripheral blood mononuclear cells to human ovarian carcinoma cells *in vitro* (71), has been shown to be well tolerated locally but has significant systemic side effects, making it an attractive candidate for I.P. immunotherapy. I.P. treatment with recombinant human *IFN*-a results in augmented NK cytotoxicity, which is associated with tumor rejection (69,76). However, augmentation of NK activity is not invariably associated with clinical response. The dominant mechanism responsible for killing tumor cells in the peritoneal cavity may involve a direct effect of IFN on cancer cells, as is seen with cytotoxic chemotherapeutic agents, rather than the enhancement of antitumor immune responsiveness (33). Also, exposure of tumor cells to *IFN*-a may make them more vulnerable to the effects of cytotoxic drugs.

In a Gynecologic Oncology Group (GOG) study, I.P. recombinant human *IFN*-a was shown to have activity in patients with minimal residual ovarian cancer; administration of 25 to 50 million units three times a week was not tolerated because of persistent general malaise, fever, and gastrointestinal toxicity (76). Treatment with the same dose once a week was tolerated for 8 to 16 consecutive weeks. Notably, there was an absence of significant neurotoxicity and renal toxicity. Although most of the side effects of single-agent recombinant *IFN*-a seem to be complementary with *cisplatin*, the general malaise and gastrointestinal toxicity produced by both could potentially be additive when these agents are combined. Similar results were reported in another trial of I.P. *IFN*-a in the Netherlands (77). The toxicity encountered in this trial was similar to that seen in the phase I GOG trial (76). In a follow-up phase II trial conducted by the GOG, there was a 28% surgically documented response rate (7 of 25 patients) in patients with platinum-sensitive minimal residual tumors (78). Overall, 53 surgically evaluated patients have been treated in these three trials, with 21 (40%) responses and 13 (25%) complete responses (76,77 and 78). All of the responding patients had microscopic or small residual disease. These results suggest that the use of high-dose I.P. recombinant *IFN*-a given frequently can result in the regional control of very small volume disease confined to the peritoneal cavity. However, survival data are not available on these patients.

Experimental evidence suggests that synergistic antitumor responses occur when various IFNs are combined with cytotoxic agents (79,80). *IFN* can act synergistically with *cisplatin* to kill ovarian cancer cells *in vitro* (80,81). This synergy is seen only when tumor cells are exposed to IFN before the cytotoxic agent (78,81,82), presumably because IFN makes the tumor cells more susceptible to the cytotoxic effects of the drug. *In vivo* studies have shown IFN to potentiate the cytotoxicity of *cyclophosphamide* and *cisplatin* (80,83).

Because of the significant *in vitro* synergy between *cisplatin* and other agents, a search for tolerable and effective combinations was undertaken. Italian workers (84) reported treatment of ovarian cancer with weekly doses, alternating between 50 million units of I.P. recombinant human *IFN*-a and *cisplatin.* In this trial, the surgically documented complete response rate was 50%, with responses confined to those patients who started their treatment with minimum residual disease. The toxicity was similar to that seen with *IFN*-a alone. Therefore, the combination of I.P. *cisplatin* and *IFN*-a appeared to be tolerated in these patients and resulted in an appreciable response rate. The survival time of those patients who had a complete response was in general longer than in those who were nonresponsive. However, because response rates were similar to those reported in other studies of single-agent I.P. *cisplatin*, it was unclear whether the addition of *IFN*-a to the *cisplatin* had any significant benefit. Another phase I study conducted in the United States (85) also demonstrated that combined I.P. therapy with *cisplatin* and recombinant *IFN*-a was well tolerated and active in patients with residual ovarian carcinoma after systemic chemotherapy. In a GOG study of combined I.P. *IFN*-a and *cisplatin*, a very low response rate (7% partial response) was seen (86), contrary to the results of other phase I and II trials of I.P. *cisplatin* and *IFN*-a in patients with residual small-volume ovarian cancer, in which response rates of 20% to 40% have been noted (63,64,66,84,85). In the GOG study, however, most evaluable patients had extensive carcinomatosis that was *cisplatin* resistant, and the maximum tumor diameters were greater than 1 cm. In a follow-up phase II study of *IFN*-a alternating with *cisplatin* in patients with platinum-sensitive minimal residual disease, the surgically documented response rate was 28% (5 of 18 patients) (87).

In a phase I clinical trial in South Africa in which patients with advanced ovarian cancer and ascites confined to the peritoneal cavity were treated with I.P. recombinant *IFN*-a, some in combination with *cisplatin*, responses (control of refractory ascites) were seen in 36% of patients (84). In the phase II portion of that study, patients were treated randomly with *cisplatin* with or without *IFN*-a; the combination of *IFN*-a and *cisplatin* produced a higher response rate than did *IFN*-a alone. Also, the clinical responses correlated with synergy between these two agents in the *in vitro* antitumor effect. The authors concluded that the antitumor effect of *cisplatin* can be augmented by concomitant exposure to *IFN*-a.

Combined *IFN*-a and cytotoxic drug treatment also has been explored in cervical cancer. In a clinical trial of recombinant *IFN*-a plus *doxorubicin* in patients with advanced or recurrent cervical cancer, partial clinical responses were seen in 35% of subjects; fever and malaise were the major sources of toxicity (82).

Interferon-g also has antitumor effects *in vitro* as well as clear immune-enhancing effects *in vivo* in humans, such as the ability to enhance the expression of MHC class II molecules on monocytes seen after treatment with recombinant human *IFN*-g (88). The biologic effects of this cytokine have led to the examination of *IFN*-g therapy in gynecologic malignancies. Treatment of cervical cancer cells *in vitro* with *IFN*-g was seen significantly to enhance the lysis of the tumor cells by specific cytotoxic T lymphocytes that had been activated by exposure to the tumor cells (89).

In a phase I trial at the Memorial Sloan-Kettering Cancer Center, recombinant human *IFN*-g was administered I.P. to patients with refractory ovarian cancer. This treatment was shown to be well tolerated when given weekly, and was associated with a 150- to 200-fold pharmacokinetic advantage compared with systemic exposure (68). However, no clinical responses were observed. In a cooperative European trial, patients with residual ovarian cancer after initial *cisplatin*-based chemotherapy were treated I.P. with recombinant human *IFN*-g; approximately one third of evaluable patients achieved a complete response (90). The difference between the high response rate in this trial and the failure of the Memorial Sloan-Kettering Cancer Center study (68) in a similar patient population, may have been due to the higher dose intensity in the European study. In a more recent French study, recombinant human *IFN*-g was evaluated for its efficacy and tolerability as second-line treatment in patients with persistent ovarian cancer at second-look laparotomy (91). One hundred eight patients with residual disease at second-look laparotomy were treated I.P. with *IFN*-g (20×10^6 IU/m^2, administered I.P. twice a week for 3 to 4 months); 32% achieved a surgically documented response, including 23% with a complete response. The 3-year survival rate in responders was 62%. Overall, the results of this study support the potential value of I.P. *IFN*-g as adjuvant treatment in ovarian cancer.

Tumor Necrosis Factor-a

In various preclinical studies, *TNF*-a displayed significant antineoplastic activity against a variety of malignant cell lines (92,93 and 94). However, in phase I trials of *TNF*-a delivered systemically, there was limited clinical activity with considerable systemic toxicity, especially fevers, rigors, and hypotension (95,96,97 and 98). As with other cytokines and biologic response modifiers, it had been hoped that I.P. *TNF* would produce an increased antitumor response with lower systemic side effects.

In a phase I trial, I.P. administration of recombinant human *TNF*-a was shown to be safe and to have a marked pharmacokinetic advantage over systemic administration. Administration of a 50 µg/m^2 I.P. dose of recombinant human *TNF* resulted in peak peritoneal cavity TNF levels of between 15,000 and 59,000 pg/mL, compared with undetectable systemic levels (<50 pg/mL), with TNF levels between 14,000 and 33,000 pg/mL persisting in the peritoneal cavity for up to 6 hours (87). Although the TNF was not detectable in plasma, patients experienced mild emesis, temperature elevations, and chills.

In another study, I.P. recombinant human *TNF* was used to control malignant ascites (99). Twenty-three patients with peritoneal cancer and symptomatic ascites were treated with a weekly infusion of *TNF;* 87% of evaluable patients experienced successful control of malignant ascites. On the basis of this report, further studies are indicated of I.P. *TNF* for the control of malignant ascites.

The potential of *TNF* to augment the antitumor effect of a cytotoxic chemotherapeutic agent offers another potential immunotherapeutic strategy. Even very low doses of *TNF* can significantly augment the antitumor properties of drugs like *cisplatin, doxorubicin*, and *cyclophosphamide in vitro* (92,100). Therefore, the use of low-dose *TNF* therapy, administered in conjunction with cytotoxic chemotherapy, could offer a therapeutic advantage and/or minimize the toxicity of *TNF* immunotherapy.

Interleukin-2

Interleukin-2 also has been used for systemic experimental immunotherapy. In an early study, recombinant human *IL-2* administered I.V. to patients with progressive melanoma, renal, colonic, or ovarian cancer induced lymphocytosis, increased the numbers of cells expressing the IL-2 receptor and the number of detectable circulating IL-2–activated killer cells (LAK) cells, and augmented NK cytotoxicity (101). The I.P. administration of *IL-2* also has been the subject of some studies (67,87). The major rationale for developing the I.P. route of administration is the observation that IL-2 activity against malignant tumors *in vitro* is enhanced with increasing drug concentrations (101,102). In a phase I trial, administration of *IL-2* I.P. resulted in a 100-fold increase in peritoneal cavity exposure compared with systemic administration (70). In a phase I to II study of I.P. *IL-2* in refractory ovarian cancer, 2 of 13 patients had a complete response (102). Systemic toxicities were mild and included fever, fatigue, myalgias, diarrhea, emesis, and abdominal pain.

Induction of Local Cytokine Production by Paclitaxel

Although *paclitaxel* is known to have biologic effects that can inhibit tumor cell growth directly, such as stabilizing microtubules and blocking cell mitosis, the effectiveness of this drug in ovarian cancer exceeds that of other antimitotic chemotherapeutic agents, suggesting that it may have additional, perhaps indirect, modes of action. Proinflammatory cytokine gene expression has been examined in a series of cell lines and tumor explants from human ovarian cancer tissue, in which *paclitaxel* induced the secretion of IL-8, but not IL-6 or IL-1 (103). In this study, *paclitaxel* did not induce IL-8 in breast carcinoma, endometrial stromal, or T-lymphocytic or monocytic cultures. These results suggest that the *paclitaxel*-induced expression of this chemokine *in vivo* may enhance local antitumor host immune responses by inducing the transcription of cytokine and/or growth factor genes in ovarian cancer cells. Subsequent studies have led to the identification of *paclitaxel*-responsive regulatory elements in the IL-8 promoter region (104). A more recent study identified the region of *paclitaxel* responsible for the induction of IL-8 in ovarian cancer cells, and found a direct correlation between the ability to induce IL-8 production and cytotoxicity; analogs that most markedly upregulated IL-8 expression proved to be the most cytotoxic (105). However, it is not known whether any of the *in vivo* therapeutic effects of *paclitaxel* treatment are due to the induction of inflammatory cytokine production and/or to the enhancement of antitumor immune responses by *paclitaxel*-induced cytokines.

Adoptive Immunotherapy

Adoptive immunotherapy, involving the *ex vivo* enhancement of antitumor immune cell responses followed by the administration of such effector cells, has provided another immune system–based approach for antitumor therapy (106,107,108,109,110,111,112 and 113). Adoptive immunotherapy, involving the infusion of autologous *LAK cells*, has been studied extensively and shown to produce tumor regression in various animal and human tumors (106). Exposure of peripheral blood mononuclear cells to IL-2 leads to the generation of cytotoxic effect cells (LAK cells) that are cytotoxic for a variety of tumor cells. Experimental treatment of human subjects with autologous, *ex vivo*-generated *LAK cells* and *IL-2* has yielded some responses (36,66,106,107,108,109,110,111,112,113 and 114). However, the overall response rate to *LAK* treatment was low. This type of adoptive immunotherapy also can result in high morbidity, and is impractical in most medical settings (111).

Another application of adoptive immunotherapy is the *ex vivo* generation of immune effector cells from *TIL* by their activation and expansion *in vitro* by exposure to *IL-2*, and administration of the *ex vivo*-activated *TIL* concurrently with *IL-2* (112,113). A promising approach explored in animal studies involves the targeting of activated T lymphocytes with a *bifunctional monoclonal antibody* that binds to the CD3/T-cell receptor complex (on the activated effector T lymphocyte) as well as to a tumor-associated antigen (on the target tumor cell) (114). This approach has the potential advantage of targeting a large fraction of the activated T lymphocytes to the tumor cells by circumventing the natural T-cell receptor specificities of such effector cells, and also has the potential to reduce some of the side effects associated with other forms of adoptive immunotherapy that are more nonspecific.

Systemic *IL-2* administration in various forms of human cancer, with or without *LAK cells* or *TIL*, has been the subject of much investigation (108,109,110,111,112 and 113). In a phase I trial, recombinant *IL-2* and *LAK cells* were administered I.P. after systemic administration of *IL-2* (70,115). Partial clinical responses were observed in several patients with ovarian or colon cancers (115). However, considerable toxicity was seen, including fever, chills, emesis, hypotension, abdominal pain, fluid retention, bone marrow suppression, liver function abnormalities, and infection. Several patients had extensive peritoneal cavity fibrosis, possibly resulting from the release by IL-2–activated cells of various growth factors and cytokines capable of stimulating collagen synthesis.

Tumor-infiltrating lymphocyte immunotherapy has been examined in ovarian cancer; in seven patients with advanced or recurrent epithelial ovarian cancer treated with the adoptive transfer of *TIL* after a single dose of *cyclophosphamide*, one complete response and four partial responses were seen (116). When 10 additional patients were treated with a *cisplatin*-containing chemotherapeutic regimen as well as *TIL*, seven complete responses and two partial responses were seen. Four of the seven patients who had a complete response had no recurrence after 15 months of follow-up. These results suggest that *TIL*-based immunotherapy of ovarian cancer may achieve complete response rates without *IL-2* administration.

Enhancement of Specific Immune Responses to Human Papillomavirus–Infected Cervical Epithelial Cells

Human papillomavirus—specifically, HPV subtypes 16, 18, 31, and 45—has been implicated as the major etiologic agent in cervical cancer. HPV-infected dysplastic and cancerous cervical epithelial cells consistently retain and express two of the viral genes, *E6* and *E7*, that respectively interact with and disrupt the function of the p53 and retinoblastoma (Rb) tumor suppressor gene products. Factors other than infection with HPV, such as cellular immune function, play an important role in determining whether the infection of cervical epithelial cells regresses or progresses to cancer. Hence, it may be possible to develop prophylactic and/or therapeutic vaccines to HPV, as well as treatment approaches based on the enhancement of host immune function (117,118 and 119). Candidate vaccines and immunotherapeutic approaches have shown efficacy in preclinical studies, and human clinical trials are planned or in progress (119,120,121 and 122). Effective therapeutic vaccines will need to enhance cellular immune responses to HPV-positive malignant tissue. Prophylactic vaccines will need to induce the production of neutralizing antibodies for HPV antigens to prevent transmission, as well as induce effective cellular immunity to allow the elimination of HPV-infected cells. Therapeutic vaccines may be better suited for the treatment of preinvasive disease because by the time frank cervical cancer develops, molecular changes other than those induced by HPV infection may result in a less responsive tumor cell phenotype (118).

Intraperitoneal Gene Therapy

Gene therapy–based approaches to the treatment of gynecologic malignancies have gained significant attention as more has been learned about the molecular basis of these cancers, allowing for potential interventions at the molecular level for therapeutic purposes. Potential gene therapy approaches may involve the expression of cytokine genes or other genes associated with the enhancement of antitumor immune responses *(genetic immunopotentiation).* Other approaches aim to target dysfunctional oncogenes or tumor suppressor genes *(mutation compensation)* or to deliver molecular chemotherapy (123,124,125 and 126).

Several preclinical animal studies on gene therapy for gynecologic cancers have been carried out. In one study, retroviral-mediated delivery of *BRCA1 gene therapy* for ovarian cancer in nude mice was found to be effective in reducing tumor burden and to be minimally toxic (127). In another study, I.P. gene therapy, using *wild-type p53-expressing adenovirus* in nude mice implanted with a human ovarian cancer cell line that had a *p53* mutation, did not result in a statistically significant survival advantage over treatment with a control adenovirus vector (128). In addition, human ovarian tumor cells growing in immunodeficient mice responded to gene therapy with adenovirus-mediated transfer of herpes simplex thymidine kinase followed by *ganciclovir* (129,130).

Various human protocols, including studies on gene therapy for ovarian and cervical cancer, have been proposed and/or have entered phase I clinical trials.

However, significant problems exist, including limitations in the ability to deliver therapeutic genes at a sufficiently high level, and with specificity, into tumor cells. In a phase I clinical trial of patients with recurrent or persistent epithelial ovarian cancer treated with I.P. retroviral-mediated delivery of *BRCA1 gene therapy*, minimal toxicity was seen, the vector was found to be fairly stable and well expressed in patient tissues, and stable disease was seen in most patients (127). Certainly, much new information on the potential of gene therapy for gynecologic cancers will result from ongoing studies.

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4 Chemotherapy

Robert C. Young and Maurie Markman

General Principles

Tumor Growth and Chemotherapy

Drugs capable of the relatively selective destruction of malignant cells are now used routinely in patients with cancer. A wide variety of such agents are available, and the selection of drugs is often difficult. Furthermore, because most antineoplastic agents have a narrower therapeutic index than drugs of other types, careful thought should be given to the factors outlined in Table 4.1 before the institution of antineoplastic chemotherapy.

1. *Natural History of the Particular Malignancy* a. Diagnosis of a malignancy made by biopsy b. Rate of disease progression c. Extent of disease spread
2. *Patient's Circumstances and Tolerance* a. Age, general health, underlying diseases b. Extent of previous treatment c. Adequate facilities to evaluate, monitor, and treat potential drug toxicities d. The patient's emotional, social, and financial situation
3. *Likelihood of Achieving a Beneficial Response* a. Cancers in which chemotherapy is curative in some patients (e.g., ovarian germ cell tumors) b. Cancers in which chemotherapy has demonstrated improvement in survival (e.g., epithelial ovarian cancer) c. Cancers that respond to treatment but in which improved survival has not been clearly demonstrated (e.g., cervical cancer) d. Cancers with marginal or no response to chemotherapy (e.g., melanoma)

Table 4.1 Issues To Be Considered Before Using Antineoplastic Drugs

It is important to understand clearly the natural history of each patient's malignancy. **The use of chemotherapeutic agents should be restricted to patients whose malignancies have been proven by biopsy.** In some instances, second opinions regarding definitive histologic diagnoses should be obtained before the institution of chemotherapy. When doubt exists concerning the diagnosis, it is preferable to delay initial therapy and not use response to chemotherapy as a diagnostic trial.

The decision to use chemotherapy also depends on a thorough knowledge of the extent of the patient's disease as well as the rate of progression of that disease. Limited evidence of metastatic spread or documented slow disease progression may warrant withholding chemotherapy for a period. Because all chemotherapeutic agents produce toxicity, it is important that there be an evaluable tumor so that response can be assessed. It is inappropriate, in general, to administer antineoplastic agents unless benefit to the patient can be objectively determined. Thus, **except in rare instances, the ability to determine tumor response to chemotherapy is an important factor in treatment decisions.**

The patient's particular circumstances may play a major role in decisions regarding chemotherapy. The extent of previous therapy and the patient's age, general health, and other complicating illnesses form an important part of the physician's decision and may substantially affect tolerance to antineoplastic drug treatment. In addition, the patient's emotional, social, and even financial status must be respected and evaluated before a final decision is made.

Chemotherapy should not be used unless facilities are available for careful monitoring and treatment of the resulting toxicities. If such facilities are not available and chemotherapy clearly is required, the patient should be referred to a physician or another facility that has that capability.

The decision to use chemotherapy depends heavily on the probability of achieving a useful response. Not all cancers respond to chemotherapy in similar quantitative and qualitative ways. Nevertheless, **tumors can be grouped into four categories by their likelihood of chemotherapeutic response:**

1. **In the first group of tumors (e.g., ovarian germ cell tumors, choriocarcinoma), antineoplastic therapy is curative for most patients.** Obviously, a decision not to treat patients with diseases known to be curable with chemotherapy is, with rare exceptions, inappropriate. Even substantial toxicity is acceptable if the probability of cure is high.
2. **In the second group (e.g., epithelial ovarian cancer), chemotherapy improves patient survival but does not restore a normal life expectancy.** Patients with these tumors usually benefit from chemotherapy, and it should be offered unless there are exceptional circumstances.
3. **In the third group (e.g., uterine sarcoma), responses to chemotherapy occur, but improved survival has not yet been achieved for a significant number of patients.**

2. **In the second group (e.g., epithelial ovarian cancer), chemotherapy improves patient survival but does not restore a normal life expectancy.** Patients with these tumors usually benefit from chemotherapy, and it should be offered unless there are exceptional circumstances.
3. **In the third group (e.g., uterine sarcoma), responses to chemotherapy occur, but improved survival has not yet been achieved for a significant number of patients.**
4. **In the fourth group (e.g., melanoma), few, if any, responses to chemotherapy are seen.** In such cases, the use of chemotherapy should be restricted, and every effort should be made to include these patients in well designed, prospective clinical trials testing new treatment approaches.

Differential Sensitivity

For any particular antineoplastic agent to be effective, it must have greater toxicity for the malignant cells than for the patient's normal cells. In that sense, all useful chemotherapeutic agents have greater activity against tumors than against normal tissues. The window between antitumor effect and normal tissue toxicity may be small, because most chemotherapeutic agents work by disrupting DNA or RNA synthesis, affecting crucial cellular enzymes, or altering protein synthesis.

Normal cells also use these vital cellular processes in ways similar to those of malignant cells, particularly fetal or regenerating tissue or normal cell populations in which constant cell proliferation is required (e.g., bone marrow, gastrointestinal epithelium, and hair follicles). As a result, the differential effect of antineoplastic drugs on tumors compared with normal tissues is quantitative rather than qualitative, and some degree of injury to normal tissue is produced by every chemotherapeutic agent. The normal tissue toxicity produced by most chemotherapeutic agents correlates with the intrinsic cellular proliferation of the target tissue. This explains why toxicities, such as blood count suppression, mucosal injury, and alopecia, are commonly seen with most chemotherapeutic regimens.

Therapeutic Index

For any particular chemotherapeutic agent, the net effect on the patient is often referred to as the drug's *therapeutic index* (i.e., a ratio of the doses at which therapeutic effect and toxicity occur). Cancer chemotherapy requires a balance of therapeutic effect and toxicity to optimize the therapeutic index. Because the window of toxicity is often narrow for available chemotherapeutic agents, successful chemotherapy depends on pharmacologic and biologic factors.

Biologic Factors Influencing Treatment

Cell Kinetic Concepts

Both normal and tumorous tissues have a certain growth capacity and are influenced and regulated by various internal and external forces. The differential growth and regulatory influences occurring in both normal and tumorous tissues form the basis of effective cancer treatment. The exploitation of these differences forms the basis for the effective use of both radiation therapy and chemotherapy in cancer management (1).

Patterns of Normal Growth

All normal tissues have the capacity for cellular division and growth. However, normal tissues grow in substantially different patterns. There are three general types of normal tissue growth, classified as *static, renewing*, and *expanding*.

1. The *static* population comprises relatively well differentiated cells that, after initial proliferative activity in the embryonic and neonatal period, rarely undergo cell division. Typical examples are striated muscle and neurons.
2. The *expanding* population of cells is characterized by the capacity to proliferate under special stimuli (e.g., tissue injury). Under those circumstances, the normally quiescent tissue (e.g., liver or kidney) undergoes a surge of proliferation with regrowth.
3. The *renewing* population of cells is constantly in a proliferative state. There is constant cell division, a high degree of cell turnover, and constant cell loss. This occurs in bone marrow, epidermis, and gastrointestinal mucosa.

Understanding these patterns of normal tissue growth partially explains some of the most common types of toxicity seen with cancer treatments. Normal tissues with a static pattern of growth are rarely seriously injured by drug therapy, whereas renewing cell populations, such as bone marrow, gastrointestinal mucosa, and spermatozoa, are commonly injured.

Cancer Cell Growth

Tumor cell growth represents a disruption in the normal cellular brake mechanisms that exist; consequently, continued proliferation and eventual death of the host result. Although cell proliferation occurs continuously in human tumors, there is evidence that it does not take place more rapidly in cancers than in their normal-tissue counterparts. It is not the speed of cell proliferation but the failure of the regulated balance between cell loss and cell proliferation that differentiates tumorous tissues from normal tissues.

Gompertzian Growth

The characteristics of cancer growth have been assessed by multiple studies in animals and more limited studies in humans. When tumors are extremely small, growth follows an exponential pattern, but later seems to slow. Such a growth pattern is known as *Gompertzian growth.* Strictly speaking, this means exponential growth with exponential growth retardation over the entire duration of tumor growth. More simply, **Gompertzian growth means that as a tumor mass increases, the time required to double the tumor's volume also increases.**

Doubling Time

The doubling time of a human tumor is the time it takes for the mass to double its size. There is considerable variation in doubling times of human tumors. For example, embryonal tumors, lymphomas, and some malignant mesenchymal tumors have relatively fast doubling times (20 to 40 days), whereas adenocarcinomas and squamous cell carcinomas have relatively slow doubling times (50 to 150 days). In general, metastases have faster doubling times than primary lesions.

If it is assumed that exponential growth occurs early in a tumor's history and that a tumor starts from a single malignant cell, then

1. A 1-mm mass will have undergone approximately 20 tumor doublings.
2. A 5-mm mass (a size that might be first visualized on a radiograph) will have undergone 27 doublings.
3. A 1-cm mass will have undergone 30 doublings. Were such a lesion discovered clinically, the physician would assume that the tumor had been detected early. The reality is that it would have already undergone 30 doublings, or been present approximately 60% of its life span.

Unfortunately, our current clinical techniques recognize tumors late in their growth, and metastasis may well have occurred long before there is obvious evidence of the primary lesion. The second implication from this kinetic information is that in late stages of tumor growth, a very few doublings in tumor mass have a dramatic impact on the size of the tumor. Once a tumor becomes palpable (1 cm in diameter), only three more doublings would produce an enormous tumor mass (8 cm in diameter).

Cell Cycle

Information on growth patterns and doubling times relates to the growth of the tumor mass as a whole. The kinetic behavior of individual tumor cells has been well described and a classic cell cycle model has been produced (Fig. 4.1).

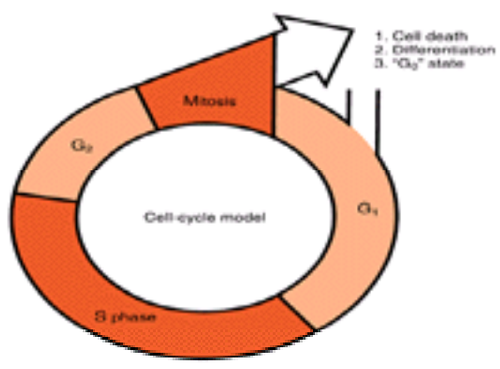


Figure 4.1 The cell cycle. After cell division, a cell can either (1) die, (2) differentiate, or (3) enter resting (G_0) phase. Cells in the latter two phases can reenter the cycle at G_1.

Figure 4.1 The cell cycle. After cell division, a cell can either (1) die, (2) differentiate, or (3) enter resting (G_0) phase. Cells in the latter two phases can reenter the cycle at G_1.

1. *M phase (mitotic phase)* of the cell cycle is the phase of cell division.
2. *G_1 phase (postmitotic phase)* is a period of variable duration when cellular activities and protein and RNA synthesis continue. These G_1 cells can differentiate or continue in the proliferative cycle.
3. *S phase (DNA synthetic phase)* is the period in which new DNA replication occurs.
4. *G_2 phase (postsynthetic phase)* is the period in which the cell has a diploid number of chromosomes and twice the DNA content of the normal cell. The cell remains in this phase for a relatively short time and then enters the mitotic phase again.
5. *G_0 phase (the resting phase)* is the time during which cells do not divide. Cells may move in and out of the G_0 phase.

The generation time is the duration of the cycle from M phase to M phase. Variation occurs in all phases of the cell cycle, but the variation is greatest during the G_1 period. The events controlling this variation are not well understood.

These cell cycle events have important implications for the cancer therapist (2). Differential sensitivities to chemotherapy and radiation therapy are associated with different proliferative states. Dividing cancer cells that are actively traversing the cell cycle are very sensitive to chemotherapeutic agents. Cells in a resting state (G_0) are relatively insensitive to chemotherapeutic agents, although they occupy space and contribute to the bulk of the tumor.

Cell Kinetics

In cell kinetic studies performed on human tumors, the duration of the S phase (DNA synthesis phase) is relatively similar for most human tumors, ranging from a low of 10 hours to a high of approximately 31 hours. The length of the cell cycle in human tumors varies from slightly more than 0.5 day to perhaps 5 days. With cell cycle times in the range of 24 hours and doubling times in the range of 10 to 1,000 days, it is clear that only a small proportion of tumor cells are in active cell division at any one time.

Two major factors that affect the rate at which tumors grow are the *growth fraction* and *cell death*. **The growth fraction is the number of cells in the tumor mass that are actively undergoing cell division.** There is a marked variation in the growth fraction of tumors in human beings, ranging from 25% to almost 95%. In the past, it was thought that human tumors contained billions of cells, all growing slowly. In actuality, only a small fraction of cells in a tumor mass are rapidly proliferating; the remainder are out of the cell cycle and quiescent.

Tumor growth may be altered by the following:

1. *Cytotoxic chemotherapy*, which alters both the generation time and the growth fraction of tumors.
2. *Hormones*, which appear to alter the growth fraction without changing the generation time.
3. *Radiation therapy*, which alters both the generation time and the growth fraction.
4. *Alterations in oxygen tension and vascular supply*, which alter the growth fraction without altering generation time.
5. *Immunologic therapies*, which seem to alter both generation time and growth fraction.

Cell Cycle–Specific Versus Nonspecific Drugs

Antineoplastic agents have complex mechanisms of action and alter cells in a wide variety of ways. Different drugs have different sites of action in the cell cycle, and their effectiveness is also a function of the proliferative capacity of the tissue involved. With the use of some of these kinetic concepts, it is possible to classify chemotherapeutic agents on the basis of their cell cycle specificity and their site of maximal drug action within the cell cycle (Table 4.2).

Classification	Examples
Cell cycle–specific, proliferation-dependent	Hydroxyurea, cytosine arabinoside
Cell cycle–specific, less proliferation-dependent	5-Fluorouracil, methotrexate
Cell cycle–nonspecific, proliferation-dependent	Cyclophosphamide, actinomycin D, carboplatin, cisplatin
Cell cycle–nonspecific, less proliferation-dependent	Paclitaxel, topotecan, nitrogen mustard

Table 4.2 Cell Cycle-Specificity of Chemotherapeutic Agents

Cell Cycle Nonspecific Cell cycle–nonspecific agents kill in all phases of the cell cycle and are not too dependent on proliferative capacity.

Cell Cycle Specific At the other end of the spectrum, cell cycle–specific agents, such as hydroxyurea, depend on the proliferative capacity and on the phase of the cell cycle for their action. The agents kill in only one portion of the cell cycle, and cells not in that phase are not injured. They tend to be most effective against tumors with relatively long S phases and those tumors in which there is a relatively high growth fraction and a rapid rate of proliferation. Between these two broad classifications, there is a spectrum of drugs with variable degrees of cell cycle and proliferation dependence.

In addition to cell cycle and proliferation sensitivity, chemotherapeutic agents may exert a greater effect in a particular phase of the cell cycle. Thus, chemotherapeutic agents can be grouped according to their site of action in the cell cycle and the extent of their dependence on proliferative activity (Table 4.3).

Portion of Cell Cycle	Drugs
G_1	Actinomycin D
Early S	Hydroxyurea, cytosine arabinoside, 5-fluorouracil, methotrexate
Late S	Doxorubicin, daunomycin
G_2	Bleomycin, radiation, etoposide, teniposide, carboplatin, cisplatin, topotecan
M	Taxol, vincristine, vinblastine

Table 4.3 Site of Action in the Cell Cycle

Log Kill Hypothesis

From knowledge of basic cellular kinetics, there have emerged certain concepts of chemotherapy that have proved useful in the design of chemotherapeutic regimens. In experimental tumor systems in animals, the animal's survival is inversely proportional to the number of cells implanted or to the size of the tumor at the time treatment is initiated (3). Treatment immediately after tumor implantation or when the tumor is subclinical in size results in more cures than when the tumor is clinically obvious and large.

Chemotherapeutic agents appear to work by first-order kinetics; that is, they kill a constant fraction of cells rather than a constant number. This concept has important conceptual implications in cancer treatment. For instance, a single exposure of tumor cells to an antineoplastic drug might be capable of producing 2 to 5 logs of cell kill. With typical body tumor burdens of 10^{12} cells (1 kg), a single dose of chemotherapy is unlikely to be curative. This explains the need for intermittent courses of chemotherapy to achieve the magnitude of cell kill necessary to produce tumor regression and cure. It also provides a rationale for multiple-drug or combination chemotherapy.

The cure rate would be significantly improved if small tumors were present, but cell masses of 10^{1} to 10^{4} cells are too small for clinical detection. This is the basis for using *adjuvant chemotherapy* in early stages of disease when subclinical numbers of cancer cells are suspected.

Drug Resistance and Tumor Cell Heterogeneity

The clinical utility of a particular chemotherapeutic agent or drug combination may be compromised severely when *drug resistance* develops. Chemotherapeutic agents often are active when initially used in cancer treatment, but tumors commonly become resistant during chemotherapy. Hence, patients often have an initial remission followed by a recurrence that is no longer responsive to the drugs that were initially effective.

A variety of cellular mechanisms are involved in drug resistance. Resistant tumor cells may display increased deactivation or decreased activation of drugs, they may be associated with increased drug efflux, or they may resist normal drug uptake. In some instances, altered specificity to an inhibiting enzyme or increased production of the target enzyme occurs to explain drug resistance on a pharmacologic basis.

Goldie-Coldman Hypothesis

It has been suggested that spontaneous mutation to phenotypic drug resistance occurs in rapidly growing malignant tumors: the somatic mutation theory (4). **This theory suggests that most mammalian cells start with intrinsic sensitivity to antineoplastic drugs but develop spontaneous resistance at variable rates.** This concept—the Goldie-Coldman hypothesis—has been applied to the growth of malignant tumors and has important clinical implications.

Goldie and Coldman developed a mathematical model that relates curability to the time of appearance of singly or doubly resistant cells. Assuming a natural mutation rate, the model predicts a variation in size of the resistant fraction in tumors of the same size and type, depending on the mutation rate and the point at which the first mutation develops. Given such assumptions, the proportion of resistant cells in any untreated tumor is likely to be small, and the initial response to treatment would not be influenced by the number of resistant cells. In clinical practice, this means that a complete remission could be obtained even if a resistant cell line were present. The failure to cure such a patient, however, would be directly dependent on the presence of resistant cell lines.

This model of spontaneous drug resistance implies that:

1. Tumors are curable with chemotherapy if no permanently resistant cell lines are present and if chemotherapy is begun before resistant cells develop.
2. If only one antineoplastic agent is used, the probability of cure diminishes rapidly with the development of a single resistant line.
3. Minimizing the emergence of drug-resistant clones requires multiple effective drugs or therapies and requires that they be applied as early as possible in the course of the patient's disease.
4. The rate of spontaneous mutation to resistance occurs at approximately the natural frequency of 1 in 10,000 to 1 in 1,000,000 cell divisions.

This model predicts that alternating cycles of treatment should be superior to the sequential use of particular agents because sequential use of antineoplastic drugs would allow for the development and regrowth of a doubly resistant line. The intrinsic frequency of spontaneous mutation to drug resistance is also likely to be influenced by etiologic factors responsible for tumor development. Lung or bladder cancers, for instance, result from exposure to multiple carcinogenic chemicals and may have a higher spontaneous mutation rate than is seen in other tumors. Under these circumstances, numerous drug-resistant clones may be present even before the tumors are clinically evident. This would explain the inability of antineoplastic therapy to cure a number of the common malignancies.

Pleiotropic Drug Resistance

The Goldie-Coldman model has focused attention on mechanisms of drug resistance. If the failure of drug treatment depends on the spontaneous appearance of resistant cells, an understanding of drug resistance is crucial to therapeutic success. A wide variety of mechanisms for drug resistance have been described, although these mechanisms usually confer resistance to a particular drug or drug family. The phenomenon of pleiotropic drug resistance occurs when certain drug-resistance mechanisms confer cross-resistance to structurally dissimilar drugs with different mechanisms of action (5).

Some pleiotropic resistant cells contain a cell surface P glycoprotein with a molecular weight of 170 kilodaltons (kd). In general, the appearance of pleiotropic drug resistance is associated with impaired ability of the cell to accumulate and retain antineoplastic drugs. It has been further demonstrated that this P glycoprotein is directly related to the expression of resistance, and cells that revert to sensitive ones lose this membrane glycoprotein.

DNA can be transferred from resistant cells into sensitive cells, producing a transfer of pleiotropic resistance to unexposed cells. The gene responsible for this multidrug resistance has been isolated, and the production of monoclonal antibodies offers a possible approach to reversing this pleiotropic resistance.

Dose Intensity

For many years, it has been taught that full doses of chemotherapy were necessary to obtain optimal clinical results. Substantial laboratory and clinical evidence now exists to support this concept. Studies in human solid tumors *in vitro* frequently demonstrate steep dose–response curves, suggesting the importance of full drug dosage. In clinical trials, higher doses of certain chemotherapeutic agents often produce responses after conventional doses have failed. In testicular and ovarian cancer, for example, twofold or threefold increases in *cisplatin* dosage produce clinical responses in patients who have relapsed after conventional doses.

A systematic analysis of dose intensity has been performed for breast and ovarian cancer (6), and it is now possible to compare different chemotherapeutic regimens by converting the drug dosage in each individual program to milligrams per meter squared per week.

Dose intensity = Drug (mg)/Surface area (M^2)/Time (weeks)

When results of chemotherapy trials are analyzed and compared, it is important that dose intensity be optimized and that drug intensity be reported.

Most of the data on the clinical impact of dose intensity come from retrospective analyses, but several prospective trials of dose intensity in ovarian cancer have produced mixed results. A large Gynecologic Oncology Group (GOG) trial of dose-intensive versus standard-dose *cisplatin* and *cyclophosphamide (Cytoxan)* in patients with advanced ovarian cancer failed to demonstrate improved duration of remission or survival, although the dose-intense regimen was double the relative dose intensity of the standard regimen (7). Several additional randomized trials have confirmed the results of the GOG trial (8,9 and 10), although at least one well designed trial has suggested some benefit associated with dose intensity in ovarian cancer (11). However, the current general consensus of opinion among ovarian cancer clinical investigators is that there is no clinically relevant dose response for ovarian cancer at concentrations of standard drugs achievable without some form of bone marrow protection.

Other approaches are now being explored to increase the intensity of drug regimens so as to increase remission rates and durations. These have included intensifying chemotherapy with the use of bone marrow or stem cell transplantation or hematopoietic growth factors to enhance marrow recovery.

Bone marrow transplantation is being used on an experimental basis in advanced, poor-prognosis, and refractory ovarian cancer. Although higher response rates are often achieved, the toxicity of these regimens often has been severe (mortality rate of 5% to 10%), and no survival benefit has been documented. Peripheral stem cell transplantations are also being studied and offer the advantage of not requiring marrow harvest under general anesthesia. More recent studies are attempting to treat patients who have demonstrated an excellent response to initial standard-dose chemotherapy, but who have persistent, small-volume residual disease documented at the time of a second-look surgical procedure (laparotomy or laparoscopy).

Attempts are also being made to reduce dose-limiting myelotoxicity by using *granulocyte–macrophage colony-stimulating factor (GM-CSF)* or *granulocyte colony-stimulating factor G-CSF*. Although these therapies accelerate the recovery of granulocytes after treatment and often reduce the duration of hospitalization after bone marrow transplantation, they are expensive and have yet to be shown to alter the therapeutic outcome. In addition, there is no study that documents any benefit from the routine prophylactic use of these hematopoietic growth factors during conventional chemotherapy.

Recombinant human interleukin-11 has been demonstrated to increase platelet counts and decrease the need for platelet transfusions (12). A role for this new bone marrow stimulatory agent in the routine treatment of ovarian cancer remains to be defined.

Pharmacologic Factors Influencing Treatment

Pharmacologically, it is useful to describe effective chemotherapy as concentration over time of the active agent or its metabolite at the primary site of antitumor action. Although it is not possible to determine exact pericellular pharmacokinetics, substantial information on important pharmacokinetic factors is available (13).

Drug effect = Drug concentration × Duration of exposure = C × T

Because direct measurements often are not possible, considerable focus is given to the plasma concentration × time (C × T) analyses. A number of important factors influence this pharmacokinetic result, including route of administration and drug absorption, transport, distribution, biotransformation, inactivation, excretion, and interactions with other drugs.

Route of Administration and Absorption

Traditionally, drugs have been given *orally, intravenously, intramuscularly*, or *intraarterially.* More recently, considerable attention has been given to the *intrapleural* or *intraperitoneal* administration of chemotherapeutic agents, particularly in ovarian cancer (14). The intraperitoneal approach is based on the concept that the pleural or peritoneal clearance of the agent is slower than its plasma clearance and, as a result, an increased concentration of the drug in the pleural or peritoneal cavity is maintained while plasma concentrations are low.

Studies of a wide variety of chemotherapeutic agents have demonstrated a differential concentration of 30- to 500-fold, depending on the molecular weight, charge, and lipid solubility of the particular drug. Clinical trials in ovarian cancer have been performed with *cisplatin, paclitaxel (Taxol)*, and drug combinations (14). Clinical trials using intraperitoneal *cisplatin* have resulted in 30% negative third-look laparotomies in patients with minimal residual disease.

The first direct evidence intraperitoneal drug delivery may improve outcome in ovarian cancer was provided by the results of a randomized trial comparing intravenous *cisplatin* to intraperitoneal *cisplatin* in women with small-volume residual advanced ovarian cancer (15). This study demonstrated the regional drug treatment strategy was associated with a statistically significant improvement in overall survival. Of note, because this study was initiated in 1985, patients received intravenous *cyclophosphamide* rather than *paclitaxel*, in addition to *cisplatin.*

An ongoing GOG trial is examining the role of both intraperitoneal *cisplatin* and *paclitaxel*, compared with intravenous drug delivery of the two agents. This trial will likely be the definitive study in defining a role for intraperitoneal drug delivery in the management of ovarian cancer because it examines the two most active agents in the disease delivered either systemically or regionally.

Drug Distribution

Antineoplastic agents usually produce their antitumor effect by interacting with intracellular target molecules. As a result, the ability of a particular drug or active metabolite to arrive at the cancer cell in sufficient concentration for lethal effect is of major importance. After absorption, drugs may be bound to serum albumin or other blood components; their ability to penetrate various body compartments, vascular spaces, and extracellular sites is highly influenced by plasma protein binding, relative ionization at physiologic pH, molecular size, and lipid solubility.

Sanctuary Sites Unique circumstances may produce sanctuary sites, which are areas where the tumor is inaccessible to anticancer drugs and the drug concentration over time is insufficient for cell kill. Examples of such sanctuary sites include the cerebrospinal fluid and areas of large tumor masses with central tumor necrosis and low oxygen tension.

Cell Penetration Although some drugs enter the target cell by simple diffusion, in some instances cellular penetration is an active process. As an example, many of the alkylating agents depend on a carrier transport system for cellular penetration. For large macromolecules, it may be necessary for pinocytosis to accomplish cellular entry.

Drug Metabolism

Many antineoplastic agents are active as intact molecules, but some require metabolism to an active form. Many of the antimetabolites require phosphorylation for cell entry. The alkylating agent, *cyclophosphamide*, requires absorption and liver metabolism to be activated. Attention to these unique metabolic requirements is needed for appropriate drug selection. For example, if direct installation of an alkylating agent is required, an agent that is active as an intact drug should be selected (e.g., *thiotepa* or *nitrogen mustard*), rather than *cyclophosphamide*, because the latter drug requires hepatic biotransformation and would not be active locally. Not only is initial activation important, but the rate of metabolic degradation of the active drug or metabolite is important in determining antitumor activity. As an example, a major mechanism of drug resistance in ovarian cancer is increased metabolism of alkylating agents due to increased intracellular enzymes (e.g., glutathione-S-transferase).

Excretion

Most chemotherapeutic agents are excreted through the kidney or liver. Because overall kidney or liver function is critical to normal drug excretion, it is necessary to modify the dosage of certain agents when either of these organs is functionally impaired. Certain drugs [e.g., *vincristine, doxorubicin (Adriamycin)*], are excreted primarily through the liver, and others (e.g., *methotrexate*) are excreted almost entirely by the kidney. Most experimental protocols and cooperative group trials contain formulas for dose modification for specific organ impairments that influence drug excretion.

Drug Interactions

Commonly, multiple drugs are administered to patients during a hospital stay. These include chemotherapeutic agents as well as non–cancer-related drugs. Consequently, there are multiple opportunities for clinically important drug interactions to occur during cancer treatment. These interactions may increase or decrease the antitumor activity of a particular agent, or they may increase or modify its toxicity (16). Types of drug interaction of potential importance include those listed in Table 4.4.

Effect	Caused by:	Interacting Drug	Resulting in	Bioavailable Drug
↓ Renal function/excretion	Nephrotoxic antibiotics	Methotrexate; cisplatin	↓ Excretion	↑
↓ Hepatic metabolism/biliary excretion	Vincristine	Adriamycin	↓ Excretion	↑
↑ Displacement from albumin or plasma proteins	Sulfonamides; salicylates	Methotrexate; cisplatin	↓ Binding	↑
↑ Intestinal absorption	Neomycin	Methotrexate	↓ Absorption	↓
↑ Direct chemical interaction	Mannitol	Cisplatin	↑ Excretion	↓
↑ Direct effect on metabolism	Phenobarbital Methotrexate 5-Fluorouracil	Cyclophosphamide 5-Fluorouracil Methotrexate	↑ Metabolism ↑ Activation ↓ Metabolism	↑ ↑ ↓

Table 4.4 Drug Interactions in Cancer Chemotherapy

Important drug interactions with antineoplastic drugs include:

1. The alkylating agents are highly reactive compounds and may produce direct chemical or physical inactivation when multiple drugs are mixed.
2. Intestinal absorption of certain chemotherapeutic agents is altered by antibiotics that suppress bowel flora (e.g., reduced absorption of oral *methotrexate*), resulting in its decreased circulating level.
3. Drugs such as *cisplatin* or *methotrexate* bind to albumin or plasma proteins and may be displaced from that binding by drugs that bind to similar sites, such as aspirin or sulfa, thereby increasing the circulating level of bioavailable *cisplatin* or *methotrexate.*
4. Alterations in drug activation may occur, as when *methotrexate* increases *5-fluorouracil* activation; conversely, drug interaction may antagonize antitumor effect, as when *5-fluorouracil* impairs the antifolate action of *methotrexate.*
5. The nephrotoxic antibiotics frequently alter *methotrexate* excretion and may increase the renal toxicity of *cisplatin.*

Principles of Combination Chemotherapy

Antineoplastic agents are now commonly used in combinations (17). Combination chemotherapy has become the standard approach to management of ovarian germ cell tumors as well as many other adult solid tumors, including Hodgkin's disease, non-Hodgkin's lymphomas, breast cancer, and testicular cancer. The enthusiasm for combinations results from several significant limitations inherent in single-agent chemotherapy. In addition, there is a solid theoretic basis for combination chemotherapy from a knowledge of cellular kinetics, drug metabolism, drug resistance, and tumor heterogeneity.

Limitations of Single-Drug Therapy

The major limitations of single-agent chemotherapy are:

1. Toxicity limits the dose and duration of drug administration and thus restricts the tumor cell kill achievable.
2. Adoptive mechanisms allow cell survival and eventual regrowth of resistant tumor cells in spite of lethal effects produced in the bulk of the tumor.
3. Spontaneous development of drug resistance.
4. Multidrug or pleiotropic drug resistance.

Several different mechanisms of resistance are seen with antineoplastic agents, and some of these are listed in Table 4.5. Most problems inherent in single-drug therapy cannot be corrected by simply altering the dose or schedule of that single drug. As a result, increasing use has been made of multidrug combination chemotherapy.

Mechanism	Example Drug
Insufficient activation of drug	Intraperitoneal cyclophosphamide, 6-mercaptopurine, 5-fluorouracil
Insufficient drug intake or defective drug transport	Methotrexate, daunomycin, paclitaxel
Increased activation	Cytosine arabinoside
Increased utilization of an alternative biochemical pathway (salvage)	Cytosine arabinoside, 5-fluorouracil
Increased concentration of the target enzyme	Methotrexate
Decreased requirement for a specific metabolic product	L-Asparaginase
Rapid DNA repair of a drug-related lesion	Alkylating agents, cisplatin, carboplatin
Gene amplification	Methotrexate
Altered enzyme expression	Topotecan

Table 4.5 Mechanisms of Resistance to Anticancer Drugs

Combination Chemotherapy Mechanisms

Different chemotherapeutic agents may act in different phases of the tumor cell cycle. Use of multiple drugs with different cellular kinetic characteristics reduces the tumor mass more completely than any individual chemotherapeutic agent while minimizing the impact of single-drug resistance. For instance, if a cell cycle–nonspecific agent is administered, producing a 2 log cell kill in a tumor mass with 10^9 cells, and no further therapy is given, a minor tumor response will occur, followed by tumor regrowth and no impact on survival. If a cell cycle–specific agent produces a similar degree of cell kill, only the cells coming into cell cycle will be affected by such an agent. Simply by using combinations or sequences of cell cycle–specific and nonspecific agents, log kill can be enhanced in tumors. With identification of appropriate combinations and proper sequencing, sufficient log kill may be achieved to produce a cure.

Drug Resistance

Combination chemotherapy can help to circumvent spontaneous mutations to drug resistance. After initial cell kill, the residual tumor may contain drug-resistant cells. **The probability of the emergence of drug-resistant cells in any given population is reduced if two or more agents with different mechanisms of action can be used in a tightly sequenced treatment scheme.**

Drug Interaction

Drug interactions may be additive, synergistic, or antagonistic. Combinations that result in improved therapy because of increased antitumor activity or decreased toxicity are said to be *synergistic. Additive* therapies produce enhanced antitumor activity equivalent to the sum of both agents acting singly. Finally, antitumor agents may actually *antagonize* the effect of each other, producing a lesser therapeutic effect than when used singly. For example, *5-fluorouracil* prevents the antifolate action of *methotrexate* when used before *methotrexate* administration.

Schedule Dependency

In some instances, the same drugs used in different sequences may produce a widely varied effect, suggesting the importance of schedule dependency. An example is the reduced cardiac toxicity demonstrated for weekly low-dose *doxorubicin* compared with high-dose bolus *doxorubicin.* Although schedule dependency has been an important, well documented phenomenon in experimental tumors, its importance is less well defined for human cancer chemotherapy.

The general principles that allowed the development of successful combinations are shown in Table 4.6. Although these cannot be used in every regimen and some overlap in toxicities is common, these concepts are a central feature of most of the regimens now being used successfully in cancer treatment.

1. The drugs used must be active as single agents against the particular tumor.
2. The drugs should have different mechanisms of action to minimize emergence of drug resistance.
3. The drugs should have a biochemical basis of at least additive and preferably synergistic effects.
4. The drugs chosen should have a different spectrum of toxicity so they can be used for maximum cell kill at full doses.
5. The drugs chosen should be administered intermittently so that cell kill is enhanced and prolonged immunosuppression is minimized.

Table 4.6 Important Factors in the Design of Drug Combinations

Remission

Once a treatment regimen has been selected, it is necessary to have some standardized way to evaluate the response to drug treatment. The terms *complete remission* and *partial remission* are used frequently and provide a convenient way to describe responses and compare various published regimens.

Complete Remission **Complete remission is the complete disappearance of all objective evidence of tumor as well as the resolution of all signs and symptoms referable to the tumor.** Complete regressions of cancer are those associated in general with significant prolongation of survival.

Partial Remission **Partial remission is an at least 50% reduction in the size of all measurable lesions along with some degree of subjective improvement and the absence of any new lesions during therapy.** Partial remissions translate in general into improved well-being for the patient but only occasionally are associated with longer overall survival.

Finally, various terms indicate lesser responses, such as *objective response* or *minor response*, but such responses rarely result in any significant improvement in survival.

Dose Adjustment

Patients vary in their tolerance to chemotherapy, and thus some mechanism for tailoring the treatment to a particular patient is necessary. One convenient method involves the use of a “sliding scale.” A typical scheme for adjusting chemotherapy based on myelosuppression is presented in Table 4.7. Doses of myelosuppressive agents are reduced if the patient proves very sensitive to the regimen but can be returned to full levels if tolerance improves in subsequent courses.

If White Blood Count Before Starting the Next Course Is:	*Then Dosage Is:*
>4,000/mm³	100% of all drugs
3,999–3,000/mm³	100% of nonmyelotoxic agents and 50% of each myelotoxic agent
2,999–2,000/mm³	100% of nonmyelotoxic agents and 25% of each myelotoxic agent
1,999–1,000/mm³	50% of nonmyelotoxic agents and 25% of myelotoxic agents
999–0/mm³	No drug until blood counts recover
If the Platelet Count Before Starting Next Course Is:	***Then Dosage Is:***
>100,000/mm³	100% of all drugs
50,000–100,000/mm³	100% of nonmyelotoxic drugs and 50% of myelotoxic drugs
<50,000/mm³	No drug until blood counts recover

Table 4.7 Drug Dose Adjustments for Combination Chemotherapy (Sliding Scale Based on Bone Marrow Toxicity)

Many experimental protocols provide for an escalation of drug dose if no significant toxicity is experienced with initial courses of therapy. A sliding scale offers the best opportunity to give the maximum amount of therapy possible. The sliding scale presented is based only on bone marrow toxicity. If the drugs used in any particular combination have other serious toxicities, such as renal or hepatic toxicity, then sliding scales based on the other toxicities are used to minimize toxicity but maximize therapeutic effect.

As an example, because *carboplatin* is cleared renally and occasional severe marrow toxicity occurs, dose-adjustment scales based on renal function have been developed. Dose adjustments are based on glomerular filtration rate (GFR) or creatinine clearance and the target serum concentration multiplied by the *area under curve (AUC)* for the drugs' antitumor activity (18). The formula is:

$$\text{Dose (mg)} = \text{Target AUC} \times (\text{GFR} + 25)$$

The desired target AUC is 4 to 6 mg/mL for previously treated patients and 5 to 7.5 mg/mL for those previously untreated. The use of these dose-adjustment schemes tailored to the particular toxicity allows for safer administration of chemotherapeutic agents.

Treatment Evaluation

A great number of combination regimens are in use in gynecologic malignancies. Many are established as treatments of choice for particular tumors, and others are experimental. In evaluating any particular combination, several important points should be considered:

1. Has the regimen been used for a number of years, and has it been demonstrated to be effective by more than one investigator for a particular stage or stages of disease?
2. Has the regimen been published with adequate discussion of the toxicities inherent in the treatment?
3. Does the regimen contain unusual forms of treatment that require unique facilities?
4. Is the combination made up of drugs that are available commercially?

Drug Toxicity

Antineoplastic drugs are among the most toxic agents used in modern medicine. Many of the toxic side effects, particularly those to organ systems with a rapidly proliferating cell population, are dose related and predictable. Usually the mechanism of toxicity is similar to the mechanism that produces the desired cytocidal effect on tumors. Even organs with limited cell proliferation can be damaged by chemotherapeutic agents in either a dose-related or an idiosyncratic fashion. In almost all instances, chemotherapeutic agents are used in doses that produce some degree of toxicity to normal tissues.

Severe systemic debility, advanced age, poor nutritional status, or direct organ involvement by primary or metastatic tumor can result in unexpectedly severe side effects of chemotherapy. Idiosyncratic drug reactions also can have severe and unexpected consequences. As a result, careful monitoring of patients receiving cancer chemotherapy is a major responsibility of physicians who elect to use this approach to cancer management (19).

Hematologic Toxicity

The proliferating cells of the erythroid, myeloid, and megakaryocytic series of the bone marrow are highly susceptible to damage by many of the commonly used antineoplastic agents. Granulocytopenia and thrombocytopenia are predictable side effects of most of the commonly used antitumor agents and are seen with all effective regimens of combination chemotherapy. The severity and duration of these side effects are variable and depend on the drugs, the dose, the schedule, and the patient's previous radiation or chemotherapy.

In general, acute granulocytopenia occurs 6 to 12 days after administration of most myelosuppressive chemotherapeutic agents and recovery occurs in 21 to 24 days; platelet suppression occurs 4 to 5 days later, with recovery after white cell count recovery. Several agents are unique in producing delayed bone marrow suppression, among them *mitomycin C* and the *nitrosoureas.* Marrow suppression from these drugs commonly occurs at 28 to 42 days, with recovery 40 to 60 days after treatment.

Granulocytopenia **Patients with an absolute granulocyte count of less than 500/mm^3 for 5 days or longer are at high risk of rapidly fatal sepsis.** The wide use of prophylactic, empiric, broad-spectrum antibiotics in febrile granulocytopenic patients with cancer has significantly decreased the incidence of life-threatening infections. Granulocytopenic patients should have their temperature checked every 4 hours and must be examined frequently for evidence of infection. The availability of hematopoietic growth factors such as *G-CSF* and *GM-CSF* has enabled physicians to reduce the duration of granulocytopenia in certain patients.

Thrombocytopenia **Patients with sustained thrombocytopenia who have platelet counts of less than 20,000/mm^3 are at risk of spontaneous hemorrhage, particularly gastrointestinal or acute intracranial hemorrhage.** Routine platelet transfusions for platelet counts below 20,000/mm^3 have significantly reduced the risk of spontaneous hemorrhage. It is common to transfuse 6 to 10 units of random donor platelets to the patient with a platelet count of less than 20,000/mm^3. Repeat transfusions at intervals of 2 to 3 days for the duration of the severe thrombocytopenia are indicated. Although patients with platelet counts exceeding 50,000/mm^3 do not commonly experience severe bleeding, transfusion at this level is indicated:

1. If the patient manifests active bleeding
2. If the patient has active peptic ulcer disease
3. Before and during surgical procedures

A posttransfusion platelet count performed 1 hour after platelet administration should show an appropriate incremental increase. If no posttransfusion platelet increase occurs, it is likely that there has been previous sensitization to random donor platelets, and the patient requires single-donor human leukocyte antigen (HLA)-matched platelets for future transfusions.

Recombinant interleukin-11 (rhIl-11) has been approved for use as an agent to increase platelet counts and decrease the need for platelet transfusions in patients experiencing or anticipated to have severe thrombocytopenia due to chemotherapy (12). The drug is administered subcutaneously beginning 6 to 24 hours after chemotherapy (50 µg/kg once daily) and continued until the platelet count exceeds 50,000/mm^3. Treatment with *rhIl-11* should be discontinued at least 2 days before the next chemotherapy.

Gastrointestinal Toxicity

The gastrointestinal tract is a frequent site of serious antineoplastic drug treatment toxicity. Mucositis caused by a direct effect on the rapidly dividing epithelial mucosal cells is common; concomitant granulocytopenia allows the injured mucosa to become infected and serve as a portal of entry for bacteria and fungi into the bloodstream. Impaired cellular immunity due to underlying disease or corticosteroid therapy also can contribute to extensive infection of the gastrointestinal tract. Other side effects related to the gastrointestinal tract include impaired intestinal motility resulting from the autonomic neuropathic effect of vinca alkaloids (*vincristine* and *vinblastine*) and nausea and vomiting, induced by many anticancer drugs.

Upper Gastrointestinal The onset of mucositis is frequently 3 to 5 days earlier than that of myelosuppression. Lesions of the mouth and pharynx are difficult to distinguish from candidiasis and herpes simplex infection. Esophagitis due to direct drug toxicity can be confused with radiation esophagitis or infections with bacteria, fungi, or herpes simplex because they all produce dysphagia and retrosternal burning pain. Oral candidiasis (thrush) responds to oral *chlortrimazole*, 10 mg five times daily. Esophageal or severe oral candidiasis usually responds to a 7-day course of intravenous *amphotericin B*, 0.5 mg/kg/ day. Mucocutaneous herpes simplex clears more rapidly with intravenous *acyclovir*, 750 mg/m^2/day. Symptomatic management of painful upper gastrointestinal inflammation includes warm saline mouth rinses and topical anesthetics, such as viscous *lidocaine.* Intravenous fluids or hyperalimentation may be required.

Lower Gastrointestinal Mucositis in the lower gastrointestinal tract is invariably associated with diarrhea. Serious complications include bowel perforation, hemorrhage, and necrotizing enterocolitis.

Necrotizing enterocolitis **includes a spectrum of severe diarrheal illnesses that can be fatal in a granulocytopenic patient.** Broad-spectrum antibiotic therapy may predispose the patient to necrotizing enterocolitis. Symptoms of necrotizing enterocolitis include watery or bloody diarrhea, abdominal pain, sore throat, nausea, vomiting, and fever. Physical examination usually reveals abdominal tenderness and distention. **Most cases of necrotizing enterocolitis are seen in patients who are treated with *clindamycin* and are caused by the anaerobic bacteria *Clostridium difficile.*** The treatment of choice for a *C. difficile* infection is oral *vancomycin*, 125 mg four times daily for 10 to 14 days.

Immunosuppression

Most anticancer drugs are capable of producing suppression of cellular and, to a lesser extent, humoral immunity. The magnitude and duration of the immunosuppression vary with the dose and schedule of drug administration and have been inadequately characterized for most chemotherapeutic agents. However, most of the acute immunosuppressive side effects do not persist after completion of drug treatment. Laboratory studies suggest a marked decrease in host defenses during treatment associated with a rebound to complete or nearly complete restoration 2 to 3 days after treatment is completed. This short-term immunosuppressive effect has led to increased use of intermittent chemotherapy regimens to allow immunologic recovery during courses of treatment.

Dermatologic Reactions

Several important drug toxicities involve skin reactions. **Skin necrosis and sloughing may result from extravasation of certain particularly irritating chemotherapeutic agents, such as *doxorubicin, actinomycin D, mitomycin C, vinblastine, vincristine*, and *nitrogen mustard.*** The extent of necrosis depends on the quantity of drug extravasated and can vary from local erythema to chronic ulcerative necrosis. Management often includes immediate removal of the intravenous line, local infiltration of corticosteroids, ice pack therapy four times a day for 3 days, and elevation of the affected limb. Long-term monitoring of the affected area is required, and surgical debridement and full-thickness skin grafting are often necessary for severe lesions.

***Alopecia* is the most common side effect of many anticancer drugs.** Although not intrinsically injurious, it has major emotional consequences for patients. Agents commonly associated with severe hair loss include the anthracycline antibiotics, the vinca alkaloids, *paclitaxel*, and *cyclophosphamide*, but most commonly used drug combinations produce variable degrees of alopecia. Alopecia is virtually always reversible if the patient is able to discontinue chemotherapy. Hair regrowth usually begins 10 days to several weeks after treatment is completed. Attempts to minimize alopecia by using cold caps have been variably effective.

Generalized allergic skin reactions can occur with chemotherapeutic agents, as they do with other drugs, and can sometimes be severe. Other skin reactions occasionally seen with chemotherapeutic agents include increased skin pigmentation *(bleomycin)*, photosensitivity reactions, transverse banding or nail loss, folliculitis *(actinomycin D, methotrexate)*, and radiation recall reactions *(doxorubicin).*

Liposomal *doxorubicin*, an agent demonstrated to be active in platinum-refractory ovarian cancer, can produce a painful dermatologic syndrome characterized by desquamation of the skin, most often involving the hands and feet (20). Blistering, focal or disseminated, can also be observed.

Hepatic Toxicity

Modest elevations in aminotransferase, alkaline phosphatase, and bilirubin levels are frequently seen with many anticancer agents, but they resolve soon after treatment is completed. Nevertheless, more severe reactions do occur. Long-term administration of *methotrexate* induces hepatic fibrosis that can progress to frank cirrhosis. The cirrhosis and drug-induced hepatitis should be managed by withdrawal of the toxic agent, with the same supportive measures that are used for hepatitis or cirrhosis of any cause.

Preexisting liver disease or exposure to other hepatotoxins may increase the risk. Antimetabolites, such as *6-mercaptopurine* and *6-thioguanine*, can produce reversible cholestatic jaundice. Transient liver enzyme abnormalities are seen with *cytosine arabinoside (Ara-C, Cytosar-U)*, the *nitrosoureas*, and L-*asparaginase. Mithramycin*, an agent occasionally used to control hypercalcemia, frequently causes marked elevations in liver enzyme levels associated with clotting disorders and renal insufficiency. Interim lactate dehydrogenase levels and prothrombin times should be followed if multiple courses of *mithramycin* are to be used.

Pulmonary Complications

Patients with cancer have a wide variety of problems that can manifest as pulmonary complications. Respiratory compromise due to lung metastases, pulmonary emboli, radiation pneumonitis, tumor-induced neuromuscular dysfunction, and pneumonia all may be significant complications. In addition, direct pulmonary toxicity from commonly used anticancer drugs sometimes is seen.

Interstitial Pneumonitis Interstitial pneumonitis with pulmonary fibrosis is the usual pattern of lung damage associated with cytotoxic drugs. Agents likely to cause such an effect are *bleomycin, alkylating agents*, and the *nitrosoureas.* The physical and chest radiologic findings are not easily distinguishable from those of interstitial pneumonitis resulting from infectious agents, viruses, or lymphangitic spread of cancer.

Management of drug-induced interstitial pneumonitis includes discontinuation of the suspected agent and supportive care. Steroids may have some benefit in the hypersensitivity to *mitomycin C* and *procarbazine.* There is little evidence of benefit in cases of pneumonitis and fibrosis secondary to alkylating agents, the nitrosoureas, and the antitumor antibiotics.

Cardiac Toxicity

Cardiac toxicity is seen with several important cancer chemotherapeutic agents. Although the myocardium consists of largely nondividing cells, drugs of the anthracycline antibiotic class, specifically *doxorubicin* and *daunomycin*, can cause severe cardiomyopathy.

The risk of cardiac toxicity increases with the total cumulative dose of *doxorubicin.* For this reason, a cumulative dose of 500 mg/m^2 of ideal body surface area is now widely used as the maximum tolerable dose of *doxorubicin*. With careful and frequent monitoring of left ventricular function by means of ejection fraction studies, therapy can be continued to higher doses if no satisfactory alternative exists. More infrequently, anthracyclines and *paclitaxel* can cause acute arrhythmias that usually disappear within a few days of drug treatment. They appear not to be related to total drug dose. Anthracycline cardiac toxicity is potentiated by radiation.

The medical management of cardiomyopathy induced by anthracyclines is supportive but usually unsatisfactory. Early detection of cardiac compromise with radionuclide cardiac scintigraphy before the clinical manifestations of congestive heart failure appear is important. Discontinuation of the drug at the first indication of decreasing left ventricular function minimizes the risk of cardiovascular decompensation.

Rarely, *cyclophosphamide* has been reported to produce cardiotoxicity, particularly in the massive doses used in conjunction with bone marrow transplantation. With conventional doses of *cyclophosphamide*, this complication is unlikely. *Busulfan* and *mitomycin C* have been reported to cause endocardial fibrosis and myocardial fibrosis, respectively. In some patients, *5-fluorouracil* has been reported to be a rare cause of angina pectoris.

Genitourinary Toxicity

In addition to chemotherapeutic agents, various other cancer-related complications may produce chronic azotemia or acute renal failure, including fluid depletion, infection, tumor infiltration of the kidney, ureteral obstruction by tumor, radiation damage, and tumor lysis syndrome.

Drugs that cause kidney damage include:

1. *Cisplatin*, which produces renal tubular toxicity associated with azotemia and magnesium wasting.
2. *Methotrexate*, which can precipitate in the renal tubules, causing oliguric renal failure. *Methotrexate* toxicity can be prevented by maintenance of a high urine volume and alkalinization of the urine.
3. *Nitrosoureas*, which cause a chronic interstitial nephritis with chronic renal failure.
4. *Mitomycin C*, which causes a systemic microangiopathic hemolysis and acute renal failure.

Metabolites of *cyclophosphamide* are irritants to the bladder mucosa and cause a *chronic hemorrhagic cystitis*, particularly during high-dose or prolonged treatment. Vigorous hydration and diuresis can reduce the risk of this complication.

Treatment of drug-related genitourinary toxicity requires discontinuation of the possibly nephrotoxic drugs and volume expansion to increase glomerular filtration. Specific metabolic abnormalities, such as hyperuricemia and hypomagnesemia, should be corrected. If oliguria develops or if medical management is unsuccessful in restoring acceptable kidney function, short-term peritoneal dialysis or hemodialysis may be required. Daily administration of 3 L of fluid containing 100 to 150 mEq of sodium bicarbonate per liter maintains the urinary pH above 7. Because *methotrexate* is poorly dialyzed, prolonged toxic levels can result if *leucovorin* rescue therapy is not continued until the *methotrexate* concentration is less than 5×10^{-8} M.

N-acetylcysteine or *mesna* (sodium mercaptoethanesulfonate) has been used in conjunction with very high doses of *cyclophosphamide* or *ifosfamide (Ifex)* to prevent bladder toxicity by inactivating the toxic metabolite *(acrolein).* Persistent hemorrhagic cystitis that does not respond to conservative management may be treated with e-*aminocaproic acid.*

Neurotoxicity

Many antineoplastic drugs are associated with some central or peripheral neurotoxicity. These neurologic side effects usually are mild, but occasionally they can be severe.

Vinca Alkaloids The vinca alkaloids (*vincristine, vinblastine*, and *vindesine*) are commonly associated with peripheral motor, sensory, and autonomic neuropathies, which are the major side effects of *vincristine.* Toxicity first appears as loss of deep tendon reflexes with distal paresthesias. Cranial nerves can be affected, and the autonomic neuropathy can appear as adynamic ileus, urinary bladder atony with retention, or hypotension. All of these neurologic toxicities from the vinca alkaloids are slowly reversible after cessation of the offending drug.

Cisplatin *Cisplatin* produces ototoxicity, peripheral neuropathy, and, rarely, retrobulbar neuritis and blindness. High doses of *cisplatin*, often used in ovarian cancer therapy, are particularly likely to produce a progressive and somewhat delayed peripheral neuropathy. This defect is characterized by sensory impairment and loss of proprioception, whereas motor strength usually is preserved. Progression of this neuropathy 1 to 2 months after cessation of high-dose *cisplatin* has been reported.

Paclitaxel *Paclitaxel* is associated with the development of a peripheral sensory neuropathy. The incidence and severity of symptoms relate to the peak levels of the agent reached in the plasma. In addition, the combination of *paclitaxel* and *cisplatin* (or *carboplatin*) has the potential to be more neurotoxic than either agent used alone (21).

Other Drugs Rarely, *5-fluorouracil* can be associated with an acute cerebellar toxicity, apparently related to its metabolism to fluorocitrate, a neurotoxic metabolite of the parent compound. *Hexamethylmelamine* has been reported to produce peripheral neuropathy and encephalopathy. Some improvement in the peripheral neuropathy has been reported with administration of B vitamin supplements, but therapeutic effectiveness may be reduced. High-dose *cytosine arabinoside* has been associated with somnolence, ataxia, and confusion.

Vascular and Hypersensitivity Reactions

Occasionally, severe hypersensitivity reactions in the form of anaphylaxis develop with chemotherapeutic agents. In rare cases this has been associated with *cyclophosphamide, doxorubicin, cisplatin*, intravenous *melphalan*, and high-dose *methotrexate. Bleomycin* administration may be associated with marked fever reactions, anaphylaxis, Raynaud's phenomenon, and a chronic scleroderma-like reaction. The same reactions have been reported with *procarbazine, etoposide (VP-16)*, and *teniposide (VM-26).*

Hypersensitivity reactions have been seen with *paclitaxel* and are believed to be due to hypersensitivity to the *cremophor* vehicle. They can be ameliorated with intravenous infusions of *dexamethasone* (20 mg), *diphenhydramine* (50 mg), and *cimetidine* (300 mg) 30 minutes before *paclitaxel* is administered. *Carboplatin* has been noted to be associated with a significant risk for hypersensitivity reactions in patients who have been treated with more than six total courses of a platinum agent (22).

Second Malignancies

Many antineoplastic agents are mutagenic and teratogenic. The potential of these agents to induce second malignancies appears to vary with the class of agent (23). Alkylating agents (especially *melphalan*), *procarbazine*, and the *nitrosoureas* seem to be the major offenders. The cumulative 7-year risk of acute nonlymphocytic leukemia developing in patients treated primarily with oral *melphalan* for ovarian cancer is as high as 9.6% in patients receiving therapy for more than 1 year (24). Although *cisplatin* has also been suggested to be associated with the development of acute leukemia, the risk is lower than with the alkylating agents (25). Evidence from long-term studies of Hodgkin's disease suggests a major risk with combined chemotherapy and radiation therapy. In such patients, there is a risk of acute leukemia as well as an increase in solid tumors, seen particularly in the radiation ports. An increase in the frequency of acute leukemia has been reported in patients treated for Hodgkin's disease, multiple myeloma, and ovarian cancer.

The second malignancy commonly occurs 4 to 7 years after successful therapy. Encouragingly, evidence suggests that after 11 years, the risk of acute leukemia in patients treated for Hodgkin's disease decreases to that of the normal population. Also encouraging are the long-term follow-up studies in women cured of choriocarcinoma, primarily with antimetabolite therapy. In such patient populations, there is no evidence of an increased risk of second malignancy. Radiation alone appears to produce a relatively low risk of late leukemia. Chemotherapeutic regimens alone, particularly those without alkylating agents or *procarbazine*, are also associated with relatively little risk. Combination chemotherapy and limited-field radiation therapy increase the risk only slightly.

Particularly high risks are associated with:

1. Extensive radiation therapy plus combination chemotherapy
2. Prolonged alkylating agent therapy (>1 year)
3. Prolonged maintenance therapy
4. Age older than 40 years at initial treatment

Gonadal Dysfunction

Many cancer chemotherapeutic agents have profound and lasting effects on testicular and ovarian function. Chemotherapeutic agents, particularly alkylating agents, can cause azoospermia and amenorrhea. Secondary sexual characteristics related to hormonal function usually are less disturbed. Prolonged intensive combination chemotherapy commonly produces azoospermia in men, and recovery is uncommon.

The onset of amenorrhea and ovarian failure is accompanied by an elevation of the serum follicle-stimulating hormone and luteinizing hormone and a decrease in the serum estradiol level. Occasionally, this hormonal pattern can be seen before the onset of amenorrhea. If the characteristic pattern is seen, patients should be advised to consider conception because these findings predict premature ovarian failure and early menopause.

When short-term intensive chemotherapy is used, particularly with antimetabolites, vinca alkaloids, or antitumor antibiotics, injury to the reproductive system is less common. For example, men treated for testicular cancer, children with acute leukemia, and women cured of gestational trophoblastic disease or ovarian germ cell malignancies usually have recovered reproductive capacity after therapy.

Chemotherapy in Pregnancy Risk of congenital abnormalities from these drugs is highest during the first trimester of pregnancy, especially when antimetabolites (e.g., *cytosine arabinoside* or *methotrexate*) and alkylating agents are used. Chemotherapy administered during the second or third trimesters usually is not associated with an increase in fetal abnormalities, although the number of patients studied is relatively small.

Metabolic Abnormalities

Inappropriate Antidiuretic Hormone Secretion Inappropriate antidiuretic hormone secretion is characterized by hyponatremia, high urine osmolality, and high urinary sodium values and is associated with several malignancies, most commonly small cell carcinoma of the lung. It can also be seen as a complication of vinca alkaloid chemotherapy. Symptoms are primarily neurologic and include altered mental status, confusion, lethargy, seizures, and coma. The severity of symptoms is related to the rapidity of development of hyponatremia. The diagnosis rests on:

1. The documentation of hyponatremia
2. The presence of a urine that is hypertonic to plasma
3. The exclusion of hypothyroidism or adrenal insufficiency

Hyperuricemia Hyperuricemia may be a complication of effective cancer chemotherapy in certain tumors, particularly hematologic malignancies where rapid tumor lysis is seen in response to initial treatment. Rapid tumor lysis produces release of predominant intracellular ions and uric acid and can result in life-threatening hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia. Renal failure associated with hyperuricemia can be severe. Prevention of the *tumor lysis syndrome* requires maintenance of a high urinary output, maintenance of high urinary pH (above 7.0), and prophylactic use of the xanthine oxidase inhibitor, *allopurinol*, as discussed in Chapter 17.

Antineoplastic Drugs

Alkylating Agents

This class of antineoplastic agent acts primarily by chemically interacting with DNA. These drugs form extremely unstable alkyl groups that react with nucleophilic (electron-rich) sites on many important organic compounds, such as nucleic acids, proteins, and amino acids. These interactions produce the primary cytotoxic effects.

Mechanism

Alkylating agents commonly bind to the N-7 position of guanine and to other key DNA sites. In doing so, they interfere with accurate base pairing, cross-link DNA, and produce single- and double-stranded breaks. This results in the inhibition of DNA, RNA, and protein synthesis.

Because some effects of alkylating agents are similar to those of irradiation, these drugs are often called *radiomimetic.* Most of the effective alkylating agents are bifunctional or polyfunctional and have two or more potentially unstable alkyl groups per molecule. These bifunctional alkylating agents allow cross-linkage of DNA that results in cellular disruption.

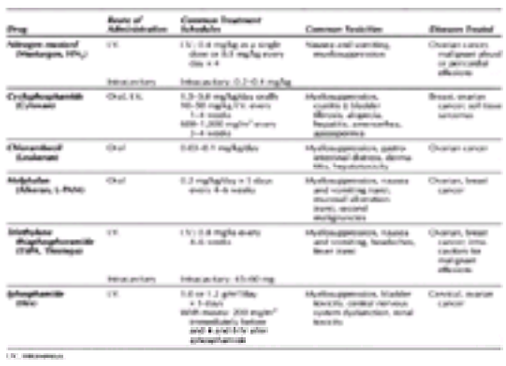
Because all alkylating agents have similar mechanisms of action, there tends to be cross-resistance to other agents of the same class.

Drugs

Although several hundred alkylating agents exist, those most commonly in use include *nitrogen mustard (Mustargen), cyclophosphamide (Cytoxan), melphalan (Alkeran), thiotepa, chlorambucil (Leukeran), busulfan (Myleran)*, and *ifosfamide (Ifex).*

In addition to the more common alkylating agents, several antineoplastic agents of different types are usually classified as alkylating-like agents, although their precise mechanism of action is less well understood and is probably not exclusively alkylation. These include the *nitrosoureas, BCNU (carmustine), methyl-CCNU (semustine), CCNU (lomustine), DTIC (dacarbazine)*, and the platinum analogs, *cisplatin* and *carboplatin.*

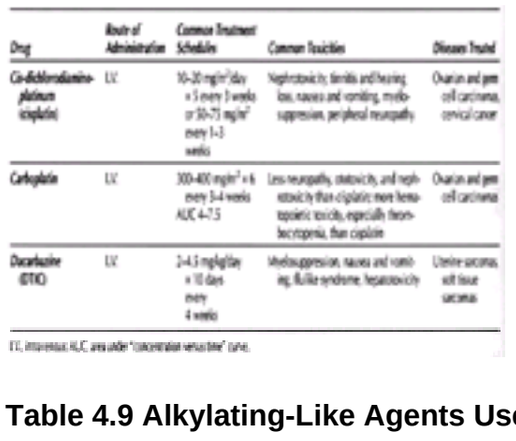
The characteristics of the commonly used alkylating agents are listed in Table 4.8 and the alkylating-like agents are listed in Table 4.9.



Drug	Route of Administration	Common Treatment Schedules	Common Toxicities	Diseases Treated
Nitrogen mustard (Mechlorgen, HN_2)	I.V.	I.V.: 0.4 mg/kg as a single dose or 0.2 mg/kg every day × 4	Nausea and vomiting, myelosuppression	Ovarian cancer; malignant pleural or pericardial effusions
	Intracavitary	Intracavitary: 0.2–0.4 mg/kg		
Cyclophosphamide (Cytoxan)	Oral, I.V.	0.3–0.8 mg/kg/day orally 90–50 mg/kg IV.: every 1–4 weeks 600–1,200 mg/m² every 2–4 weeks	Myelosuppression, cystitis & bladder fibrosis, alopecia, hepatitis, amenorrhea, azoospermia	Breast, ovarian cancer, soft tissue sarcomas
Chlorambucil (Leukeran)	Oral	0.03–0.1 mg/kg/day	Myelosuppression, gastrointestinal distress, dermatitis, hepatotoxicity	Ovarian cancer
Melphalan (Alkeran, L-PAM)	Oral	0.2 mg/kg/day × 5 days every 4–6 weeks	Myelosuppression, nausea and vomiting (rare), neuronal ulceration (rare), secondary malignancies	Ovarian, breast cancer
Isophosphamide (IFEX, Mitoxana)	I.V.	I.V.: 0.8 mg/kg every 4–5 weeks	Myelosuppression, nausea and vomiting, headaches, bleed cystitis	Ovarian, breast cancer; less common for malignant effusions
	Intracavitary	Intracavitary: 40–60 mg		
Ifosphamide (Ifex)	I.V.	1.0 or 1.2 g/m²/day × 5 days With mesna: 200 mg/m² immediately before and 4 and 8 hr after ifosfamide	Myelosuppression, bladder toxicity, cerebral nervous system dysfunction, renal toxicity	Cervical, ovarian cancer

I.V., intravenous.

Table 4.8 Alkylating Agents Used for Gynecologic Cancer



Drug	Route of Administration	Common Treatment Schedules	Common Toxicities	Diseases Treated
Cis-dichlorodiammine-platinum (cisplatin)	I.V.	10–20 mg/m²/day × 5 every 3 weeks or 50–75 mg/m² every 1–3 weeks	Nephrotoxicity, tinnitus and hearing loss, nausea and vomiting, myelosuppression, peripheral neuropathy	Ovarian and germ cell carcinoma, cervical cancer
Carboplatin	I.V.	300–400 mg/m² × 1 every 3–4 weeks AUC 4–7.5	Less neuropathy, ototoxicity, and nephrotoxicity than cisplatin; more hematopoietic toxicity, especially thrombocytopenia, than cisplatin	Ovarian and germ cell carcinoma
Dacarbazine (DTIC)	I.V.	2–4.5 mg/kg/day × 10 days every 4 weeks	Myelosuppression, nausea and vomiting, flu-like syndrome, hepatotoxicity	Uterine sarcoma, soft tissue sarcoma

I.V., intravenous; AUC, area under "concentration versus time" curve.

Table 4.9 Alkylating-Like Agents Used for Gynecologic Cancer

Antitumor Antibiotics

The antitumor antibiotics are antineoplastic drugs that, in general, have been isolated as natural products from fungi found in the soil (20). These natural products usually have extremely complex and different chemical structures, although they function in general by forming complexes with DNA.

Mechanism

The interaction between these drugs and DNA often involves intercalation, in which the compound is inserted between DNA base pairs. A second mechanism thought to be important in their antitumor action is the formation of free radicals capable of damaging DNA, RNA, and vital proteins. Other effects include metal ion chelation and alteration of tumor cell membranes. This class of antineoplastic agents is thought to be *cell cycle–nonspecific.*

Drugs

Major drugs in this family include the anthracycline antibiotics *doxorubicin (Adriamycin), liposomal doxorubicin (Doxil)*, and *daunorubicin (Daunomycin)* as well as *actinomycin D (Dactinomycin), bleomycin (Blenoxane), mitomycin C (Mutamycin)*, and *mithramycin.*

Anthracyclines The anthracyclines are antibiotics isolated from the fungi, *Streptomyces.* These pigmented compounds have an anthraquinone nucleus attached to an amino sugar and have multiple mechanisms of action. Because of the planar structure of the anthraquinone moiety, these agents act as intercalators in the DNA double helix. In addition, they are known to chelate divalent cations and are avid calcium binders. These agents cause single-stranded DNA breaks, inhibit DNA repair, and actively generate free radicals that are capable of producing DNA damage. Anthracyclines are capable of reacting directly with cell membranes, disrupting membrane structure, and altering membrane function.

Bleomycin *Bleomycin* was also isolated from the *Streptomyces* fungus. Its structure contains a DNA-binding fragment and an ion-binding unit. It appears to produce its antitumor action primarily by producing single- and double-stranded breaks in DNA, mainly at sites of guanine bases. The drug is primarily excreted in the urine, and increased toxicity may be seen in patients with impaired renal function.

Mitomycin C *Mitomycin C* is another antibiotic that was isolated from the *Streptomyces* fungus. It is activated *in vivo* into an alkylating agent that can bind DNA, producing cross-links and inhibition of DNA synthesis. In addition, it has a quinone moiety that can generate free radical reactions similar to those seen with the anthracycline antibiotics. It is administered intravenously and is degraded primarily by metabolism. Renal clearance is not a major mechanism of excretion.

Mithramycin *Mithramycin* is an antitumor antibiotic isolated from another *Streptomyces* species. It has intrinsic antitumor properties and is also effective in the management of hypercalcemia. Its primary mechanism of action seems to be the inhibition of RNA synthesis, although it binds to DNA and produces inhibition of DNA and protein synthesis.

Some of the important characteristics of the antitumor antibiotics are listed in Table 4.10.

Drug	Route of Administration	Common Treatment Schedules	Common Toxicities	Diseases Treated
Actinomycin D (dactinomycin, Cosmegen)	I.V.	0.3–0.5 mg/m² I.V. × 1 dose every 3–4 weeks	Nausea and vomiting, skin necrosis, mucosal ulceration, myelosuppression	Germ cell ovarian tumors, choriocarcinoma, soft tissue sarcoma
Bleomycin (Blenoxane)	I.V., S.C., I.M., I.P.	10–20 units/m² 1–2 times/week to total dose of 400 units for infusions; 60–120 units	Fever, dermatologic reactions, pulmonary toxicity, anaphylactic reactions	Cervical, germ cell ovarian tumors, malignant effusions
Mitomycin C (Mutamycin)	I.V.	10–20 mg/m² every 6–8 weeks	Myelosuppression, facial recession, nausea and vomiting, mucosal ulcerations, nephrotoxicity	Breast, cervical, ovarian cancer
Doxorubicin (Adriamycin)	I.V.	60–90 mg/m² every 3 weeks or 20–33 mg/m² every day × 3 every 3 weeks	Myelosuppression, alopecia, cardiotoxicity, facial vesiculation, nausea and vomiting, mucosal ulcerations	Ovarian, breast, endometrial cancer
Mithramycin (Mithracin)	I.V.	20–30 mg/kg/day every 4–8 weeks; hypercalcemia: 25 mg/kg every 3–4 days	Nausea and vomiting, hemorrhagic diathesis, hepatotoxicity, renal toxicity, fever, myelosuppression, facial flushing	Hypercalcemia of malignancy
Liposomal Doxorubicin (Doxil)	I.V.	40–50 mg/m² every 4 weeks	Palmar-plantar erythrodysesthesia, myelosuppression, stomatitis	Ovarian cancer

I.V., intravenous; S.C., subcutaneous; I.M., intramuscular; I.P., intraperitoneal

Table 4.10 Antitumor Antibiotics Used for Gynecologic Cancer

Antimetabolites

The antimetabolite family of antineoplastic agents interacts with vital intracellular enzymes, leading to their inactivation or to the production of fraudulent products incapable of normal intracellular function. In general, their structures resemble analogs of normal purines and pyrimidines, or they resemble normal substances that are vital for cell function. Some antimetabolites are active as intact drugs, and others require biotransformation to active agents.

Mechanism

Although many of these agents act at different sites in biosynthetic pathways, they appear to exert their antitumor activity by disruption of functions crucial to the viability of the cell. These effects are usually more disruptive to actively proliferating cells; thus, the antimetabolites are classed in general as *cell cycle–specific* agents.

Drugs

Although hundreds of antimetabolites have been investigated in cancer treatment, only a few are commonly used. They include:

1. The folate antagonist, *methotrexate*, which inhibits the enzyme dihydrofolate reductase
2. The purine antagonists, *6-mercaptopurine (6-MP, Purinethol)* and *6-thioguanine*
3. The pyrimidine antagonists, *5-fluorouracil (5-FU, Fluorouracil)* and *cytosine arabinoside (Ara-C, Cytosar-U)*
4. The ribonucleotide reductase inhibitor, *hydroxyurea (Hydrea)*

In most instances, the antimetabolites are used not as single drugs but in combinations because of their cell cycle specificity and their capacity for complementary inhibition. Antimetabolites commonly used in the treatment of gynecologic malignancies are summarized in Table 4.11.

Drug	Route of Administration	Common Treatment Schedules	Common Toxicities	Diseases Treated
5-fluorouracil (fluorouracil, 5-FU)	I.V.	10–15 mg/kg/week	Myelosuppression, nausea and vomiting, anorexia, alopecia	Breast, ovarian cancer
Methotrexate (MTX, amethopterin)	P.O., I.V., intrathecal	Oral: 15–40 mg/day × 5 days; I.V.: 240 mg/m² with leucovorin rescue; intrathecal: 12–15 mg/m²/week	Mucosal ulceration, myelosuppression, hepatotoxicity, allergic pneumonitis with intrathecal: meningeal irritation	Choriocarcinoma; breast, ovarian cancer
Hydroxyurea (Hydrea)	P.O., I.V.	1–2 gram/m²/day for 2–6 weeks	Myelosuppression, nausea and vomiting, anorexia	Cervical cancer
Cyclophosphamide (Cytoxan)	I.V.	800–1000 mg/m²/week × 3 weeks, followed by 1 week rest, then repeated	Myelosuppression, fever	Ovarian, breast cancer

I.V., intravenous; P.O., oral.

Table 4.11 Antimetabolites Used for Gynecologic Cancer

Plant Alkaloids

The most common plant alkaloids in use are the vinca alkaloids, natural products derived from the common periwinkle plant *(Vinca rosea)*, although the epipodophyllotoxins and *paclitaxel* are used frequently in gynecologic malignancies (Table 4.12). Like most natural products, these compounds are large and complex molecules, but *vincristine* and *vinblastine* differ only by a single methyl group on one side chain.

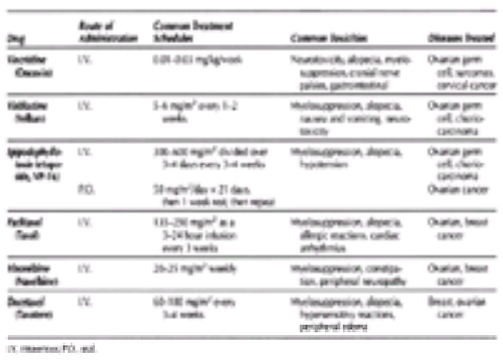


Table 4.12 Plant Alkaloids

Mechanism

Vincristine and *vinblastine* act primarily by binding to vital intracellular microtubular proteins, particularly tubulin. Tubulin binding produces inhibition of microtubule assembly and destruction of the mitotic spindle, and cells are arrested in mitosis. In general, this class of antineoplastic agent is believed to be *cell cycle–specific.* At high concentrations, these drugs also have effects on nucleic acid and protein synthesis.

Paclitaxel (Taxol) has a unique mechanism of action: it binds preferentially to microtubules and results in their polymerization and stabilization. *Paclitaxel*-treated cells contain large numbers of microtubules, free and in bundles, that result in disruption of microtubule function and, ultimately, cell death. Renal clearance is minimal (5%).

Drugs

Vinblastine is used primarily in the treatment of ovarian germ cell tumors. Its primary toxicity is myelosuppression. In contrast, *vincristine* causes little myelosuppression. Its primary dose-limiting toxicity is peripheral neuropathy. *Vincristine* is used primarily in cervical carcinoma and genital tract sarcomas.

A second family of plant alkaloids has been documented to have significant antitumor properties. Members of this family, known as the *epipodophyllotoxins*, are extracts from the mandrake plant. Although the primary plant extracts had tubulin-binding properties similar to those of the vinca alkaloids, the active derivatives, *etoposide* and *teniposide*, do not seem to function either by inhibiting mitotic spindle formation or by tubulin binding. Rather, they appear to function by causing single-stranded DNA breaks. Unlike many of the other compounds that act primarily by DNA interactions, these agents appear to be *cell cycle–specific* and *schedule dependent.* The drugs are poorly water soluble and thus are administered intravenously. The dose-limiting toxicity is myelosuppression. Other toxicities include an infusion rate–limited hypotension, nausea, vomiting, anorexia, and alopecia.

Paclitaxel is a complex agent in the class of drugs known as taxanes. Its major toxic effects include bone marrow suppression, alopecia, myalgias, arthralgias, and hypersensitivity reactions. The most common dose-limiting toxicity is granulocytopenia, although with certain schedules the limiting toxicity is peripheral sensory neuropathy. The drug is active in cancers of the ovary, endometrium, cervix, and breast.

Docetaxel, a more recently approved taxane antineoplastic agent, is also active in ovarian and breast cancer. The dose-limiting toxicity of *docetaxel* is bone marrow suppression, principally neutropenia.

Topoisomerase-1 Inhibitors

This new class of antineoplastic agents exerts its cytotoxic effect through inhibition of the enzyme topoisomerase-1 (Table 4.13). This is a critically important enzyme in DNA replication, repair, and transcription. Topoisomerase-1 inhibitors bind to the enzyme–DNA complex, leading to permanent strand breaks and cell death.

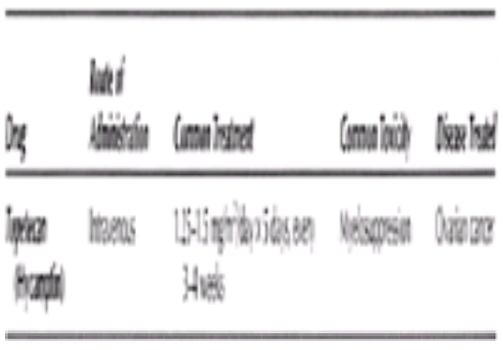


Table 4.13 Topoisomerase-1 Inhibitor

Topotecan (Hycamptin), the first topoisomerase-1 inhibitor approved for clinical use in the United States, is active in platinum-refractory ovarian cancer. The major toxicity of the agent is bone marrow suppression (26,27).

Other Agents

In addition to the antineoplastic agents summarized previously, there is another group of commonly used drugs that do not fall into any particular class. They have unique or poorly understood mechanisms. The only such agent commonly used in gynecologic malignancies is *hexamethylmelamine (Hexalen)* (Table 4.14).

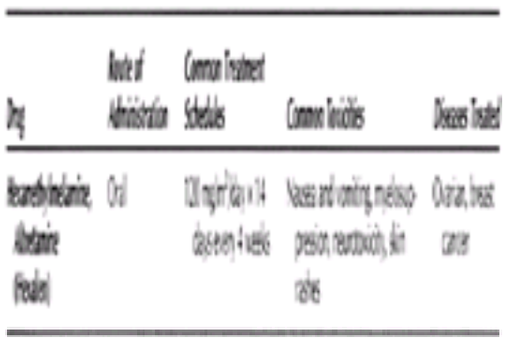


Table 4.14 Miscellaneous Agent

New Drug Trials

A number of chemotherapeutic agents have been studied experimentally but are not commercially available. Many of these agents have already demonstrated activity against human tumors, but sufficient evidence to allow human experimentation has not yet been acquired. In addition, many investigational agents are being studied in phase I and phase II trials.

Phase I Trials These studies define the spectrum of toxicity of a new chemotherapeutic agent and are complete when the dose-limiting toxicity of any particular dose and schedule has been defined.

Phase II Trials These studies usually use the dose established from phase I trials and apply this dose and schedule to selected tumor types of importance.

Phase III Trials These studies compare one effective treatment with another in a randomized fashion.

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5 Radiation Therapy

Patricia J. Eifel

Radiation therapy plays a major role in the management of patients with gynecologic malignancies. For patients with cervical cancer, it is the primary treatment for those with advanced disease (1,2), yields cure rates equal to those of radical surgery for early tumors (3,4), and reduces local recurrences after surgery for patients with high-risk features (5,6). For women with endometrial cancer, irradiation reduces local recurrence of high-risk cancers after hysterectomy (7) and is potentially curative primary treatment for patients with inoperable cancers (8,9). Postoperative, adjuvant, whole-abdominal radiation therapy improves the long-term survival rates of selected patients with ovarian cancer (10,11). Radiation therapy is also the primary curative treatment for most patients with invasive vaginal cancer (12) and has an expanding role in the management of carcinomas of the vulva (13,14).

Computer technology and information systems have transformed many aspects of radiation practice in the past two decades, making possible computed tomography (CT)-and magnetic resonance imaging (MRI)-based three-dimensional treatment planning, computer-controlled treatment delivery, and remote afterloading brachytherapy. These techniques enable radiation oncologists to restrict radiation dose distributions to specified target volumes, but challenge us to refine our knowledge of human anatomy and the disease processes used to define those volumes.

Radiation biologists and clinicians have also continued to advance our understanding of the molecular mechanisms involved in radiation-induced cell death, the nature of drug–radiation interactions, and the importance of radiation dose, time, and fractionation. **Published randomized, clinical trials have demonstrated a significant improvement in pelvic disease control and survival when concurrent chemotherapy was added to radiation therapy for patients with locally advanced cervical cancer** (15,16 and 17). These results have led to one of the most significant changes in the standard treatment of gynecologic cancers in decades.

The basic principles of radiation therapy, biology, and physics are reviewed and an overview of the indications and techniques of radiation therapy specific to gynecologic malignancies is presented.

Radiation Biology

Radiation Damage and Repair

Cellular Effects of Ionizing Radiation

In this context, ***cell death*** **is defined as the loss of clonogenic capacity (i.e., the ability of the cell to reproduce).** Almost certainly, the critical target for most radiation-induced cell death is the DNA in the cell's nucleus. Photons or charged particles interact with intracellular water to produce highly reactive free radicals. These in turn interact with DNA to produce strand breaks that interfere with the cell's ability to reproduce. Although this interaction may cause a cell's “reproductive death,” the cell may continue to be metabolically alive for some time. Radiation-induced damage may not be expressed morphologically until days or months later, when the cell attempts to divide. In some cases, a damaged cell may undergo a limited number of divisions before it dies, having lost the ability to reproduce indefinitely.

Biologists have recognized that apoptosis may also play an important role in radiation-induced cell death (18). In contrast to the more typical mitotic cell death described previously, apoptosis may occur before cell division or after the cell has completed mitosis. Studies suggest that the plasma membrane and nuclear DNA may both be important targets for this type of cell death. Apoptosis appears to be a particularly important mechanism of radiation-induced cell death in certain postmitotic normal tissues, including human salivary glands and lymphocytes. Radiation-induced apoptosis has also been observed in some proliferating normal tissues and tumors. Biologists are actively studying the pathways that regulate the expression of radiation-induced apoptosis in the hope that they can be exploited to improve local tumor control.

Cell Survival Curves

The effects of ionizing radiation on the survival of *in vitro* mammalian cell populations are typically expressed graphically as dose–response or "cell survival" curves (19). Typically, the surviving fraction of cells is plotted (on an exponential scale) against the dose of radiation (on a linear scale). From experimental data using single doses of sparsely ionizing radiation [e.g., x-rays, gamma (g)-rays, electrons, or protons], a survival curve is produced that typically has two components (Fig. 5.1):

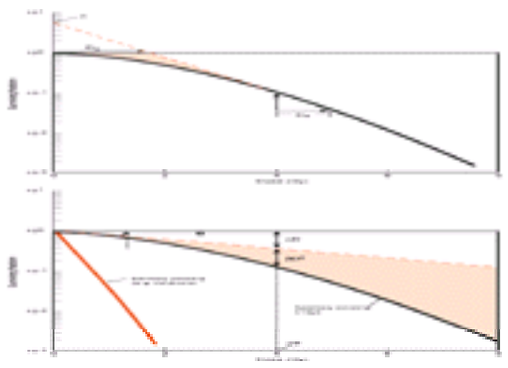

Figure 5.1 Parameters commonly used to characterize the relationship between radiation dose and cell survival in mammalian culture. *Top:* **The multitarget or N-D_0 model.** N is the extrapolation number. N and Dq measure the width of the shoulder. D_0 represents the slope of the final exponential portion of the survival curve. The multitarget model provides an accurate description of experimental data in the exponential portion of the survival curve. *Bottom:* **The linear-quadratic model more accurately describes the shape of the initial shoulder portion of the curve.** Because the shoulder has more influence on fractionated radiation, the linear-quadratic model is more often used to predict the results of fractionated clinical radiotherapy. (Modified from Hall EJ. *Radiobiology for the radiologist*, 4th ed. Philadelphia: JB Lippincott, 1994, with permission.)

1. A shoulder region
2. An exponential region

Several mathematical models, based on different hypothetical mechanisms of cell killing, have been devised to describe radiation dose–response relationships. These include:

1. The multitarget or N-D_0 model
2. The linear-quadratic model (also referred to as the a/b model)

The *multitarget model* (Fig. 5.1, *top*) is described by the expression $\log_e N = D_q/D_0$, where N and D_q measure the width of the shoulder and D_0 is the slope of the final exponential portion of the survival curve. This model derives from the *classic target theory* that states that each cell contains multiple sensitive targets, all of which must be hit to kill the cell. The presence of a shoulder region is believed to reflect accumulation of *sublethal injury* in some of the irradiated cells (20). Although the multitarget model accurately describes the exponential portion of the dose–response relationship, it is a poor fit to experimental data in the shoulder region. In particular, it fails to predict the approximately linear initial slope (D_1) of the initial portion of the shoulder (Fig. 5.1, *bottom*).

The a/b model describes the dose–response relationship according to the equation $S = e^{-(\alpha D + \beta D^2)}$, where S is the surviving fraction, D is the dose of radiation, and a and b are constants (Fig. 5.1, *bottom*). This model presupposes two components to cell death, one that is proportional to the dose (aD) and one that is proportional to the square of the dose (bD^2). The dose at which the linear and quadratic components are equal is a/b (Fig. 5.1, *top*). This model fits experimental data particularly well for the first few logs of cell death, which are most relevant to fractionated and low–dose-rate (LDR) irradiation, but is continuously bending on a log-linear plot. This bend is inconsistent with experimental data that demonstrate a straight line on a log-linear plot for the distal portion of the cell survival curve.

Fractionation

Conventional radiation therapy usually is given in a fractionated course with daily doses of 180 to 200 cGy per fraction. Hypothetical cell survival curves for normal tissue and tumor cells illustrate the advantage of fractionation (Fig. 5.2). When a dose of radiation is divided into multiple smaller doses separated by an interval sufficient to allow maximum repair of sublethal injury, a relatively shallow dose–response curve is achieved, reflecting a repetition of the shoulder of the single-dose survival curve. The slope of the fractionated cell survival curve depends on the character of the shoulder (N and D_q). The sparing effect of fractionation is greatest for cells whose response to radiation is characterized by a relatively broad shoulder, reflecting the cells' greater ability to accumulate and repair sublethal damage during the interfraction interval (Fig. 5.2, *bottom*). The *in vivo* and *in vitro* responses of many normal tissues and some poorly responsive tumors reflect this type of fractionation response. In contrast, most tumors and some "acutely responding" normal tissues (i.e., bone marrow, intestinal crypt cells) have a dose–response curve with a relatively narrow shoulder and therefore demonstrate relatively little fractionation effect. **The difference between the *fractionation sensitivity* of tumors and normal tissues is an important determinant of the *therapeutic ratio* of fractionated radiation.**

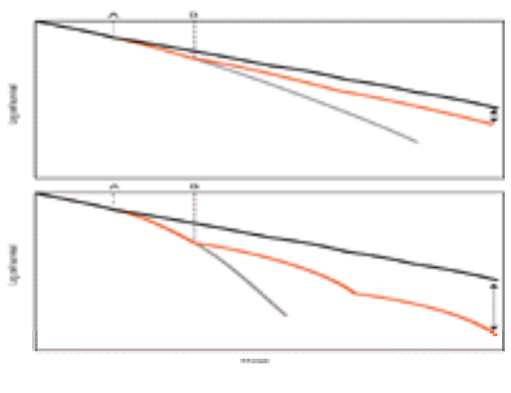

Figure 5.2 The relationship between radiation dose and the surviving fraction of cells treated *in vitro* with a single-dose *(black curves)* or a fractionated dose of radiation *(red and gray curves).* For most tumors and acutely responding normal tissues, the cellular response to single doses of irradiation is described by a curve with relatively little initial "shoulder" *(A)*. Cellular survival curves for late-responding normal tissues have a more pronounced shoulder, suggesting that these cells have a greater capacity to accumulate and repair sublethal radiation injury *(B)*. When the total dose of radiation is delivered in several smaller fractions, the response to each fraction is similar and the overall radiation survival curve reflects multiple repetitions of the initial portion of the single dose survival curve. Note that the total dose required to kill a specific proportion of the cells increases as the dose-per-fraction decreases. Compared to the *top* figure, the *bottom* figure shows the effect of halving the fraction size, which leads greater cell kill in the late-responding tissues, reflected by a more pronounced shoulder. The differential effects of fractionated irradiation on tumor and normal tissues *(arrows)* reflect the greater capacity of late-responding tissues to accumulate and repair sublethal radiation injury. (From Karcher KH, Kogelnik HD, Reinartz G, eds. *Progress in radio-oncology II.* New York: Raven Press, 1982:287–296, with permission.)

The Dose Rate Effect

So far, this discussion of cell survival curves and fractionation has referred to radiation given in acute exposures (e.g., at a rate of 100 cGy per minute or greater). At these dose rates, the shoulder of the survival curve is pronounced. However, as the dose rate is decreased, cells have a greater and greater opportunity to repair sublethal injury during the exposure. The slope of the survival curve becomes increasingly shallow and the shoulder less apparent (Fig. 5.3), until a dose rate is reached at which all sublethal injury is repaired. In experimental systems, the dose rate effect appears to be much more pronounced for normal tissue cells than for tumor cells. This differential effect implies a favorable therapeutic ratio that is exploited with LDR intracavitary and interstitial brachytherapy.

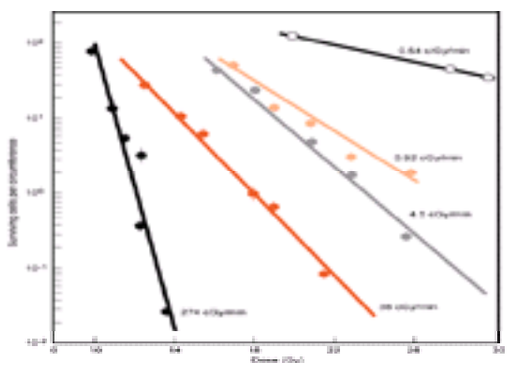

Figure 5.3 Response of mouse jejunal crypt cells to different dose rates of g-rays. The mice were given total-body irradiation and the proportion of surviving crypt cells was determined by counting regenerating microcolonies in the crypts 3.5 days after irradiation. There is a dramatic difference in cell killing because of repair of sublethal injury at low dose rates. In this system, the lowest dose rate (0.54 cGy/minute) causes little reduction in the number of surviving cells even after high doses because repopulation during the long exposure balances the cell killing from radiation.

The Four R's

The biologic effect of a given dose of radiation is influenced by the dose, fraction size, interfraction interval, and the time over which the dose is given. Four factors, classically referred to as “the four R's of radiobiology,” govern the influence of time, dose, and fractionation on the cellular response to radiation. These are:

1. Repair
2. Repopulation
3. Redistribution
4. Reoxygenation

Repair

Because fractionated irradiation permits greater recovery of sublethal injury during treatment, a higher total dose of radiation is required to achieve a given biologic effect when the total dose is divided into smaller fractions. The broader the shoulder of the survival curve, the greater the increase in dose required to achieve the level of cell death comparable with that achieved by a single dose. Two-dose experiments with varying interfraction intervals indicate that a space of at least 4 hours, and probably more than 6 hours, is necessary to complete repair of accumulated sublethal injury. Clinical studies tend to confirm these findings; for this reason, altered fractionation protocols usually require a minimum interval of 4 to 6 hours between treatments.

Repopulation

Repopulation refers to the cell proliferation that occurs during the delivery of radiation. The magnitude of the effect of repopulation on the dose required to produce a given level of cell death depends on the doubling time of the cells involved. For cells with a relatively short doubling time, a significant increase in dose may be required to compensate for a protraction in the delivery time. This phenomenon may be of considerable practical importance. Repopulation of acutely responding normal tissues (e.g., skin, mucosal surfaces) is one factor that limits contraction of a course of fractionated irradiation. However, unnecessary protraction probably reduces the effectiveness of a dose of radiation by permitting time for repopulation of malignant clonogens during treatment (21,22). In addition, cytotoxic treatments, including chemotherapy, radiation, and possibly surgical resection, may actually trigger an increase in the proliferation rate of surviving clonogens. This *accelerated repopulation* may increase the detrimental effect of treatment delays and may influence the effectiveness of sequential multimodality treatments (23,24).

Redistribution

Studies of synchronized cell populations have shown significant changes in the radiosensitivity of cells passing through different phases of the cell cycle (25). **Cells are usually most sensitive to radiation in the late G_2 phase and during mitosis and are most resistant in the middle to late S and early G_1 phases.** When asynchronous dividing cells receive a fractionated dose of radiation, the first dose tends to synchronize the cells by killing off those in sensitive phases of the cell cycle. Cells remaining in the S phase then begin to progress to a more sensitive phase of the cell cycle during the interval before the next fraction is given. This redistribution of cells to a more sensitive phase of the cell cycle tends to increase the overall cell death achieved from a fractionated dose of ionizing radiation, particularly if the cells have a relatively short cell cycle time.

Reoxygenation

The sensitivity of fully oxygenated cells to sparsely ionizing radiation is approximately three times that of cells irradiated under anoxic conditions. This makes oxygen the most effective known radiation sensitizer. The molecular interactions responsible for the oxygen effect are not completely understood, but it is believed that oxygen stabilizes reactive free radicals produced by the ionizing events. The ratio between the dose needed to achieve a given level of cell death under oxygenated versus hypoxic conditions is referred to as the *oxygen enhancement ratio* (OER) (Fig. 5.4).

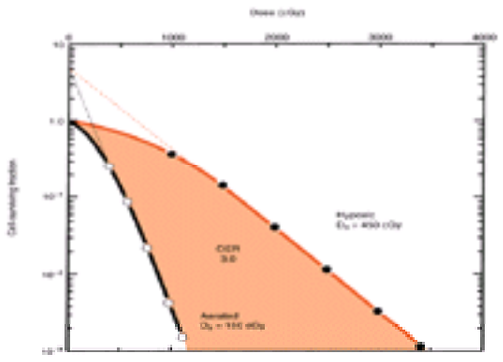

Figure 5.4 Survival curves for mammalian cells irradiated under aerated and hypoxic conditions. The dose required to produce a given level of damage is approximately three times greater under hypoxic/anoxic than under fully oxygenated conditions. The ratio of doses is the oxygen enhancement ratio (OER). Sometimes the shoulder also is reduced under hypoxic conditions. (Reproduced from Hall EJ. *Radiobiology for the radiologist* 2nd ed. Philadelphia: Harper & Row 1978 with permission.)

Although most normal tissues are fully oxygenated, significant hypoxia occurs in at least some solid tumors, rendering the resulting hypoxic cells relatively resistant to the effects of radiation. However, the clinical importance of tumor hypoxia is less certain because, initially, hypoxic cells tend to become better oxygenated during a course of fractionated radiation (26). This phenomenon, called *reoxygenation*, tends to increase the response of tumors to a dose of radiation if it is fractionated because tumor hypoxia is decreased.

Treatment Strategies

Many treatment strategies have been explored to overcome the relative radioresistance of hypoxic cells in solid human tumors (16,17,18 and 19). These include:

1. Hyperbaric oxygen or carbogen breathing
2. Red cell transfusion
3. Pharmacologic agents (e.g., *misonidazole*) that act as hypoxic cell sensitizers
4. High linear energy transfer (LET) radiation

Unfortunately, none of these approaches has clearly demonstrated an improvement in outcome; most of the studies, however, have been severely compromised by technical or logistical problems. Numerous studies have documented the poorer outcome of anemic patients with cervical cancer, but all have been compromised by possible confounding risk factors (27,28 and 29). An early study of transfusion in anemic patients with locally advanced cervical cancer (27) hinted at an improved local control when oxygen-carrying capacity was increased. However, this small study has never been repeated, and the results remain inconclusive. **Tumor hypoxia continues to be one probable cause of the failure of irradiation to control some tumors** (e.g., advanced cervical cancers with a significant population of hypoxic tumor cells) (20).

Linear Energy Transfer and Relative Biologic Effectiveness

Photons and high-energy electrons produce sparsely ionizing radiation, whereas larger atomic particles (e.g., neutrons and a particles) produce much more densely ionizing radiation. The rate of deposition of energy along the path of the beam is referred to as its LET (30). The biologic effects of densely ionizing (high-LET) radiation beams differ in several important ways from those of more sparsely ionizing radiation:

1. There is little or no reparable injury and therefore no shoulder on the tumor cell survival curve.
2. The magnitude of cell death from a given dose is greater, increasing the terminal slope of the survival curve.
3. The OER is diminished.

The unit of *relative biologic effectiveness (RBE)* is used to compare the effects of different radiation beams, and is defined as the ratio between the dose of a test radiation and that of 250-kV x-rays needed to produce a specific biologic effect. The RBE may differ somewhat according to the tissue and biologic end point being studied.

In practice, few facilities exist for the production of high-LET beams, and their use has had no major impact on the results of treatment for gynecologic malignancies.

Hyperthermia

Temperature is another factor that can modify the effect of ionizing radiation (19). Supraphysiologic temperatures alone can be toxic to cells because heat is preferentially toxic to cells in a low-pH environment (frequent in areas of hypoxia) and to cells in the relatively resistant S phase of the cell cycle. Temperatures in the range of 42°C to 43°C sensitize cells to radiation both by reducing the shoulder and by increasing the slope of the cell survival curve. Because of the different vascular supplies of tumors and normal tissues, hyperthermia may produce greater temperature elevations in tumors, increasing the possible therapeutic advantage when heat is combined with irradiation. Although biologists and clinicians have been trying to find ways to exploit this effect for many years, they have been hampered by technological limitations in the ability selectively to heat deep-seated tumors (31). Although the technology has improved since the late 1970s, it has not yet had a significant impact on the treatment of gynecologic malignancies.

Radiation Effects and Drugs

Drugs and radiation interact in a number of ways to modify cellular responses. Steel and Peckham (32) categorized these interactions into four groups: spatial cooperation, additivity, surpraadditivity, and subadditivity.

Spatial Cooperation (Independent Action)

Drugs and radiation act independently with different targets and mechanisms of action so that the total effect of the combination is equal to that of each agent separately. For example, a site that is protected from chemotherapy (e.g., the brain) may be treated with radiation to prevent recurrence. Alternatively, a drug may destroy microscopic distant disease, while radiation sterilizes local tumor.

Additivity

Two agents act on the same target to cause damage that is equal to the sum of their individual toxic effects.

Supraadditivity

A drug potentiates the effect of radiation, causing a greater response than would be expected from simple additivity.

Subadditivity

The amount of cell death that results from the use of two agents is less than that expected from simple additivity but may be greater than expected from either treatment alone.

Clinically, it is difficult to determine which mode of interaction occurs when two agents are used concurrently. When a greater response is observed than would be expected from radiation alone, the interaction is often described as synergistic, but may only be additive or even subadditive.

The addition of a cytotoxic drug to radiation is most likely to be useful if the dose-limiting toxicity of the drug is different from that of radiation therapy, and if there is a greater potentiation of tumor cell death than of toxic effects on normal tissues. When this happens, the therapeutic ratio is improved.

Treatment Strategies

There is no clinical evidence that sequential chemotherapy and radiation are more effective than radiation alone (33). However, a number of prospective, randomized studies have now been reported to demonstrate a clear supraadditive effect when chemotherapy and radiation were given concurrently to patients with locoregionally advanced cervical cancer (15,16 and 17,34,35). The most successful arms in all of these studies included concurrent *cisplatin*, and several included *5-fluorouracil (5-FU)*, a drug that has been demonstrated to be an effective radiation sensitizer in other tumor systems. A number of groups have also reported using concurrent chemoradiation therapy in patients with advanced vulvar cancer, usually with *cisplatin, 5-FU*, or *mitomycin C* (36,37,38 and 39), although the value of concurrent chemotherapy is less clearly established in this setting.

Therapeutic Ratio

Ionizing radiation interacts with all the tissues in its path. Radiation can be considered an effective cancer treatment only if there is a differential biologic effect on tumor and normal tissues. **The difference between tumor control and normal tissue complications is referred to as the *therapeutic gain* or *therapeutic ratio*.**

In general, the relationship between the probability of tumor cure or normal tissue injury and the dose of radiation can be described by a sigmoid curve (Fig. 5.5). At relatively low radiation doses, there is an insufficient amount of cell death to produce any likelihood of tumor cure. As the dose is increased, a threshold is reached at which some cures begin to be observed. For most tumor systems, the likelihood of cure rises rapidly as the radiation dose is increased beyond this threshold and reaches a plateau. The shape and slope of the dose–response curve vary according to the tumor type and size (40,41). A similar sigmoid relationship is seen when the likelihood of complications is plotted against the radiation dose. If the sigmoid curve for normal tissue complications is to the right of the curve for tumor control probability, then treatment with doses that fall between the two curves achieves a greater probability of tumor control than complications. The difference between these curves represents the therapeutic ratio. The primary goal of radiation research efforts is to improve the therapeutic ratio by increasing the separation between these dose–response curves.

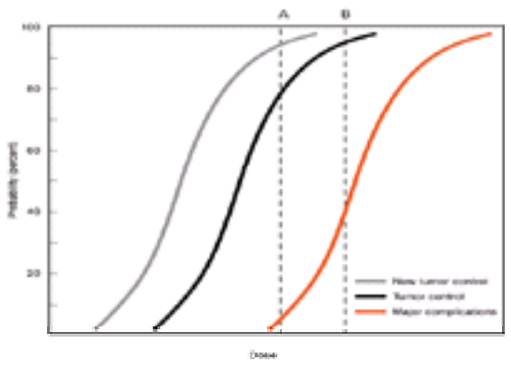

Figure 5.5 Theoretic sigmoid dose–response curves for tumor control and severe complications. The therapeutic ratio is related to the distance between the two curves. Dose A controls tumor in 80% of cases with a 5% incidence of complications. Dose B yields a 10% to 15% increase in the tumor control probability but a much greater risk of complications, narrowing the therapeutic ratio. A left shift of the tumor control probability curve (e.g., by the addition of sensitizing drugs) broadens the window for complication-free cure *(gray curve).*

Effects of Radiation on Normal Tissues

The extent of radiation damage to normal tissues depends on a number of factors, including the radiation dose, the organ, the volume of tissue irradiated, and the division rate of the irradiated cells. **Tissues that have a rapid turnover rate (i.e., tissues whose functional activity requires constant cell renewal) tend to manifest radiation injury soon after exposure, often during a fractionated course of radiation therapy.** Examples of *acutely reacting tissues* include most epithelia (e.g., skin, hair, gastrointestinal mucosa, bone marrow, and reproductive tissues). In contrast, **injury to tissues whose cells have low turnover rates and whose functions do not require rapid cell renewal tends to be manifested months or years after exposure to radiation.** Examples of *late-reacting tissues* are the connective tissues, muscle, and neural tissues.

Acute Reactions

Acute reactions to pelvic radiation such as diarrhea are usually associated with mucosal denudation, which in turn stimulates an increase in cell proliferation (42). This regenerative response usually can keep pace with weekly doses of 900 to 1,000 cGy given in five fractions. This empirically derived schedule is the most common one used for clinical radiation therapy because it produces acceptable acute complications. If treatment is accelerated to deliver the dose over much shorter periods, the regenerative capacity of the epithelium may be overwhelmed, and the acute reaction may be so severe that a break in treatment may be needed to allow for epithelial regeneration. The severity of acute reactions also depends on the volume of the normal tissues irradiated and the specific nature of the tissues.

Late Reactions

The pathogenesis of late radiation complications (i.e., those that occur months to years after radiation therapy) differs from that of acute reactions but is still incompletely understood. It has been hypothesized that late effects of radiation result from:

1. Damage to vascular stroma that causes an epithelial proliferation with decreased blood supply and subsequent fibrosis (43)
2. Damage to slowly or infrequently proliferating parenchymal stem cells that eventually results in loss of tissue or organ function (42)

Because late-reacting tissues are not proliferating rapidly, the duration of a course of radiation treatment does not alter their tolerance. However, late-responding normal tissues tend to be quite sensitive to changes in the dose per fraction, resulting in a strong correlation between the risk of late complications and the radiation fraction size. Thus, if a dose of radiation is divided into a few large fractions, the acute normal tissue response is similar to that from the same dose divided into many smaller fractions over the same time, but the late effects are greater with large fractions. This fractionation effect is responsible for the advantage of altered fractionation schedules in clinical settings, where late normal tissue reactions are severely dose limiting (44,45 and 46) (Fig. 5.2).

Treatment Strategies

A variety of altered fractionation schemes have been devised to exploit the differential sensitivity of tumor and normal tissues to fractionation and the possible effects of tumor cell repopulation. These include:

1. *Hyperfractionation:* **The dose per fraction is reduced, the number of fractions and total dose are increased, and the overall treatment time is relatively unchanged.**
2. *Accelerated fractionation:* **The dose per fraction is unchanged, the overall treatment duration is less, and the dose is unchanged or decreased.**

***Hyperfractionation* With *hyperfractionation*, treatment is usually given two or more times daily with at least 4 to 6 hours between fractions to allow repair of sublethal injury.** This scheme should permit delivery of a higher dose of radiation without increasing the risk of late complications or the overall duration of treatment. These fractionation schemes may have an advantage if the increased dose delivered per day does not cause unacceptable acute effects and if the patients are willing to accept the added inconvenience of two or three treatments daily.

***Accelerated Fractionation Accelerated fractionation* schemes do not reduce the risk of late effects and tend to increase the acute effects of treatment but may be advantageous because treatment is completed over a shorter time, reducing tumor cell repopulation during treatment (46).** However, such schemes are likely to be of limited value in the management of gynecologic malignancies because acute side effects tend to limit the rate of treatment delivery.

Hypofractionation *Hypofractionation* schedules are usually avoided when treatment is likely to cure the patient because the a/b of late-responding normal tissues is less than that of most tumors, so large fractions have a therapeutic disadvantage. Malignant melanoma, which appears to have a relatively low a/b, may be a rare exception to this. Hypofractionated schedules are frequently used for palliative treatment because they are convenient and produce rapid symptom relief. However, the necessary reduction in dose reduces the likelihood of complete eradication of tumor within the treatment field.

Combinations of Surgery and Radiation

Because surgery and radiation are both effective treatments, clinicians have tried to improve locoregional control or reduce treatment morbidity by combining the two modalities. **Theoretically, surgery may remove bulky tumor that may be difficult to control with tolerable doses of radiation, and radiation may sterilize microscopic disease at the periphery of the surgical bed.** The two modalities have been combined in a number of ways:

1. Preoperative radiation
2. Diagnostic surgery (surgical staging) followed by definitive irradiation
3. Intraoperative radiation
4. Surgical resection followed by postoperative irradiation
5. Combinations of these approaches

Preoperative Radiation

Preoperative radiation **is sometimes used to sterilize possible microscopic disease at the margins of a planned operative site. This is most useful when the surgeon anticipates close margins adjacent to a critical structure, such as the urethra or anus in a patient with locally advanced vulvar cancer.**

Until relatively recently, the most familiar example of preoperative irradiation in gynecologic oncology practice was the use of a preoperative intracavitary radiation treatment before hysterectomy for endometrial cancer. Preoperative radiation devitalizes cells that could in theory implant or disseminate at the time of surgery. Although preoperative irradiation has never been proven to improve the survival rate of patients with clinical stage I disease, it is an effective way to reduce the incidence of vaginal recurrence. However, **preoperative irradiation has largely been abandoned in favor of postoperative treatment, which can be planned when information from the surgical specimen is available, and which avoids unnecessarily treating patients with very early stage disease.** Preoperative irradiation is still frequently used to treat patients with stage II endometrial cancer that grossly involves the cervix and is used in some patients with bulky cervical cancers. This is because the dose deliverable to paravaginal tissues is much greater when the uterus is still in place to hold an intrauterine applicator than it is after surgery when only an intravaginal applicator is possible.

Some studies have suggested that lower doses of radiation may be required to sterilize microscopic disease in a tumor bed undisturbed by surgery because an intact vascular supply is better able to deliver oxygen. Because the risk of operative complications is increased after high-dose radiation, lower doses are usually given when surgical resection is anticipated than when a tumor is treated definitively with radiation. This poses the greatest risk of preoperative therapy—if the tumor remains unresectable, the effectiveness of additional irradiation is markedly decreased by the long interval between treatments.

Intraoperative Radiation

In some cases, *intraoperative radiation* can be delivered with a permanent implant (using ^{125}I or ^{198}Au), with afterloading catheters in the operative bed (using ^{192}Ir), or with a special electron beam or orthovoltage unit in the operating room. These approaches deliver radiation directly to the site of maximum risk when the target can be visualized directly and normal tissues nearest the treatment area can be removed from the radiation field. The latter is an important physical advantage of intraoperative external-beam techniques that must counterbalance the biologic disadvantage to any normal tissues remaining in the field when an entire dose is delivered in a single large fraction.

Postoperative Radiation

Postoperative radiation **has been demonstrated to improve local regional control and even survival in several settings important to gynecologic oncologists:**

1. **Vulvar cancer**—postoperative pelvic and groin irradiation reduces groin recurrence and improves the survival rate of patients with multiple positive inguinal nodes (14).
2. **Endometrial cancer**—postoperative pelvic irradiation reduces the incidence of pelvic recurrences in patients with high-risk stage I disease (7).
3. **Cervical cancer**—postoperative pelvic radiation reduces pelvic recurrences in patients with lymph node involvement and in those with high-risk features in the cervical specimen (5,6).

Combined therapy is optimized when the treatment plan exploits the complementary advantages of the two treatments. This requires close cooperation between specialists at the time of the patient's initial evaluation. Because its morbidity is often greater than that of single-modality treatment, combined treatment should usually be limited to situations where it is likely to improve survival, permit organ preservation, or significantly reduce the risk of local recurrence compared with the expected results from either modality alone (33).

Physical Principles

Ionizing Radiations Used in Therapy

Ionizing radiations lie on the high-energy [>124 electron volts (eV)] portion of the electromagnetic spectrum and are characterized by their ability to excite, or ionize, atoms in an absorbing material. The nuclear decay of radioactive nuclei can produce several types of radiation, including uncharged g-rays, negatively charged b particles (electrons), positively charged a particles (helium ions), or neutrons. The resulting ionizing radiations are exploited therapeutically in brachytherapy treatments (using ^{226}Ra, ^{137}Cs, ^{186}Ir, and other isotopes) or to produce teletherapy beams (e.g., ^{60}Co). The average energy of the photons produced by the decay of radioactive cobalt is 1.2 MeV.

Today, most external-beam therapy is delivered by linear accelerators that produce photon beams (x-rays) by bombarding a target such as tungsten with accelerated electrons. Varying the energy of the accelerated electrons produces therapeutic x-rays of different energies. X-rays and g-rays are both composed of energy quanta called *photons*, which differ only in that x-rays are produced by extranuclear forces and g-rays by intranuclear forces.

Interactions of Radiation with Matter

X-Rays and g-Rays

Photons interact with matter by means of three distinct mechanisms:

1. *Photoelectric effect* is most important at energies used for diagnostic energies. However, this type of absorption resulted from kilovoltage therapy beams commonly used before the 1960s. Absorption by the photoelectric effect is proportional to Z^3, where Z is the atomic number of the absorbing material. This is responsible for the increased absorption of bone that provides contrast between bone and soft tissue for diagnostic x-ray beams of 250 kV or more, but the increased bone absorption, high skin dose, and poor penetration make these beams unsuitable for most modern therapy applications.
2. Modern therapeutic beams of 1 to 20 MV produce photons that interact with tissues primarily by *Compton scatter*. In this process, incident photons interact with loosely bound outer shell electrons, ejecting them from the atom. Both the photon and the electron go on to interact with other atoms, causing additional ionizations. Compton scatter absorption is independent of Z but varies according to the density of the absorbing material. This accounts for the poor contrast of radiation portal verification films.
3. *Pair production* absorption is related to Z^2 in soft tissue but begins to dominate only at photon energies of more than approximately 30 MeV, so pair production is of limited importance to current radiation therapy planning.

Photons that are absorbed by Compton scatter produce an increasing number of scattered electrons and ionizations as they penetrate beneath the surface of an absorbing material. This creates a buildup region just below the surface that is responsible for the *skin-sparing* characteristic of modern high-energy therapeutic beams (Fig. 5.6). The maximum dose from a megavoltage beam is reached at 0.5 to 3.0 cm below the skin surface, depending on the photon energy. At greater depths, the dose decreases at a fairly constant rate that is related to the beam energy. The greater skin-sparing effects and penetration of energy beams of 15 MeV or more make them particularly useful for pelvic treatment.

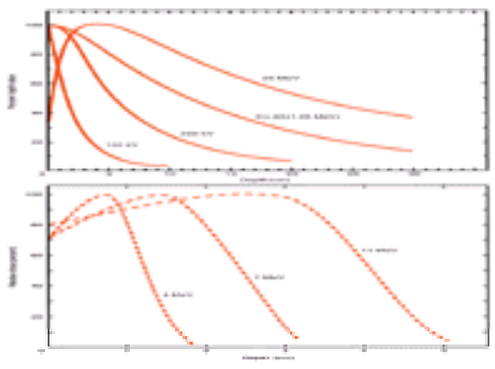

Figure 5.6 *Top:* **Depth–dose curves for selected x-ray and g-ray beams.** As the energy increases, the depth of maximum dose (D_{max} or D_{100}) increases. For kilovoltage beams, the dose is maximum at the skin surface. With appositionally directed megavoltage beams (e.g., ^{60}Co or 25-MeV photon beams), the maximum dose is reached at a depth beyond the skin surface, producing *skin sparing*. High-energy beams also penetrate more deeply, making them more useful for treatment of deep-seated pelvic tumors. *Bottom:* **Depth–dose curves for electron beam fields of selected energies.** The depth of maximum dose increases with increasing energy. At depths just below the maximum, the dose falls off rapidly, sparing deeper tissues.

Electrons and Other Particles

Several types of particle beams are used in radiation therapy.

Electrons When these very light particles interact with matter, they tend to lose most of their energy in a single interaction. The dose from an electron beam is relatively homogenous up to a depth that is related to the beam's energy (Fig. 5.6). Beyond this depth, the dose decreases very rapidly to nearly zero. Electrons are used to treat relatively superficial targets, without delivering a significant dose to underlying tissues. The approximate depth at which the rapid falloff in dose occurs can be estimated by dividing the electron energy by 3.

Protons These are much heavier charged particles than electrons. Protons scatter minimally as they interact with matter, depositing increasing amounts of energy as they slow down and then stop at a depth related to their initial energy. This results in rapid deposition of most of their energy at depth (called the *Bragg peak*), with a steep falloff in dose to near zero shortly after the peak. Modulating the energy can spread this peak out. The absence of an exit dose makes proton beams ideal for conformal therapy, and interest in their use has increased as the cost of producing proton generators has become somewhat more reasonable.

Neutrons Neutrons are neutral particles that tend to deposit most of their energy in a single intranuclear event. The falloff of a neutron dose is similar to that of a photon beam of 4 to 6 MV, but these densely ionizing beams have a high RBE that has been of interest to clinical investigators. However, clinical studies of neutron treatments in cervical cancer patients were plagued by high complication rates (47), and neutrons are rarely, if ever, used to treat gynecologic tumors today.

Measurement of Absorbed Dose

Absorbed dose is a measure of the energy deposited by the radiation source in the target material. **The unit currently used to measure radiation dose is the Gray (Gy), equal to 1 joule per kilogram of absorbing material. Before the early 1980s, absorbed doses of radiation were measured in "rad," where 1 rad = 1 cGy, and 1 Gy = 100 rad.**

Safe delivery of radiation depends on precise calibration of radiation source activities and machine output. These are measured using sensitive ionization chambers in *phantoms* that simulate tissue density. Periodic calibrations of equipment and sources are a vital part of quality assurance in any radiation oncology department.

Inverse Square Law

The dose of radiation from a source to any point in space varies according to the inverse of the square of the distance from the source to the point (48). This relationship is particularly important for brachytherapy applications because it results in a rapid falloff of dose as distance from an intracavitary or interstitial source is increased.

Radiation Techniques

Radiation therapy is delivered in three ways:

1. *Teletherapy*—x-ray therapy delivered at a distance from the body (external-beam therapy)
2. *Brachytherapy*—radiation sources are placed within or adjacent to a target volume (intracavitary or interstitial therapy)
3. *Radioactive solutions*—solutions containing isotopes (e.g., radioactive colloidal gold or ^{32}P) are introduced into a cavity (e.g., peritoneum) to treat the walls of the cavity

Teletherapy

Many factors influence the dose distribution in tissue from a single external beam of photons. Among others, these include:

1. The energy of the beam (determined by its voltage)
2. The distance from the source to the patient
3. The size of the radiation field
4. The patient's contour and the angle of the beam's incidence
5. The density of tissues in the target volume (particularly air vs. soft tissue)
6. A variety of beam-shaping devices placed between the radiation source and the patient that alter the shape or distributions of the radiation dose

Modern linear accelerators permit many variations in these elements (Fig. 5.7). A rotational gantry permits *isocentric* beam arrangements that maintain a fixed distance between the beam's source and a point within the patient. This facilitates accurate patient setup and treatment planning.

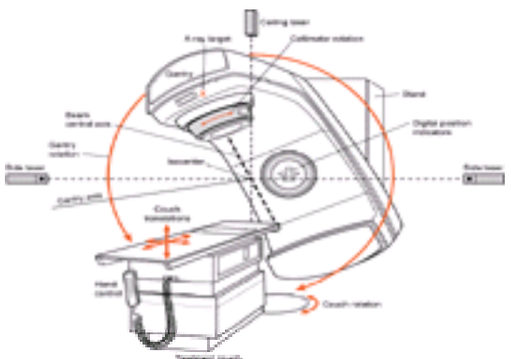

Figure 5.7 Diagram of a therapeutic linear accelerator. Patients are positioned on the treatment couch with a system of lasers that are aligned precisely with the center of the radiation beam. Collimators in the treatment head that is located on a rotating gantry define the size and rotation of the radiation field. The treatment couch can also be rotated about the central axis of the radiation beam. Beam-modifying devices such as shielding blocks and wedges can be attached to a tray beneath the collimator (not shown). (From Karzmark CJ, Nunan CS, Tanabe E. *Medical electron accelerators.* New York: McGraw-Hill, 1993, with permission.)

Most radiation therapy treatment plans combine two or more beams to create a dose distribution designed to:

1. Maximize the dose of radiation delivered to the target
2. Produce a relatively homogeneous dose within the volume of interest to minimize hot or cold spots that would increase the risks of complications or recurrence, respectively
3. Minimize the dose delivered to uninvolved tissues taking into account the different tolerances of various normal tissues

The resulting treatment plan must include the primary target volume (gross tumor or tumor bed), any areas at risk for microscopic spread of disease, and a margin of tissue to account for uncertainties in the location of the target, reproducibility of the setup, and organ motion. The overall plan is often designed to deliver different doses to areas of greater or lesser risk (e.g., gross vs. microscopic residual disease) by boosting areas at greater risk with smaller treatment fields after initial treatment to a relatively large volume.

Two opposing beams (e.g., anteroposterior and posteroanterior) usually produce a relatively homogeneous distribution of dose within the intervening tissue with some sparing of the skin surface. In many cases, multiple fields may be used to "focus" the high-dose region to conform more closely to a deep target volume (Fig. 5.8). Modern technology has made it possible to use computers to optimize the beam arrangements required in treatment plans that incorporate many fields and beam-shaping devices. These *conformal* treatment plans may provide a very tight distribution of dose around the target volume. Theoretically, these approaches should improve the therapeutic ratio by making it possible to deliver higher doses to the tumor with greater sparing of normal tissues. However, because of the rapid falloff of dose outside the designated target volume, these plans require a high degree of confidence in the distribution of disease and meticulous patient immobilization.

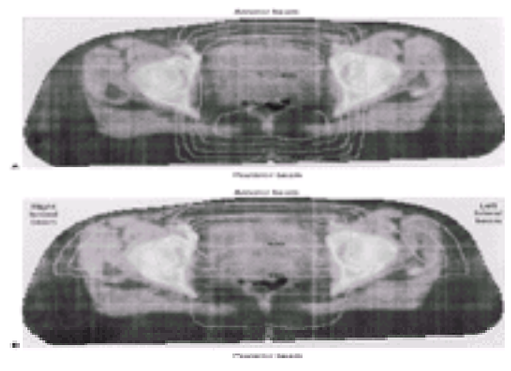

Figure 5.8 Isodose distribution for external-beam irradiation to the pelvis using an 18-MeV beam. A: A pair of parallel opposed anterior and posterior fields. **B:** Anterior, posterior, and two lateral fields (four-field box technique).

Brachytherapy

Intracavitary Treatment

Any treatment that involves placement of radioactive sources in an existing body cavity is termed *intracavitary* treatment. The most common gynecologic applications of intracavitary therapy involve placement of intrauterine or intravaginal applicators that are subsequently loaded with encapsulated radioactive sources (e.g., ^{137}Cs, ^{226}Ra, or ^{192}Ir) (Table 5.1). Applicator systems vary in their appearance and configuration, but those used for radical treatment of cervical or uterine cancer tend to have several features in common. These applicators usually consist of a hollow tube or *tandem*, and some form of intravaginal receptacle for additional sources. The greatest variation between systems is in the vaginal applicators, which differ in their shape, the orientation of sources, and the presence or absence of shielding (49,50). One applicator that is commonly used to treat intact carcinomas of the cervix is the *Fletcher-Suit-Delclos* system (Fig. 5.9). Other applicator systems, such as the *Delclos dome cylinder*, have been designed specifically for treatment of the vaginal apex after hysterectomy (51).

Element	Isotope	Half-Life	E_γ (MeV)	E_β (MeV)
Phosphorus	^{32}P	14.3 days	None	1.7 (max)
Iodine	^{125}I	60.2 days	0.028 (average)	None
	^{131}I	8.06 days	0.08–0.63	0.61 (max)
Cesium	^{137}Cs	30 years	0.662	0.514, 1.17
Iridium	^{192}Ir	74 days	0.32–0.61	0.24, 0.67
Gold	^{198}Au	2.7 days	0.41–1.1	0.96 (max)
Radium	^{226}Ra	1620 years	0.19–0.6	3.26 (max)
Cobalt	^{60}Co	5.26 years	1.17–1.33	0.313 (max)

E_γ, gamma ray energy; E_β, beta ray energy; MeV, million electron volts.

Table 5.1 Isotopes Used in Gynecologic Oncology

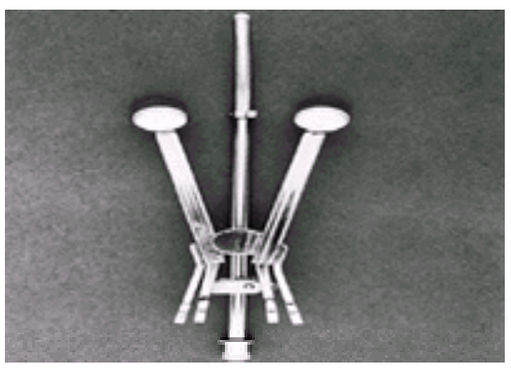

Figure 5.9 Intrauterine tandem and vaginal colpostats used for intracavitary irradiation in cervical cancer.

A typical pear-shaped isodose distribution is produced by a line of intrauterine sources and *Fletcher-Suit-Delclos vaginal colpostats* loaded with ^{137}Cs (Fig. 5.10). This approach has proven very useful in the treatment of cervical cancer because it allows a very high dose of radiation to be delivered to a small volume surrounding the applicator (e.g., the cervix and paracervical tissues) without excessively treating normal tissues that are more distant from the sources. Because of the rapid change in dose over short distances, accurate positioning of the intracavitary applicator and sources is very important. Packing or retraction of the bladder and rectum can significantly reduce the dose to portions of these organs by distancing them from the vaginal sources.

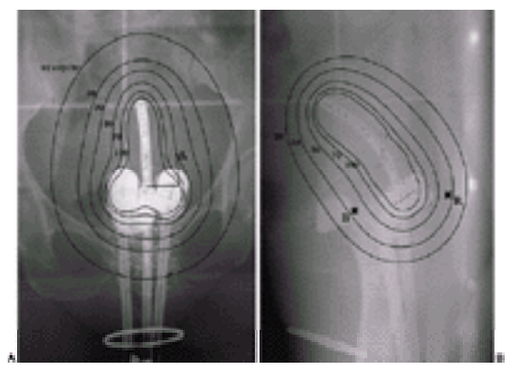

Figure 5.10 Posteroanterior and lateral views of a Fletcher-Suit-Delclos applicator system loaded with ^{137}Cs sources for treatment of invasive cervical cancer. Units on the isodose contours are centigrays per hour. **A,B:** Point *(A)*, bladder *(B)*, and rectal *(R)* reference points are indicated. (From Eifel PJ, Berek JS, Thigpen JT. Cancer of the cervix, vagina, and vulva. In: DeVita V, Hellman S, Rosenberg S, eds. *Cancer: principles and practice of oncology.* Philadelphia: JB Lippincott, 1997:1433–1477.)

To minimize the exposure of medical personnel to radiation, most modern applicator systems are *afterloaded* with radioactive sources after adequate positioning has been confirmed with anteroposterior and lateral radiographs of the pelvis. The more recent use of remote afterloading devices that automatically retract sources from the applicator to a lead-lined safe before someone enters the patient's room further reduces the radiation exposure to visitors and medical personnel.

Brachytherapy Dose Rate

Conventionally, brachytherapy has been delivered at a low dose rate, most commonly 40 to 60 cGy per hour. These dose rates take maximum advantage of the dose rate effect described earlier, differentially sparing late-responding normal tissues compared with acutely responding tissues and tumor cells. The dose of intracavitary therapy needed to treat cervical cancer radically is usually delivered in 72 to 96 hours in one or two hospital admissions. Although some investigators have tried to reduce the duration of these treatments by doubling the dose rate (from 40 to 80 cGy/hour), the limited clinical data evaluating this suggest that doubling the dose rate results in a less favorable therapeutic ratio (52).

With the advent of computer-controlled remote afterloading in the 1970s, it became possible to deliver brachytherapy treatments at high dose rates (in minutes rather than hours). *High–dose-rate (HDR) treatment* may offer practical advantages for the patient because it is typically performed on an outpatient basis, although more applications are usually required. HDR therapy has become more popular in the 1990s, particularly for intracavitary gynecologic applications. However, many centers have been reluctant to change to HDR therapy because of the theoretic radiobiologic disadvantages of large-fraction radiation and the absence of well controlled, randomized clinical trials comparing HDR and LDR regimens (53).

It is important that dose fractionation schemes used for HDR therapy have tumor control and complication rates that are approximately equivalent to those of LDR therapy. The most common HDR regimen used in the United States is probably 5 fractions of 5.5 to 6 Gy each to point A after 45 Gy to the pelvis, although there is wide variation, with practitioners using 2 to 13 fractions of 3 to 9 Gy (54). Because large single fractions of radiation permit less recovery of sublethal injury than LDR irradiation, doses of HDR that yield a rate of tumor control equivalent to that of LDR therapy might result in an increased risk of late complications. However, with intracavitary treatment of the cervix, vulnerable normal tissues (primarily the rectum and bladder) are often some distance from the tumor site and therefore may receive a significantly lower dose and dose per fraction than the prescription point (usually point A).

Most centers reduce the total brachytherapy dose to point A to convert from LDR to HDR regimens. The optimal dose per fraction is unknown, although increasing the number of fractions and concomitantly decreasing the dose per fraction appears to reduce the rate of moderate and severe complications (55,56).

For patients with relatively favorable normal tissue and tumor anatomy, careful technique, and moderate fractionation schemes (£7 Gy per fraction), results are probably similar to those achieved with LDR. However, patients with very large tumors or unfavorable anatomy may have a less favorable ratio between the doses to tumor and normal tissues. These are the patients for whom critics are most concerned about a possible loss of effectiveness (53).

Interstitial Implants

***Interstitial brachytherapy* refers to the placement of radioactive sources within tissues.** Various sources of radiation, such as ^{192}Ir and ^{125}I, may be obtained as radioactive wires or seeds. The latter may be obtained as separate sources or as strand s of sources distributed at regular intervals (usually 1 cm) in Teflon tubes. Sources may be positioned in the tumor or tumor bed in a variety of ways:

1. *Permanent implants of seeds* (usually ^{125}I or ^{198}Au), inserted using a specialized seed inserter, are sometimes used to implant pelvic or aortic lymph nodes, particularly recurrences after radiation.
2. *Temporary implants of Teflon catheters* can be placed during surgery and subsequently loaded with radioactive sources (usually ^{192}Ir). These are sometimes used to treat tumor beds (57).
3. *Transperineal needle implants* can be placed with guidance using a Lucite template with regularly spaced holes and a central obdurator that can hold a tandem or additional needles. Needles are afterloaded, usually with ^{192}Ir. These are temporary implants that are used to treat vaginal and some cervical tumors. In some cases, laparoscopy or laparotomy may be done to facilitate needle placement, particularly during implant of apical vaginal lesions. Transperineal implants can also be placed freehand, an approach that may allow better control of needle placement in selected cases. Freehand implants are particularly useful to treat urethral and vaginal tumors.

Most gynecologic interstitial implants are temporary LDR implants. Like intracavitary therapy, interstitial therapy delivers a relatively high dose of radiation to a small volume, sparing the surrounding normal tissues. However, the risk to normal tissues adjacent to the tumor or in the tumor bed may still be significant, particularly if the needle placement is inaccurate.

Some investigators have advocated the use of interstitial template brachytherapy to treat difficult cases of locally advanced cervical cancer (58) (Fig. 5.11). The ability to place sources in the lateral parametrium with this technique suggests a theoretic advantage over intracavitary treatment for patients with pelvic wall involvement. This approach may be useful for selected patients. Some investigators have claimed high local control rates with this approach (58). **However, reports of 3- to 5-year survival rates do not demonstrate a clear advantage over survival achieved with combined external beam and intracavitary therapy, and the risk of major complications is greater than that with external-beam and intracavitary treatment, particularly in inexperienced hands** (59,60). With greater clinical experience and CT- or MRI-guided dosimetry, these results may be improved. The radiation oncology community remains polarized as to the appropriateness of interstitial therapy, and as yet no randomized trials have been conducted to compare the therapeutic ratio of conventional intracavitary irradiation with that of interstitial treatment.

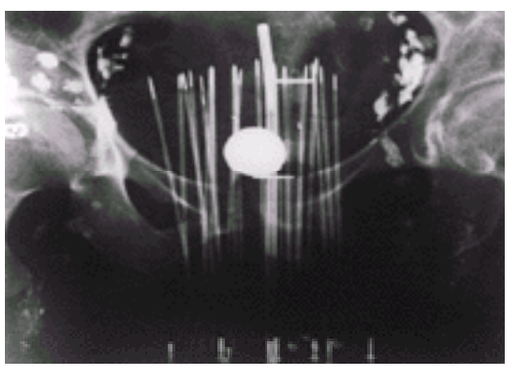

Figure 5.11 Interstitial implant for an advanced cervical cancer. (Reproduced with permission from Dr. Mark Schray, Division of Radiation Oncology, Mayo Clinic, Rochester, MN.)

Intraperitoneal Radioisotopes

Intraperitoneal radioisotopes have been used to treat epithelial ovarian cancer in an effort to address the transperitoneal spread pattern characteristic of the disease (61). Radioactive chromic phosphate (^{32}P) has largely replaced colloidal gold (^{198}Au) for peritoneal treatment. Its longer half-life (14.3 days), pure b decay, and higher mean energy (0.698 MeV) result in slightly longer exposures, fewer radiation protection problems, and deeper tissue penetration than ^{198}Au.

If distribution of a radioisotope within the peritoneum is even, it is theoretically possible to irradiate the entire peritoneal surface. However, the pattern of energy deposition within the abdomen and the dose delivered beneath the peritoneal surfaces depend on many factors, including the physical characteristics of the isotope used, the energies of its decay products, and the distribution of the isotope in the peritoneal cavity. Studies reveal that, in practice, isotope seldom is distributed uniformly to the peritoneal and omental surfaces (62). Postsurgical adhesions may limit the free flow of fluid, and this nonuniform distribution may result in underdosage of some peritoneal sites and overdosage of some normal tissues. This may result in unacceptable complications, particularly if intraperitoneal and external-beam irradiation are combined (63). Although randomized studies have demonstrated similar survival rates for patients with early ovarian cancer treated with ^{32}P or single-agent chemotherapy, the role of intraperitoneal treatment still has not been clearly established (64).

Clinical Uses of Radiation

Cervical Cancer

Although specific radiation therapy techniques may vary, the curative treatment of cervical cancer usually includes a combination of external pelvic irradiation and brachytherapy. The goal of radiation therapy is to eliminate cancer in the cervix, paracervical tissues, and regional lymph nodes (50). All of these regions can be encompassed in a pelvic radiation field. However, the dose that can be delivered to the pelvis is limited by the tolerance of intrapelvic normal tissues, especially the rectosigmoid, bladder, and small bowel. Because the bulkiest tumor is usually in the cervix, this region typically requires higher doses than the rest of the pelvis to achieve local regional control. Fortunately, it is usually possible to deliver these high doses with intracavitary therapy.

Treatment Volume

Typical external-beam fields are designed to include the primary tumor, paracervical tissues, and the iliac and presacral lymph nodes, all with 1.5- to 2-cm margins. If the common iliac or aortic nodes are involved, the treatment fields are usually extended to include at least the lower paraaortic region.

The borders of the typical anteroposterior and posteroanterior pelvic fields are:

1. *Inferior*—at the mid-pubis or 3 to 4 cm below the most distal disease in the cervix or vagina (usually demonstrated using a radiopaque vaginal marker).
2. *Superior*—at the L4-L5 interface so that the common iliac nodes are encompassed. For patients with small tumors who are at less risk for extensive nodal spread, the upper border may be placed at the L5-S1 interface.
3. *Lateral*—1 to 2 cm lateral to the pelvic lymph nodes as visualized on a lymphangiogram or at least 1 cm lateral to the margins of the bony pelvis. Appropriate shielding along the common iliac nodes decreases the amount of sigmoid and small bowel in the field.

Every effort should be made to minimize the high-dose treatment volume while adequately encompassing the tumor and its regional lymph nodes. **Using four (anterior, posterior, and right and left lateral) beams rather than an opposed pair of anterior and posterior beams** (Fig. 5.8) **can sometimes reduce the volume of tissue irradiated at a high dose.** However, great care must be taken not to shield the primary tumor, uterosacral disease, or external iliac nodes when lateral fields are used (65,66). For some patients with locally advanced tumors, the amount of tissue spared with lateral fields may be relatively small after these areas are included. The additional bone marrow treated with lateral fields may also be a consideration if chemotherapy is part of the treatment plan.

For most patients with locally advanced disease, an initial course of treatment is given with external-beam irradiation. Four to 5 weeks (40 to 45 Gy) of external-beam therapy usually decreases endocervical disease and shrinks exophytic tumor, facilitating optimal intracavitary therapy. The dose to the central tumor is then supplemented with one or two LDR intracavitary treatments or with a variable number of HDR treatments. If the initial tumor volume is small or there is an excellent tumor response, brachytherapy may be given earlier in the patient's treatment. The balance between external-beam and intracavitary therapy may vary somewhat according to the tumor extent (50). However, several studies have suggested that intracavitary therapy is critically important to successful treatment even for patients with very bulky stage IIIB tumors (1,67). Patients with International Federation of Gynecology and Obstetrics (FIGO) stage IA disease can often be treated with intracavitary irradiation alone.

For patients with carcinoma of the cervix who have vaginal hemorrhage, vaginal packing, application of *Monsel's solution* and rapid initiation of external-beam irradiation usually produces hemostasis. For patients with excessive bleeding, transvaginal irradiation (if available) or several days of accelerated pelvic radiation (e.g., 1.8 Gy twice daily) may be helpful.

Radiation Dose

The total doses of radiation to the central tumor and regional nodes are tailored to the amount of disease in those sites (68). A number of methods have been used to prescribe and specify the doses delivered with intracavitary therapy. Most radiation oncologists use some variation of the *Manchester system*, which is identified with the use of two primary reference points:

1. **Point A**—2 cm lateral and 2 cm superior to the external cervical os in the plane of the implant (Fig. 5.10)
2. **Point B**—3 cm lateral to point A

Although the doses in Gray from intracavitary and external radiation therapy may not be biologically equivalent (particularly with HDR therapy), they are frequently summed to determine the total doses to points A and B. **The total dose to point A (external-beam and LDR intracavitary therapy) believed to be adequate to achieve central disease control is usually between 75 Gy (for stage IA) and 90 Gy (for locally advanced disease). The prescribed dose to point B is 45 to 65 Gy, depending on the extent of parametrial and sidewall disease.**

Treatment planning cannot be limited to specification of these reference points. Other factors that should be considered include:

1. The position and length of the intrauterine tandem (which influence the loading of the tandem)
2. The type and position of vaginal applicators (which influence the loading of the vaginal applicators)
3. The quality of the vaginal packing
4. The size of the central tumor after external-beam treatment
5. The vaginal surface dose (usually limited to 120 to 140 Gy)
6. The proximity of the system to bladder and rectum
7. The dose rate (or fraction size)

A number of methods and reference points have been described to estimate the maximum dose to the bladder and rectum from orthogonal reference films of the implants. Three-dimensional reconstructions of intracavitary placements suggest that all of these methods are probably unreliable because they tend to underestimate the true maximum dose (69,70). For this reason, it is important qualitatively to examine each intracavitary system rather than depend solely on normal tissue reference points.

Some centers also document the total *"milligram-radium-equivalent hours (mgRaEq-hrs)"* of each intracavitary system. This number, obtained by multiplying the mgRaEq of cesium or radium in the system by the number of hours the radioactive sources are left in place, cannot be used as the sole measure of any treatment, but is sometimes used to limit the total integral dose to the pelvis. The doses to points at a substantial distance from the system are roughly proportional to the total mgRaEq-hrs because as the distance increases, the dose rate approaches that from a single-point source of similar activity. In general, after 40 to 45 Gy of external-beam irradiation, the total mgRaEq-hrs should not exceed 6,000 to 6,500.

Results of Treatment

Radiation therapy is extremely effective treatment of stage IB1 cervical cancer, with central and pelvic disease control rates exceeding 98% and 95%, respectively, and disease-specific survival rates of approximately 90% (4,71). Pelvic control rates decrease as tumor size and FIGO stage increase, although large single-institutional experiences report 5-year pelvic control rates of 60% to 70% and disease-specific survival rates of 40% to 50% even for bulky stage IIIB cancers (1,2). Although these control rates clearly indicate a need for more effective treatment of these advanced lesions, it is remarkable that such massive carcinomas, usually more than 7 cm in diameter, can be controlled even half the time with radiation therapy alone. This undoubtedly reflects the remarkable effectiveness of carefully planned combinations of external-beam and intracavitary radiation.

Studies have demonstrated a marked improvement in pelvic disease control and survival when *cisplatin*-containing chemotherapy is given concurrently with radiation for patients with locoregionally advanced disease (15,16 and 17,34,35). Several of the regimens tested in these studies also included *5-FU*. This drug is known to be a potent radiation sensitizer, particularly effective in the treatment of gastrointestinal malignancies, but its contribution to chemoradiation schedules is still being clarified.

Adjuvant Pelvic Radiation Therapy after Radical Hysterectomy

For patients with stage IB and IIA cervical cancer managed by radical hysterectomy and pelvic lymphadenectomy, lymph node involvement is probably the strongest predictor of local recurrence and death, with survival rates only approximately 50% to 60% of those of patients with positive nodes (72,73). For this reason, most clinicians recommend postoperative radiation therapy, particularly if three or more lymph nodes are involved. Radiation therapy clearly improves pelvic disease control, but it has not been possible to discern a survival advantage from retrospective studies, and no randomized studies have addressed this question (6,74). Parametrial involvement and involvement of surgical margins also predict a high rate of pelvic recurrence and are considered to be indications for postoperative therapy. A recent Southwest Oncology Group study demonstrated a 50% reduction in the risk of recurrence when *cisplatin* and *5-FU* were added to pelvic radiation (35).

For patients with negative nodes, several factors, including large tumor size (e.g., ³4 cm), deep stromal invasion (e.g., >$^{2}/_{3}$), or involvement of lymph vascular spaces predict an increased risk of pelvic recurrence after radical hysterectomy and pelvic lymphadenectomy (72,75). The Gynecologic Oncology Group has completed a study randomizing 277 patients who had at least two of these high-risk features and negative pelvic lymph nodes to receive postoperative pelvic radiation or no further treatment after radical hysterectomy and lymph node dissection (5). Analysis of this study revealed a significant reduction in the risk of recurrence (relative risk = 0.53, p = 0.008) for patients who had postoperative radiation therapy. The price of adjuvant pelvic radiation is a somewhat greater risk of major complications than that of surgery alone or radiation alone (5,76). For this reason, a National Cancer Institute Consensus Conference (33) concluded that “primary therapy should avoid the routine use of both radical surgery and radiation therapy,” suggesting that patients who are known to have high-risk factors at initial evaluation may be better treated with radical radiation therapy.

Recurrent Cervical Cancer

Patients with isolated pelvic recurrence after radical hysterectomy can sometimes be salvaged with aggressive radiation therapy. The prognosis is best for patients with isolated central recurrences that are not fixed to the pelvic wall and do not involve pelvic nodes. Five-year survival rates for these patients are as high as 60% to 70% (77). The prognosis is much poorer for patients whose tumors involve the pelvic wall or nodes; few groups report better than a 20% survival rate for these patients when they are treated with radiation alone. Some groups have reported encouraging results with combined radiation and concurrent chemotherapy (78). It probably is also reasonable to extrapolate from randomized trials that demonstrate improved survival with concurrent chemoradiation therapy for locally advanced cervical cancer to justify a similar approach to those with unfavorable pelvic recurrences.

Complications

Late complications of radical irradiation for cervical cancer occur in 5% to 15% of patients and are related to the size of the dose per fraction, the total dose administered, and the volume irradiated (79,80 and 81). The positioning of the intracavitary system also may influence complications. Late effects may be seen in the bladder with hematuria, fibrosis and contraction, or fistulas. Late effects may also occur in the rectosigmoid or terminal ileum and may involve bleeding, stricture, obstruction, fistulas, or perforation. Although late effects may occur many years after treatment, most gastrointestinal complications occur within 30 months of radiation therapy (80).

Agglutination of the apex of the vagina is common. Severe vaginal shortening is less frequent and is probably correlated with the patient's age, menopausal status, and sexual activity, and with the initial extent of disease (80,81). Unfortunately, our understanding of the factors influencing sexual dysfunction in patients treated for cervical cancer is still very incomplete.

Palliation

Radiation therapy has an important role in the palliation of metastatic cervical cancer. Short courses of palliative radiation, such as 2,000 cGy in five fractions or 3,000 cGy in ten fractions, usually alleviate symptoms related to bony metastases or paraaortic nodal disease. It also may relieve symptoms related to pressure from enlarging mediastinal or supraclavicular nodal disease. Rare patients who present with extensive, incurable metastatic disease may also be treated with short palliative courses of treatment to the pelvis. However, this should be reserved for patients with extensive, incurable disease and a short life expectancy. Otherwise, better long-term control and palliation is achieved by including brachytherapy in the local treatment.

Endometrial Cancer

The role of radiation therapy in the treatment of endometrial carcinoma is discussed in greater detail in Chapter 10, but is briefly summarized as follows:

1. Adjuvant treatment to prevent pelvic recurrence after hysterectomy and bilateral salpingo-oopherectomy
2. Preoperative treatment for patients with very extensive cervical stromal involvement
3. Curative treatment for some patients with medical problems that preclude surgery and for occasional patients with stage III disease involving the vagina
4. Curative treatment for patients with isolated vaginal or pelvic recurrence, usually using a combination of external-beam and intracavitary or interstitial radiation
5. Palliative treatment of massive pelvic or metastatic disease

In the past, disease confined to the uterus often was routinely treated with preoperative intracavitary radiation. An intracavitary line source was placed in the uterus, or the uterus was packed with multiple radium (Heyman's) capsules or cesium (Simon's) capsules (82). Preoperative radiation reduces the risk of vaginal apex recurrence but has never been proven to improve survival, although no randomized studies have been done (83,84). Because tailored postoperative irradiation appears to achieve similar pelvic control rates and avoids unnecessary treatment of some patients whose hysterectomy findings predict a negligible risk of recurrence, preoperative irradiation has been abandoned for most patients (83,85,86).

Most patients with stage I endometrial cancer have noninvasive or minimally invasive grade 1 to 2 tumors that rarely recur after hysterectomy alone and usually need no additional treatment. However, some clinicians recommend vaginal intracavitary irradiation for grade 2 tumors because vaginal recurrences are occasionally seen in this group and because the morbidity of vaginal irradiation is negligible. The use of adjuvant pelvic radiation therapy is usually confined to patients with deeply invasive lesions or other high-risk findings at surgery (e.g., lymph node involvement, cervical stromal involvement) (7,87,88). This treatment reduces the risk of pelvic recurrence but has never been proven to improve survival. Unfortunately, no randomized study of this question has had enough power to detect or rule out moderate survival improvements. The Gynecologic Oncology Group has completed a randomized trial addressing this question in patients with intermediate risk FIGO stage I cancers. A preliminary report of this study indicated that postoperative irradiation reduced the overall risk of pelvic (particularly vaginal) recurrence (89).

Uterine papillary serous cancers have a particularly poor prognosis and an inclination to spread intraperitoneally in a manner similar to that seen with ovarian cancers. These are rare cancers that usually occur in elderly women, and their optimal management has not yet been determined. However, whole abdominal irradiation appears to be valuable treatment for some patients with minimal residual disease after hysterectomy (90,91).

The potential benefit of adjuvant treatment must be balanced against the risk of complications for each patient. Extensive staging lymphadenectomy appears to increase the risk of serious bowel complications after radiation therapy (92,93).

Ovarian Cancer

Several independent investigators have established a curative role for whole abdominal and pelvic irradiation for some subsets of patients with epithelial ovarian cancer (94,95,96 and 97). Because many of the patients in these series have no known residual disease after hysterectomy, the curative potential of radiation therapy can best be determined by assessing the outcome of patients with known macroscopic residual tumor. The long-term or relapse-free survival rates from five such series (94,95,96,97 and 98) are summarized in Table 5.2. The survival rates are very similar in the four studies and appear to be related to the initial stage and volume of residual disease. The best survival rates are for patients with stage II disease and for those whose macroscopic residual disease is confined to the pelvis, where a relatively high dose of radiation can be given.

		Size of Residual Disease	
Center	*End Point*	*<2 cm*	*>2 cm*
Princess Margaret Hospital (94)	n	51	91
	10-year RFS	38%	6%
Stanford (96)	n	42	54
	15-year RFS	50%	14%
Salt Lake City (95)	n	12	10
	10-year RFS	62%	0
Walter Reed Hospital (97)	n	24	20
	10-year SR	42%	10%
Yale (98)	n	27	
	~5-year SR	41%	

RFS, relapse-free survival; SR, survival rate; n, number of patients.

Table 5.2 Evidence of Long-Term Control of Stages II and III Ovarian Cancer with Macroscopic Residual Disease Using Abdominopelvic Radiation Therapy

Whole Abdominopelvic Radiation

Because transperitoneal spread is the most common route of dissemination of ovarian cancer, radiation fields that encompass the whole peritoneal cavity are more likely to be curative than those that treat only the pelvis or lower abdomen. Normal tissues in the upper abdomen (e.g., kidney, liver, bowel, spinal cord) limit the dose of radiation that can be given to the whole abdomen to approximately 22 Gy. Somewhat higher doses can be delivered to portions of the upper abdomen that do not include the most sensitive normal structures. Because 22 Gy is insufficient to control macroscopic disease, patients with extensive upper abdominal disease cannot be expected to benefit from whole abdominal irradiation. Although a curative benefit has been established for radiation therapy, randomized studies have never determined the relative benefits of abdominopelvic radiation therapy and combination platinum-based chemotherapy in appropriately selected patients with minimal residual disease.

Abdominopelvic Radiation: Technique

Two techniques have been used to treat the whole abdomen:

1. The *moving-strip* technique: a 10-cm-high field (usually ^{60}Co) is moved by 2.5-cm increments, so that each “strip” receives eight or ten fractions, usually of 2.25 Gy each (60,61). This approach was developed when available equipment could not treat very large volumes in one field.
2. The *open-field* technique: the whole abdomen receives 1 to 1.5 Gy each day with a single pair of anteroposterior-posteroanterior fields (Fig. 5.12).

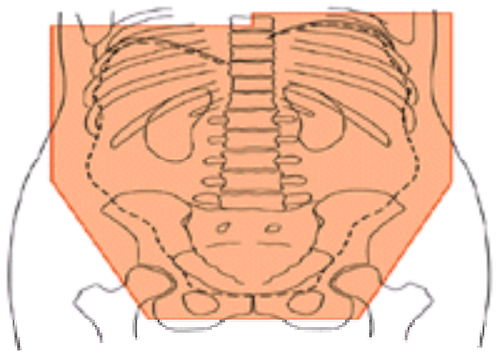

Figure 5.12 Treatment portals for carcinoma of the ovary or for uterine papillary serous carcinoma. The field must encompass the entire peritoneal cavity. Shielding is usually added to limit the dose to the kidneys to less than 18 to 20 Gy. The liver dose is usually limited to 25 Gy.

These two techniques have been compared in randomized trials that demonstrated no significant difference in survival (99,100). In the Princess Margaret Hospital Study (99), acute toxicity was similar with the two techniques, although thrombocytopenia occurred more commonly with moving-strip treatment. Late bowel complications were more common after moving-strip treatment (6% vs. 1%). This probably reflects the larger daily fraction size used to treat with moving strips. Because open-field treatment is simpler, equally effective, and less toxic, it has now become the standard technique at most centers. Most abdominopelvic techniques include a boost to the pelvis, and some investigators boost the paraaortic nodes and medial diaphragms (“T boost”) to 40 to 45 Gy after initial whole abdominal treatment (96). The design of abdominopelvic fields requires careful simulation using fluoroscopy and often CT-based planning to confirm adequate coverage of the peritoneal surfaces and diaphragms and proper shielding of sensitive structures.

Toxicity Acute toxic side effects of abdominopelvic radiation in most patients include nausea, anorexia, general fatigue, and diarrhea (94). These symptoms are usually fairly well controlled with appropriate medications. Approximately 10% of patients have bone marrow toxicity (platelet count <100,000 or neutrophil count <1,500). However, the risk of significant toxicity is much higher in patients who have this treatment after chemotherapy, depending on the drugs and duration of previous treatment. Transient, asymptomatic pneumonitis in the bases of the lungs develops in approximately 15% of patients, and up to 40% of patients have transiently elevated levels of alkaline phosphatase. Symptomatic hepatitis is rare if the dose of radiation to the liver does not exceed 27 Gy. In the absence of tumor recurrence, late bowel complications are rare, but the risk tends to increase with the extent and number of previous abdominal operations (particularly lymphadenectomy) (101).

Indications A patient's suitability for postoperative abdominopelvic radiation is determined by the extent of disease at presentation, the amount and site of residual disease, the grade of the tumor, any complicating medical conditions, and risk factors for radiation-related complications (102,103). It should be considered as primary treatment only for patients with stages I to III disease who have no macroscopic disease in the upper abdomen and minimal (<2 cm) residual disease in the pelvis (94,98,101,102,104,105).

The high response rates but frequent relapses observed after treatment of ovarian cancer with chemotherapy have encouraged many investigators to add whole abdominal radiation either as a salvage treatment for incomplete responses or as part of an up-front multimodality program. Fuks and coworkers summarized the rationale for this sequential, multimodality approach to advanced ovarian cancer (106). Many reports of sequential treatment have appeared in the literature, but because most were small, single-arm studies of patients with widely varying risk factors and initial treatments, the results are difficult to generalize. A retrospective analysis of the Toronto data suggested an improved outcome for high-risk patients treated with sequential chemotherapy and whole abdominal radiation compared with historical control subjects treated with radiation alone (107). However, three randomized studies have compared chemotherapy alone with multimodality treatment (108,109 and 110) with disappointing results. Although some patients with minimal residual disease may benefit, in general, the data do not support routine use of sequential chemotherapy and abdominopelvic irradiation. Poor tolerance after extensive chemotherapy and the possible induction of accelerated repopulation of resistant clonogens during treatment are among the reasons suggested for the failure of this approach in most hands (111,112 and 113).

improved outcome for high-risk patients treated with sequential chemotherapy and whole abdominal radiation compared with historical control subjects treated with radiation alone (107). However, three randomized studies have compared chemotherapy alone with multimodality treatment (108,109 and 110) with disappointing results. Although some patients with minimal residual disease may benefit, in general, the data do not support routine use of sequential chemotherapy and abdominopelvic irradiation. Poor tolerance after extensive chemotherapy and the possible induction of accelerated repopulation of resistant clonogens during treatment are among the reasons suggested for the failure of this approach in most hands (111,112 and 113).

Vulvar Cancer

The role of radiation therapy in the treatment of vulvar cancer has increased dramatically since the late 1970s. Improved radiation therapy equipment and techniques have reduced the toxicity that discouraged early attempts to treat the vulva with radiation, and prospective studies have increased interest in this effective modality. In particular, the landmark randomized study published by Homesley and colleagues in 1986 demonstrated a marked improvement in survival when patients with positive lymph nodes were treated with pelvic and inguinal irradiation after vulvectomy and lymphadenectomy (14). The role of radiation is explored in more detail in Chapter 13.

In brief, radiation therapy appears to offer:

1. Reduced regional recurrence and improved survival in patients with inguinal node metastases
2. Reduced risk of vulvar recurrence in patients with positive surgical margins, multiple local recurrences, or other high-risk features
3. Avoidance of exenterative surgery in patients whose disease involves the anus or urethra (114)
4. A possible alternative to inguinal lymphadenectomy in selected patients with clinically negative groins

Studies have emphasized the critical importance of careful radiation therapy technique. A number of approaches have been developed to decrease the dose to the femoral heads from groin irradiation. In most cases, adequate coverage of the volume at risk is readily achieved without risking serious femoral morbidity. However, this can be accomplished only with detailed CT-based treatment planning. Treatments that use electron beams of insufficient energy to cover the inguinal nodes cannot be expected to prevent groin recurrences.

In general, the total dose of radiation should be tailored to the amount of residual disease, with doses of approximately 45 to 50 Gy for microscopic disease and 60 Gy or higher for positive margins, extracapsular nodal extension, or macroscopic residual disease. When necessary, the dose to portions of the vulva at high risk for recurrence can be “boosted” with an *en face* electron field. This approach minimizes the amount of tissue exposed to high doses and thereby reduces acute skin reactions. A bolus may be needed to increase the dose to superficial tissues in the “buildup region” of photon and low-energy electron beams. Treatment interruptions should be minimized to avoid possible tumor proliferation during breaks in radiation therapy.

The use of concurrent “sensitizing” chemotherapy (e.g., with continuous infusion *5-FU* or *cisplatin*) to improve control rates has been explored in a number of uncontrolled studies (36,37,38,115,116,117 and 118). The encouraging response rates and long-term control of gross disease reported in these trials and the successful use of chemoradiation in cervical and anal cancer are bound to increase interest in this approach in the future.

Acute moist desquamation of the skin of the inguinal creases and vulva is expected. Symptoms may be reduced with careful local care, sitz baths, avoidance of tight clothing, and immediate treatment of superimposed fungal or bacterial infections. Superinfection with *Candida* is particularly frequent during treatment. Late complications may include lymphedema (particularly after radical node dissection). Atrophy, telangiectasia, and fibrosis of the skin or subcutaneous tissues can occur and may be related to the daily fraction size and total dose, tissue destruction from tumor, and the extent of local surgery.

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6 Pathology

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With the advent of new techniques and diagnostic modalities, the practice of gynecologic pathology has changed significantly. However, the gold standard in almost all areas of this discipline is still histopathology and cytopathology. In this chapter, we present the material relevant to the practice of gynecologic oncology.

To maximize the usefulness of the information provided by the pathologic examination, the treating clinician should work closely with the pathologist in providing all the clinically relevant information, and ensuring that all of the material examined previously at another institution is available for review. Nowhere is the importance of this close working relationship as paramount as in the frozen-section laboratory, where the pathologist benefits from the full knowledge of the clinical findings, and the oncologist from knowledge of the uses and limitations of the frozen-section technique.

Cervix

Various sexually transmitted agents (*Trichomonas, Chlamydia*, cytomegalovirus, and herpes simplex virus type 2) and components of semen have been implicated as potential carcinogens in cervical neoplasia. Among these, only human papillomaviruses (HPVs) have been strongly associated with preinvasive and invasive lesions of the cervix (1).

Human Papillomaviruses

Human papillomaviruses are circular, double-stranded DNA viruses. Over 70 types have been described. Genital HPV types fall into two broad categories based on oncogenic risk (2,3) (Table 6.1). ***Low-risk HPV* types, mostly HPV 6 and 11, are associated with condylomas and *low-grade squamous intraepithelial lesions [cervical intraepithelial neoplasia (CIN) 1, mild dysplasia].*** ***High-risk HPV* types, mostly HPV 16 and 18, are found in 50% to 80% of *high-grade squamous intraepithelial lesions [CIN 2 and 3, moderate and severe dysplasia* and *carcinoma in situ (CIS)].***

Oncogenic Risk Category	Human Papillomavirus Type
Low Risk	6, 11, 26, 42, 44, 54, 70, 73
High Risk	16, 18, 31, 33, 35, 39, 45, 51, 53, 56, 58, 66, 68

Table 6.1 Classification of Human Papillomaviruses by Oncogenic Risk

There are important differences in the physical state of HPV DNA in cervical SIL and invasive carcinomas (3). **In condylomas and low-grade squamous lesions, the viral genome is maintained as extrachromosomal circular episomes. In most carcinomas, but not in SIL, DNA of high-risk HPV types is integrated into the host cellular genome.** Integration of HPV DNA disrupts the E2 open reading frames, resulting in overexpression of two major viral oncogenes, *E6* and *E7*. E6 and E7 oncoproteins interact with p53 and Rb protein, respectively, causing their degradation and inactivation. Additional genetic events implicated in cervical carcinogenesis include chromosomal alterations (most commonly losses of chromosome 1), loss of heterozygosity (chromosomes 3, 5 and 11) and protooncogene (c-*myc* and c-Ha-*ras*) inactivation.

Human papillomavirus infections of the cervix may take the form of *condyloma acuminatum, flat condyloma* (Fig. 6.1) **or *cervical neoplasia.*** These lesions most commonly affect women of reproductive age and often are asymptomatic.

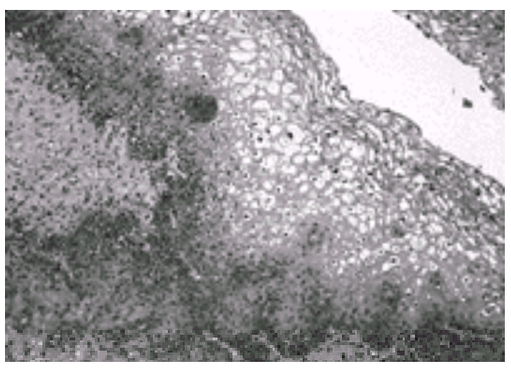


Figure 6.1 Flat condyloma without dysplasia. Koilocytes (perinuclear halo, binucleation, and nuclear hyperchromasia) are seen in the upper portion of squamous epithelium.

Squamous Lesions

Condyloma Acuminatum

***Condyloma acuminatum* is characterized by fibrovascular papillary fronds covered by a thickened squamous epithelium containing koilocytes** (Fig. 6.2). Koilocytes are squamous cells with perinuclear clearing (haloes), thickened cell borders, and mild nuclear atypia in the form of nuclear enlargement, hyperchromasia, irregularity and binucleation or multinucleation (1). These changes are most commonly confined to the upper one third of the squamous epithelium. Condylomata may also contain regions of dysplasia, which requires them to be graded the same way as CIN. Condyloma acuminatum uncomplicated by intraepithelial neoplasia is a benign lesion associated with HPV 6 and 11. **Condylomata may spontaneously regress or persist for many years. The natural history is in part related to the immune status of the patient.**

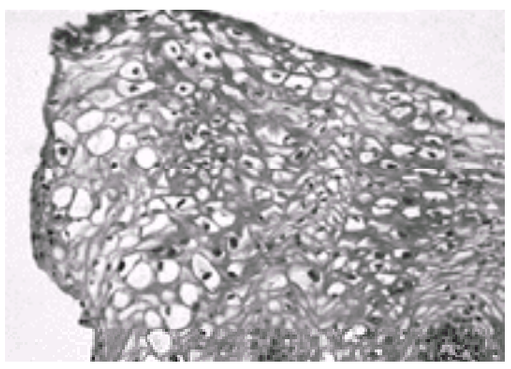


Figure 6.2 Condyloma acuminatum. Squamous epithelium with spike-like projections and koilocytosis (perinuclear halo, nuclear enlargement, and hyperchromasia).

Squamous Intraepithelial Lesions

The terminology used for *squamous intraepithelial lesions (SIL)* has evolved over time. The earliest terms reflecting the intraepithelial changes were *dysplasia* and *CIS.* Later, it was suggested that *cervical intraepithelial neoplasia (CIN)* be used instead (4). More recently, the Bethesda system for reporting cervical/vaginal smear diagnoses proposed the term *SIL* (5). Different laboratories use these terms interchangeably for reporting cervical biopsies. Table 6.2 provides the comparative usage of these terms.

Low-Grade SIL	Mild dysplasia CIN I Condyloma
High-Grade SIL	Moderate/severe dysplasia CIN 2, 3 Carcinoma in situ

SIL, squamous intraepithelial lesion; CIN, cervical intraepithelial neoplasia.

Table 6.2 Comparative Terminology for Reporting Cervical Biopsy Diagnoses

Squamous intraepithelial lesions are characterized morphologically by the presence of abnormal cell maturation, nuclear enlargement, atypia, and mitoses. Based on the extent of these changes, SIL are classified into *low (CIN 1, mild dysplasia)* and *high (CIN 2, 3, moderate and severe dysplasia and CIS)* grades. The two-tier system is supported by virologic, nuclear DNA ploidy, and cytologic findings. As reviewed earlier, the HPV types are divided broadly into low- and high-risk groups for oncogenic potential. The low-risk HPV types are predominantly seen in low-grade SIL (LSIL), and the high-risk HPV types are predominantly seen in high-grade SIL (HSIL). By nuclear ploidy analysis, LSIL display diploid/polypoid patterns, whereas HSIL display aneuploid patterns (6). **In CIN 1 and 2, the morphologic abnormalities are limited to the lower one third and two thirds of the thickness of the squamous epithelium, respectively** (Fig. 6.3, Fig. 6.4). **In CIN 3, there is full-thickness involvement of the squamous epithelium** (Fig. 6.5).

Figure 6.3 Mild squamous dysplasia and condyloma. The dysplastic changes are confined to the lower third of the epithelium, and the upper portion shows koilocytosis (condyloma).

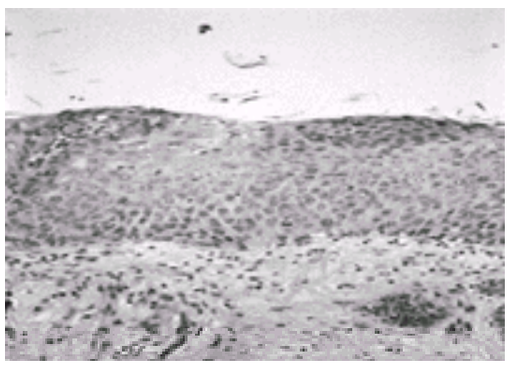


Figure 6.4 Moderate squamous dysplasia. The dysplastic cells show loss of polarity and increased mitotic activity. These changes involve the lower two thirds of the epithelium.

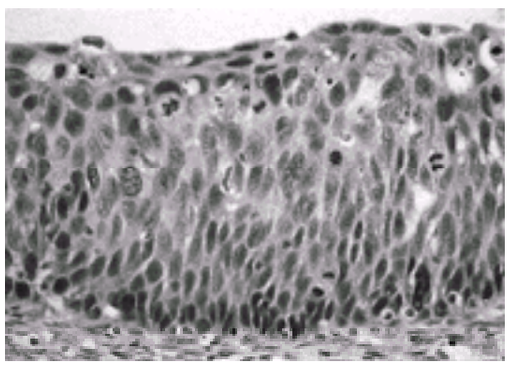


Figure 6.5 Severe squamous dysplasia. There is an almost full-thickness involvement of the squamous mucosa by dysplastic cells. Note that mitotic figures extend close to the surface of the epithelium.

Although it is difficult to predict the exact natural outcome of a SIL in a particular woman, low-grade lesions are more likely to regress and high-grade lesions are more likely to persist or progress. The cumulative data Oster calculated based on his review of the literature since 1950 showed that 60% of CIN 1 lesions regressed, 30% persisted, 11% progressed to CIS, and 1% became invasive carcinoma (7). For CIN 2, these rates were 40%, 40%, 20%, and 5%, respectively. The likelihood of regression in CIN 3 was 33%, persistence 56%, and progression to invasive carcinoma greater than 12%.

Squamous Cell Carcinoma

Squamous cell carcinoma is the most common type of malignancy of the cervix. Advanced cases appear as endophytic or exophytic masses with or without ulceration on clinical examination. However, up to 25% to 30% of patients with squamous cell carcinoma may have a grossly normal-appearing cervix. Histologically, squamous cell carcinoma is divided into three categories: large cell keratinizing, large cell nonkeratinizing, and small cell carcinomas (8). *Large cell keratinizing squamous cell carcinoma* is characterized by mature squamous cells arranged in irregularly shaped cords and nests. The histologic hallmark is the presence of squamous pearls within the nests of neoplastic squamous epithelium (Fig. 6.6). *Nonkeratinizing squamous cell carcinoma* displays rounded nests of neoplastic squamous cells often showing individual keratinization, but without formation of keratin pearls (Fig. 6.7). *Small cell squamous cell carcinoma* shows minimal evidence of squamous differentiation. The tumor cells exhibit scant cytoplasm, clumped chromatin, and small nucleoli with abundant mitotic figures. Individual cell keratinization and keratin pearls are not present. The differential diagnosis of small cell squamous cell carcinoma is undifferentiated small cell carcinoma. *Undifferentiated small cell carcinoma* is a poorly differentiated neuroendocrine tumor similar to small cell carcinoma of the lung and carries a very poor prognosis. **Because of the potential confusion created by the use of the term "small cell carcinoma" for both poorly differentiated squamous and neuroendocrine neoplasms, it is recommended that "small cell carcinoma" be used only for tumors resembling oat cell carcinoma of the lung** (1).

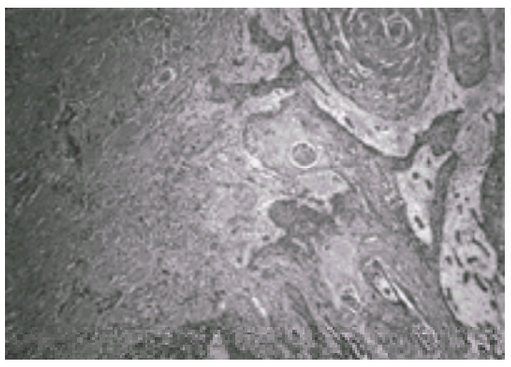


Figure 6.6 Invasive well differentiated keratinizing squamous cell carcinoma. Note infiltrating irregular nests of squamous cells with keratin pearl formation.

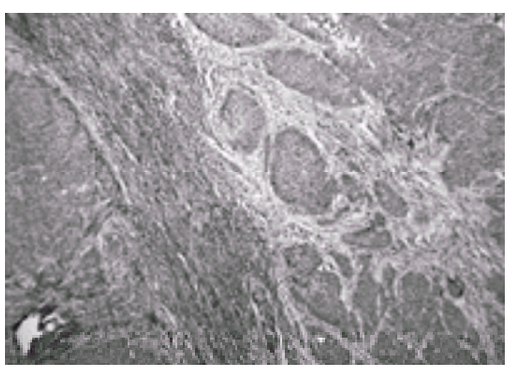


Figure 6.7 Invasive moderately differentiated nonkeratinizing squamous cell carcinoma. Invasive squamous nests do not show evidence of keratin formation and are surrounded by desmoplastic stroma.

Histologic Grading

The histologic grading of squamous cell carcinoma is based on the modification of the original Broders system (8). The tumors are divided into well, moderately, and poorly differentiated categories based on the amount of keratin, degree of nuclear atypia, and mitotic activity. There is no conclusive evidence that histologic grading or typing predicts prognosis in cervical cancer independent of stage of disease. The only pathologic parameters predictive of clinical outcome are the depth of invasion and presence or absence of vascular space involvement (9).

Microinvasive Squamous Cell Carcinoma

Microinvasive squamous cell carcinoma accounts for 7% of invasive cancers of the cervix. In the 1990s, there has been an increase in the incidence of microinvasive cancer among women who have had regular Papanicolaou (Pap) smear screening.

Microinvasive squamous cell carcinoma is defined by the International Federation of Gynecology and Obstetrics (FIGO) as stage IA tumor: invasive cancer confined to the cervix and identified only microscopically, with invasion limited to a maximum stromal depth of 3 mm for stage IA1, and no greater than 5 mm for stage IA2 (10). **In both circumstances, the maximum horizontal tumor spread should be less than 7 mm.** The diagnosis of microinvasion often requires comprehensive histologic evaluation, which is possible only on cervical conization or hysterectomy specimens. Histologic clues of microinvasion are irregular protrusions of dysplastic squamous epithelium into the underlying stroma accompanied by a desmoplastic stromal response and inflammatory infiltrate, and paradoxical maturation (mature squamous epithelium deep to more immature cells) of neoplastic squamous epithelium (Fig. 6.8). **The depth of stromal invasion is the most reliable predictor of pelvic lymph node metastases and recurrence.** The following data are from a review of several studies (8): for tumors with stromal invasion up to 1 mm, the incidence of pelvic lymph node metastasis was 0.2%, with no recurrences; for tumors with stromal invasion up to 3 mm, the incidence of pelvic lymph node metastasis was 0.7% and the recurrence rate was 0.3%; for tumors showing 3.1 to 5.0 mm of stromal invasion, the pelvic lymph node metastasis and recurrence rates were 4.3% and 1.4%, respectively.

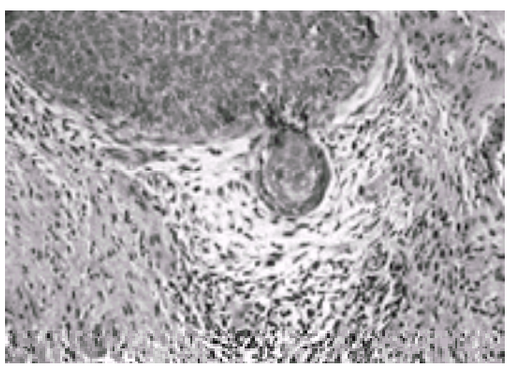


Figure 6.8 Microinvasive squamous cell carcinoma. An irregular protrusion from the overlying dysplastic epithelium is accompanied by a desmoplastic stromal response.

Lymphovascular Space Involvement

The clinical significance of lymphovascular space involvement remains controversial (11). The Society of Gynecologic Oncologists recommends the use of the term *microinvasive carcinoma* for cases with stromal invasion less than 3 mm in depth and without lymphovascular involvement. However, the evidence for more aggressive behavior in the presence of lymphovascular involvement applies mostly to tumors with greater than 3 mm stromal invasion.

Variants of Squamous Cell Carcinoma

Verrucous Carcinoma This is a rare type of very well differentiated squamous cell carcinoma (12) resembling its counterpart in the oral cavity. Grossly, it is warty and fungating, and sometimes ulcerated. Microscopically, it is characterized by a hyperplastic rather than neoplastic appearing papillomatous and exophytic squamous proliferation. The lack of fibrovascular cores helps to distinguish it from condyloma acuminatum. The deep advancing border of the neoplasm is pushing and bulbous rather than infiltrating. Its clinical course is marked by slow growth and frequent local recurrence, which may ultimately result in the death of the patient. Distant metastases are rare, but may occur after radiation therapy; thus, the usual treatment is surgical.

Papillary Squamous (Transitional) Cell Carcinoma This is a rare variant of squamous cell carcinoma with similar clinical behavior (13). Microscopically, it is characterized by papillary architecture with fibrovascular cores. The overlying epithelium is atypical, showing features of high-grade CIN. Invasive carcinoma is usually evident at the base of the tumor. Therefore, a superficial biopsy showing papillary squamous cell CIS should be considered invasive until proven otherwise. The differential diagnosis includes condyloma, papillary immature metaplasia, and verrucous carcinoma.

Lymphoepithelioma-Like Carcinoma This lesion is composed of syncytial-like aggregates of undifferentiated tumor cells surrounded by a marked inflammatory infiltrate. Histologically, it is similar to the undifferentiated carcinoma of the nasopharynx that is associated with Epstein-Barr virus. In contrast, no evidence of Epstein-Barr virus has been found in cervical lymphoepithelioma-like carcinoma (14). Lymphoepithelioma-like carcinoma has a lower incidence of regional lymph node metastases and a better 5-year survival rate compared with same-stage squamous cell carcinoma (15). The differential diagnosis includes a lymphoproliferative disorder; this problem can be resolved by the application of immunohistochemistry for epithelial and lymphoid markers.

Glandular Lesions

Endocervical Glandular Dysplasia

Endocervical glandular dysplasia (EGD) is defined as a lesion showing cytologic and architectural atypia similar to *adenocarcinoma in situ (AIS)*, but of lesser degree. Although it is logical to assume that EGD and AIS represent a continuous spectrum, evidence for such progression is lacking (16). The morphologic criteria and outcome of EGD, particularly at the mild end of the spectrum, are not well defined.

Adenocarcinoma *In Situ*

***Adenocarcinoma in situ* is defined as replacement of endocervical glandular epithelium by cytologically malignant cells** (1). The neoplastic glands lack stromal invasion. It is believed that AIS represents the preinvasive stage of adenocarcinoma based on the earlier median age of patients at the time of presentation (37 vs. 47 years), occurrence of AIS adjacent to invasive adenocarcinoma, and the high frequency of HPV 16 and 18 in both *in situ* and invasive lesions (17,18). AIS is associated with squamous dysplasia/carcinoma in over 50% of cases, suggesting similar etiologic factors and common cells of origin in both glandular and squamous lesions.

Microscopically, endocervical glands in AIS are lined by endocervical-, intestinal-, or endometrial-type cells with nuclear enlargement, hyperchromasia, mitoses, and stratification (Fig. 6.9). Complex glandular architecture is often present. These changes may be multifocal, raising concern about the efficacy of conservative management. AIS treated by conization only is associated with a significant rate of recurrence or residual disease (19), warranting close follow-up. One study showed that there was no patient with residual AIS if the cone specimen had greater than 10 mm of endocervical margin (20). However, invasive carcinoma in the background of AIS may develop over a prolonged period (up to 16 years) (17).

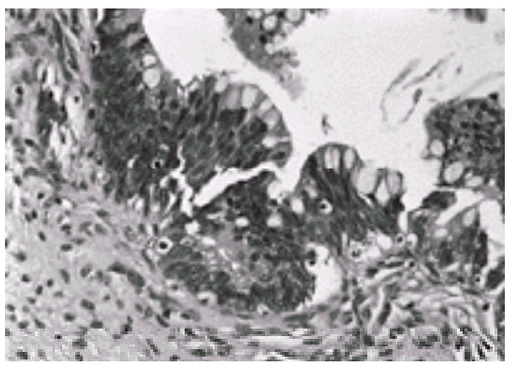


Figure 6.9 Adenocarcinoma *in situ*, intestinal type. The endocervical glands are lined by dysplastic cells that show stratification, nuclear enlargement, and hyperchromasia. Note the goblet cells.

Invasive Adenocarcinoma

The absolute and relative incidences of cervical adenocarcinoma have been increasing, particularly in women younger than 35 years of age (1). Adenocarcinoma appears grossly similar to squamous cell carcinoma. Approximately 15% of patients may have no visible lesions because the adenocarcinoma grows in the endocervical canal. Squamous dysplasia/carcinoma and/or AIS is frequently present next to the adenocarcinoma. Microscopically, adenocarcinomas exhibit a variety of morphologic patterns. The most common is the endocervical (mucinous) type. Others include endometrioid, intestinal (enteric), clear cell, serous, mesonephric, and signet-ring cell types and a mixture of more than one cell type.

The common forms of adenocarcinoma also can be graded histologically as moderately and poorly differentiated based on the architectural characteristics and degree of nuclear differentiation. In well differentiated tumors, the glands are well formed with somewhat complex architecture and are lined by tall columnar cells (Fig. 6.10). Poorly differentiated tumors are composed of pleomorphic cells that grow in solid sheets and nests. Moderately differentiated tumors have intermediate features.

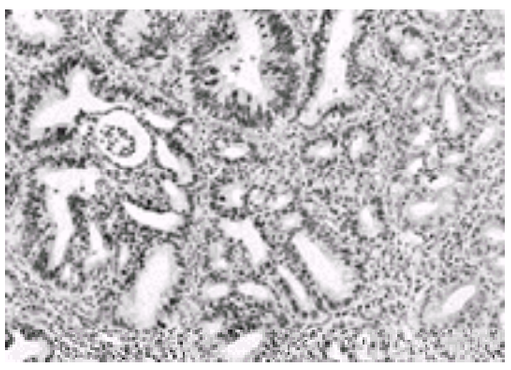


Figure 6.10 Invasive adenocarcinoma. Infiltrating glands show extensive cribriforming.

Minimal-Deviation Adenocarcinoma (Adenoma Malignum)

Minimal-deviation adenocarcinoma has a deceptively benign histologic appearance, with cytologically bland-appearing glands that vary in size and shape, simulating normal endocervical glands but extending below the usual limits of gland-bearing stroma, and at least focally surrounded by a desmoplastic stromal reaction (Fig. 6.11). Grossly, the cervix may be enlarged ("barrel-shaped") (Fig. 6.12). The prognosis of minimal-deviation adenocarcinoma is controversial. Older series report an unfavorable outcome. However, more recent studies show survival rates similar to those with same-stage well differentiated adenocarcinoma if the diagnosis is established in a timely fashion. The diagnosis of this tumor may be extremely difficult in small biopsies because of the deceptively benign histologic appearance.

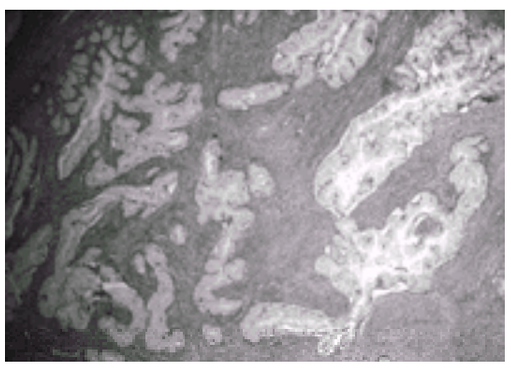


Figure 6.11 Minimal deviation adenocarcinoma. Deeply infiltrating, irregular glands are lined by benign-appearing endocervical epithelium.

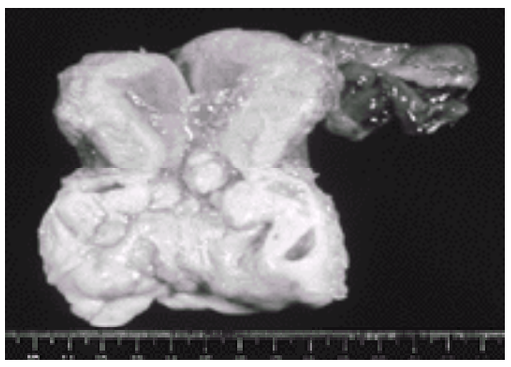


Figure 6.12 Minimal deviation adenocarcinoma. This hysterectomy specimen shows an enlarged ("barrel-shaped") cervix with wall thickening and polypoid projections.

Villoglandular Adenocarcinoma

Villoglandular adenocarcinoma tends to occur in young women, sometimes in pregnancy, and is associated with an excellent prognosis (21). It is a well circumscribed neoplasm composed of papillae with fibrovascular cores covered by stratified epithelial cells showing mild to moderate cytologic atypia and mitotic activity (Fig. 6.13). In deeper parts of the tumor, branching glands are present in a fibrous stroma. The prognosis of adenocarcinoma is closely related to the degree of differentiation, tumor size, stage, and pelvic lymph node status (22).

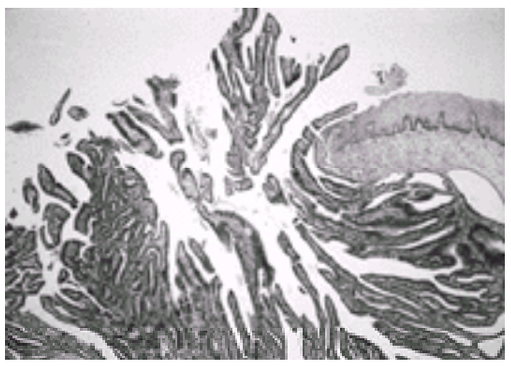


Figure 6.13 Invasive adenocarcinoma, villoglandular type. Thin, slender villous projections with exophytic and invasive growth patterns are lined by well differentiated glandular epithelium.

Other Epithelial Tumors

Adenosquamous Carcinoma

These show a mixture of malignant glandular and squamous differentiation. Reports on prognosis vary from no difference compared with adenocarcinoma and squamous cell carcinoma, to a worse prognosis.

Glassy Cell Carcinoma

Glassy cell carcinoma is a poorly differentiated tumor regarded as a dedifferentiated form of adenosquamous carcinoma (11). It tends to occur in young women and can be associated with pregnancy. Macroscopically, these are bulky tumors. Microscopically, they are characterized by large cells with a moderate amount of glassy cytoplasm, large nuclei with prominent nucleoli, distinct cell boundaries, and a prominent inflammatory infiltrate (Fig. 6.14). The clinical behavior is aggressive with poor response to radiation therapy.

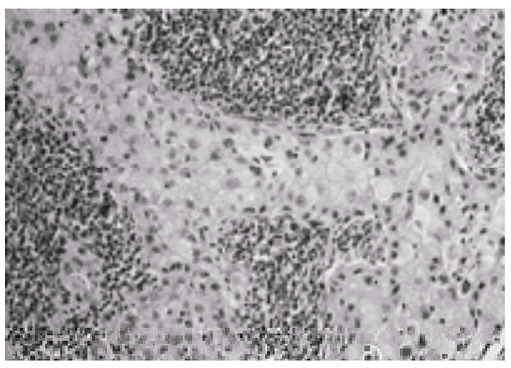


Figure 6.14 Glassy cell carcinoma. This lesion is characterized by sheets of malignant cells with abundant cytoplasm. Note the prominent inflammatory infiltrate.

Adenoid Basal Carcinoma

Adenoid basal carcinoma is a distinct neoplasm affecting women in their fourth to eighth decades (23). It typically presents in asymptomatic women with an abnormal Pap smear. The tumor has an excellent prognosis provided the typical histologic features of adenoid basal carcinoma are present. Microscopically, adenoid basal carcinoma resembles basal cell carcinoma of the skin. It is usually associated with a SIL or superficially invasive squamous cell carcinoma of the overlying cervical mucosa. Some have suggested that adenoid basal carcinoma is not a malignant tumor, and proposed the term *adenoid basal epithelioma* instead (23).

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is an aggressive neoplasm with a high incidence of local recurrence and distant metastasis (11). It preferentially affects older black women. Vaginal bleeding and a palpable exophytic cervical mass are common presenting symptoms. Microscopically, the neoplasm is composed of rounded nests and sheets of cells with a cribriform pattern. The lumens contain eosinophilic hyaline material. Mitoses and necrosis are common.

Mixed Epithelial and Mesenchymal Tumors

Mixed müllerian tumors (adenofibroma, adenosarcoma, and carcinosarcoma or malignant mixed müllerian tumor) may on occasion originate in the cervix (24). The differential diagnosis includes extension from an endometrial primary. They resemble their uterine counterparts histologically and clinically with the exception of adenosarcoma. In contrast to endometrial adenosarcomas, cervical adenosarcomas occur preodominantly in premenopausal women with a history of recurrent polyps. The rates of recurrence and metastasis are also lower compared with endometrial adenosarcomas.

Mesenchymal Lesions

Endocervical Stromal Sarcoma These are very rare tumors with the appearance of endometrial stromal sarcoma without the prominent background vascularity (24). They occur after menopause, and produce a polypoid cervical mass leading to clinical presentation with vaginal bleeding. Local recurrence and distant metastases are common.

Embryonal Rhabdomyosarcoma This lesion most commonly involves the vagina in the female genital tract (24). Cervical embryonal rhabdomyosarcoma is rare and clinically differs from vaginal embryonal rhabdomyosarcoma. It is most commonly seen in young women, whereas vaginal embryonal rhabdomyosarcoma is a disease of infancy. Macroscopically, it resembles a cervical polyp; the botryoid appearance of vaginal embryonal rhabdomyosarcoma is rare. Microscopically, cervical and vaginal embryonal rhabdomyosarcoma share the same characteristics, with a submucosal cambium layer and rhabdomyoblasts (strap cells) in the deeper edematous stroma. In contrast to vaginal embryonal rhabdomyosarcoma, cervical tumors have a favorable prognosis.

Leiomyosarcoma Rarely, primary leiomyosarcomas may arise in the cervix. Their behavior does not differ from that of their uterine counterpart.

Other Tumors

Malignant Melanoma Most malignant melanomas of the cervix are metastatic rather than primary. Primary cervical melanoma is rare (25). Its macroscopic appearance is similar to that of melanomas occurring at other sites. The prognosis is poor. FIGO staging is recommended rather than the conventional prognostic factors applied to cutaneous malignant melanoma.

Lymphoma/Leukemia Primary extranodal lymphomas of the cervix are extremely rare. In contrast, lymphoma and leukemia frequently involve the cervix in cases of advanced systemic disease (24). The most important differential diagnosis is pseudolymphomatous lesions, which are inflammatory in origin. In lymphoma, there often is a subepithelial Grenz zone of uninvolved stroma. In pseudolymphoma, the inflammatory infiltrate tends to involve the overlying epithelium. Immunohistochemistry and clonal analysis are necessary for differential diagnosis.

Metastatic Tumors

Secondary involvement of the uterine cervix is usually through direct infiltration from advanced tumors of the endometrium, vagina, bladder, urethra, and colon (25). True metastases are rare. Extragenital carcinomas that most commonly metastasize to the cervix are breast, stomach, and colon. Among other reported primary sites are lung, pancreas, kidney, and appendiceal carcinoid tumor. Malignant mesothelioma and melanoma have also been encountered.

Cervicovaginal Cytology

The Pap smear is the most successful cancer screening method to date. The dramatic decrease observed in the incidence of invasive cervical cancer in developed countries is a direct consequence of well established screening programs. Although the Pap smear can detect minor abnormalities such as infection with *Candida* or *Trichomonas vaginalis*, its main purpose is to detect treatable preinvasive/precursor lesions that can progress to invasive carcinoma. This section briefly reviews the Bethesda system for reporting cervical/vaginal cytologic diagnoses, summarizes the diagnostic criteria used in the Bethesda system, and focuses on the more recent advances in cervicovaginal cytology.

The Bethesda System

The original Bethesda system arose from a workshop sponsored by the National Cancer Institute (NCI) in Bethesda, Maryland in 1988. The purpose of the workshop was to devise a means for clear, precise, standardized communication of Pap smear diagnoses to the clinician. At this time, the classification system in use was the Papanicolaou terminology (Table 6.3). The Papanicolaou classification did not reflect contemporary understanding of cervical/vaginal cytology. In this system, there was no consistent relationship to the terminology used in biopsy diagnosis, and the original classes had been modified to the extent that they no longer had the same significance in all institutions. It was concluded at this meeting that the Papanicolaou reporting system was no longer acceptable. A second NCI meeting, which convened in 1991, evaluated the impact, advantages, and disadvantages of the Bethesda system in actual practice. Criteria for determining specimen adequacy and the specific diagnostic terms used in the Bethesda system were defined. These findings were published as the Bethesda system reference atlas (5).

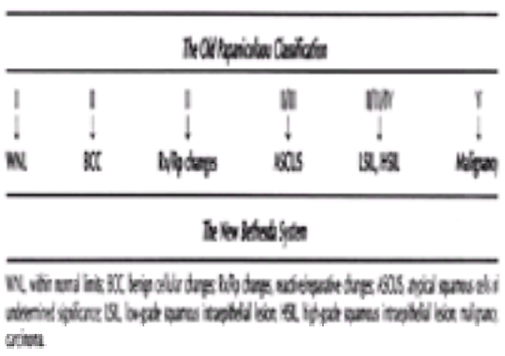


Table 6.3 Comparison of the Papanicolaou and the Bethesda Classification

The advantages of the Bethesda system can be summarized as follows: (a) it incorporates a statement regarding specimen adequacy as part of the diagnostic report; (b) it provides standardized, unambiguous diagnostic terminology to facilitate communication with the clinician and between different institutions; and (c) it eliminates Pap class numbers (26).

Format of the Pap Smear Report

In the Bethesda system (see Chapter 8, Table 8.1), the format of the cervical/vaginal cytology report consists of three parts:

1. A statement of the *adequacy* of the specimen
   Satisfactory for evaluation
   Satisfactory but limited by ...
   Unsatisfactory for evaluation
2. An optional *general categorization* of the diagnosis
   Within normal limits
   Benign cellular changes
   Epithelial cell abnormality
3. The *descriptive diagnosis*
   More specific description of any abnormalities present

Specimen Adequacy

Inclusion of a statement of adequacy is an important addition to Pap smear reporting. **Most false-negative Pap smears are a result of inadequate or poor sampling** (27,28). Therefore, systematic evaluation of specimen adequacy is essential in preventing false-negative results due to sampling. In the Bethesda system, four factors are evaluated for specimen adequacy:

1. *Correct patient and specimen identification*
2. *Pertinent clinical information:* Age of the patient and date of the last menstrual period are the minimal clinical information required. For example, the presence of endometrial cells in a Pap smear of a premenopausal woman is normal in the first half of the menstrual cycle, and may not be reported. However, in the second half of the menstrual cycle and after menopause, the presence of endometrial cells is an abnormal finding, and should be investigated to rule out endometrial disease.
3. *Technical interpretability:* Delayed fixation of the cells may render the smear uninterpretable.
4. *Sampling of the transformation zone:* Specimens in which less than 10% of a slide is covered by cells, or more than 75% of the cells are obscured by blood, inflammation, or artifacts are considered unsatisfactory. Specimens are considered satisfactory but limited for interpretation if more than 50% of the cells are obscured or if transformation zone sampling is inadequate. Adequate sampling of the transformation zone (the junction between ectocervical squamous epithelium and endocervical glandular cells) requires the presence of at least two groups of at least five endocervical columnar cells or squamous metaplastic cells. The presence of a transformation zone is important because most precursor SIL originate in this region.

Squamous Epithelial Abnormalities

The most common significant abnormality detected by the Pap smear is the spectrum of squamous lesions of the cervix (28). The squamous abnormalities range from reactive cellular changes associated with benign processes such as infections and atrophic vaginitis to atypical squamous cells of undetermined significance (ASCUS), LSIL, HSIL, and squamous cell carcinoma (Table 6.4, Fig. 6.15, Fig. 6.16, Fig. 6.17 and Fig. 6.18).

Etiology	Reactive	ASCUS	LSIL	HSIL
Nuclear size	↑ (Minimal)	↑ (Mild)	↑↑	↑↑↑
N/C ratio	Normal	↑ (Mild)	↑↑	↑↑↑
Chromatin	Uniform, finely granular	Uniform, finely granular	Uniform, finely granular with hyperchromasia or smudged/opaque dyskeratosis	Coarsely granular with hyperchromasia
Nuclear membrane	Smooth, regular	Limited irregularity may be present	May be irregular or smudged	Irregular and thick
Koilocytes	Absent	Absent	Often present	May be present

ASCUS, atypical squamous cells of undetermined significance; LSIL, low-grade squamous intraepithelial lesion; HSIL, high-grade squamous intraepithelial lesion; N/C, nuclear/cytoplasmic.

Table 6.4 Cytologic Features in Squamous Cell Abnormalities in Papanicolaou Smears

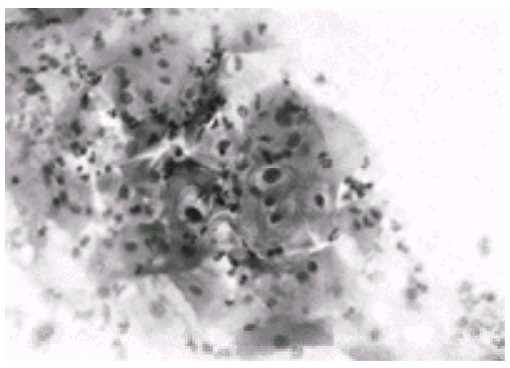


Figure 6.15 Atypical squamous cells of undetermined significance (ASCUS). This Pap smear shows superficial-type squamous cells with mild nuclear enlargement and hyperchromasia. These features are suggestive but not diagnostic of a low-grade squamous intraepithelial lesion.

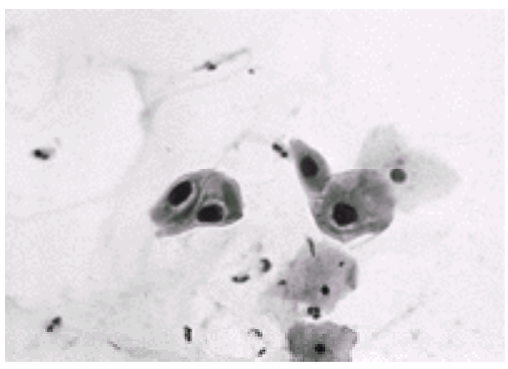


Figure 6.16 Low-grade squamous intraepithelial lesion (Pap smear). These lesions show mildly dysplastic squamous cells with nuclear enlargement, hyperchromasia, and irregular nuclear contours that are more pronounced than in Fig. 6.15.

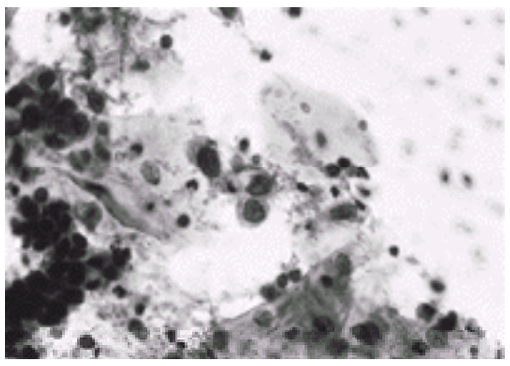
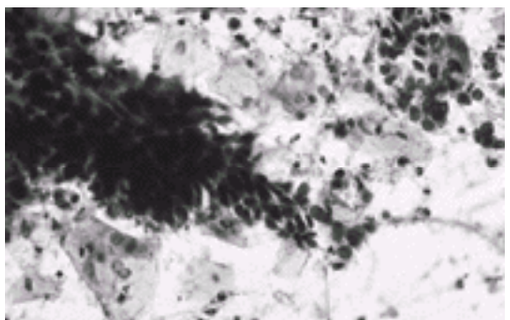


Figure 6.17 High-grade squamous intraepithelial lesion (Pap smear). The dysplastic cells seen in the center show a high nuclear-to-cytoplasmic ratio.



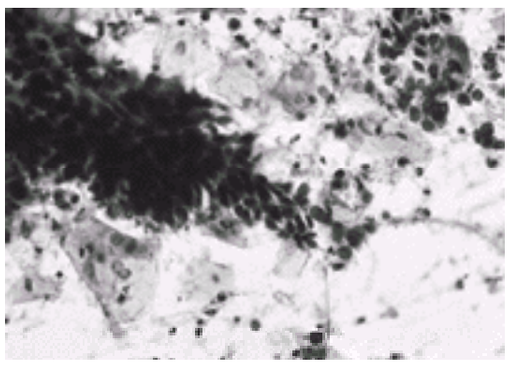


Figure 6.18 High-grade squamous intraepithelial lesion (carcinoma *in situ*; Pap smear). A cluster of overlapping, markedly dysplastic cells forms a sheet. Note single, severely dysplastic cells.

Atypical Squamous Cells of Undetermined Significance

The term *ASCUS* refers to cellular changes that are more marked than those attributable to reactive changes, but that quantitatively or qualitatively fall short of a definitive diagnosis of SIL (28) (Fig. 6.15). Because the atypia seen may be due to an exuberant but benign change or a potentially serious lesion, this finding is interpreted as of undetermined significance. **Follow-up biopsies of approximately one third of patients with ASCUS reveal SIL. Approximately 30% of these neoplastic lesions are high grade and 70% low grade.** It has been proposed that the presence of high-risk HPV types in patients with ASCUS may help to define the nature of the lesion. The Bethesda system recommends qualifying an ASCUS diagnosis as "favor a benign or a neoplastic process." It is thought that communicating the cytopathologist's degree of concern may help the clinician in determining further management in these cases. However, this type of subclassification remains controversial because of the lack of specific diagnostic criteria and marked interobserver variability.

Squamous Intraepithelial Lesions

Cytomorphologic abnormalities seen in SIL constitute a spectrum. **LSIL encompasses condyloma and CIN 1 (mild dysplasia), and HSIL encompasses CIN 2/3 (moderate/severe dysplasia and CIS),** as previously discussed. The nuclear and cytoplasmic abnormalities become more marked in higher-grade lesions, with greater nuclear irregularities, hyperchromasia, coarse nuclear granularity, and higher nuclear/cytoplasmic ratios. Squamous cell carcinoma may exhibit features of HSIL; however, additional features such as macronucleoli, markedly irregular chromatin distribution, and tumor diathesis (blood and necrotic debris) are often present.

Glandular Epithelial Abnormalities

Among the glandular lesions that can be detected by the Pap smear are *atypical glandular cells of undetermined significance (AGUS)*, adenocarcinomas of the endocervix and endometrium, and, rarely, metastatic lesions from genital (ovary) or extragenital (e.g., breast carcinoma) sites (28).

Atypical Glandular Cells of Undetermined Significance

The term *AGUS* refers to cells displaying nuclear atypia that exceed obvious reactive or reparative changes but lack unequivocal features of *in situ* or invasive adenocarcinoma. The diagnosis of AGUS should be further qualified, if possible, to indicate whether the cells are thought to be of endocervical or endometrial origin, and whether a reactive or a neoplastic process is favored. However, because the AGUS category includes a broad morphologic spectrum, ranging from atypical reactive/reparative processes to *AIS*, this distinction is not straightforward. Criteria for separating AGUS into "favor reactive" and "favor neoplastic" are not well established and suffer from poor reproducibility among pathologists. In addition, it may be very difficult to differentiate SIL with endocervical gland involvement from a true glandular dysplasia. In general, most truly neoplastic AGUS cases turn out to be SIL rather than glandular lesions on follow-up biopsy.

Adenocarcinoma *In Situ*

Most invasive endocervical adenocarcinomas are preceded by AIS (Fig. 6.19). AIS is commonly reported as "AGUS, probably neoplastic" on Pap smears. There is considerable cytologic overlap between AIS and endocervical adenocarcinoma on Pap smears. Criteria indicating invasion, such as macronucleoli and tumor diathesis, may be absent in invasive adenocarcinoma. Therefore, this distinction requires histologic evaluation.

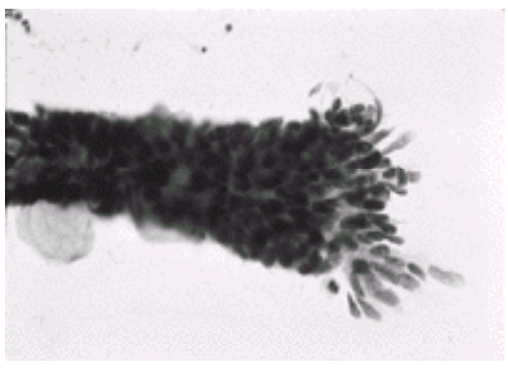


Figure 6.19 Adenocarcinoma *in situ* (Pap smear). This lesion is characterized by a cluster of columnar cells with nuclear enlargement and hyperchromasia. Note the "feathering" effect at the edges.

Adenocarcinoma

Although all adenocarcinomas share similar morphologic features, an endocervical origin can be distinguished by the retained columnar morphology of the malignant cells and the frequent feathering, palisading, and rosette formation (Fig. 6.20). In contrast, endometrial adenocarcinomas tend to shed fewer cells, the cell size and nuclei are smaller, nucleoli are less prominent, and the tumor diathesis is watery rather than necrotic (Fig. 6.21). An extrauterine origin should be suspected when cells diagnostic of adenocarcinoma are seen in a clean background without a tumor diathesis (Fig. 6.22).

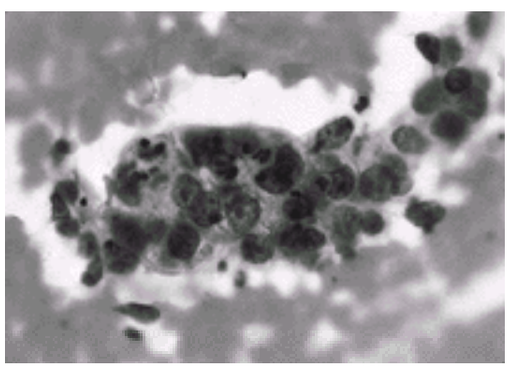


Figure 6.20 Invasive endocervical adenocarcinoma (Pap smear). This lesion shows a three-dimensional cluster of glandular cells

Figure 6.20 Invasive endocervical adenocarcinoma (Pap smear). This lesion shows a three-dimensional cluster of glandular cells with nuclear atypia and very prominent nucleoli in a bloody background.

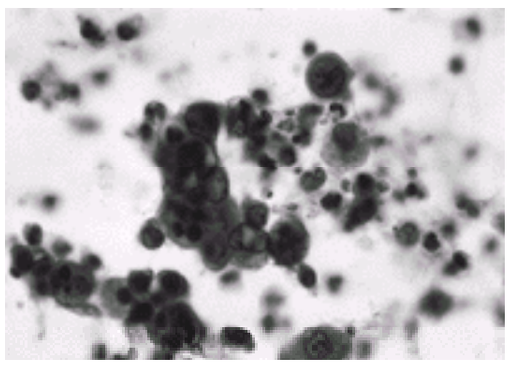


Figure 6.21 Endometrial adenocarcinoma (Pap smear). The malignant cells are smaller than in Fig. 6.20, with less prominent nucleoli. No feathering or columnar morphology is seen.

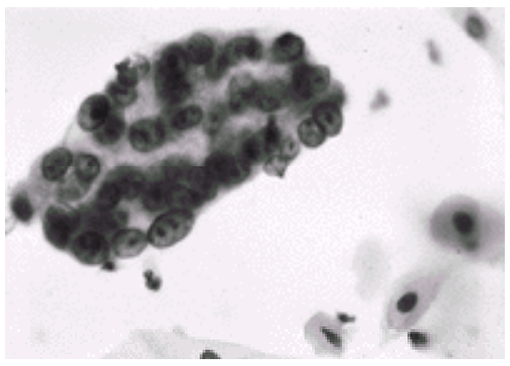


Figure 6.22 Ovarian adenocarcinoma cells seen in a Pap smear. Note the clean background.

New Technologies

Liquid-Based Technology

Liquid-based technology, also known as *monolayer*, aims to reduce false negativity by optimizing the collection and preparation of cells (28,29). Two devices are available to prepare modified smears from cells collected in a liquid medium: the ThinPrep processor (CYTYC Corporation, Boston, MA) and the CytoRich, now known as Tripath (Roche Cytology Systems, Elon College, NC). In the ThinPrep method, the cells are collected by a brush that is rinsed into a vial of preservative solution. The sample is then placed in a processing apparatus, where it is mixed, dispersed, and passed through a filter with a predetermined pore size. The cells are then touch transferred from the filter onto a glass slide and stained. Although the technology differs in the CytoRich system, the underlying concept is similar and therefore is not discussed separately in this chapter.

The advantages of the monolayer technique can be summarized as follows:

1. With the monolayer technique, mucus, blood, and inflammatory cells are removed by the fixative and the filter, providing a “clean background,” without loss of tumor diathesis. Several studies have shown a higher detection rate of LSIL and HSIL.
2. With conventional smears, it is estimated that fewer than 20% of the cells on the collection device are transferred onto the glass slide. Furthermore, the sample of cells transferred onto the slide may not be representative of the population of cells on the collection device. Rinsing the cells into a vial and homogenizing the solution provides more uniform representation of the sample.
3. It is suggested that collection of cells into a fixative solution provides immediate fixation and better cellular detail.

Several disadvantages are inherent in the monolayer technique. Because the cells are collected in a liquid medium, the cytologic features differ compared with conventional smears, requiring special training. Scattered and fewer diagnostic cells may be present on a monolayer, making it easier to overlook them. The slide preparation is more time consuming, and the overall cost is higher than for conventional smears.

Automated Screening of Conventionally Prepared Pap Smears

Two machines are used for automated screening of conventionally prepared Pap smears. The AutoPap 300 system (Neopath, Inc., Redmond, WA) is approved by the Food and Drug Administration for primary screening and quality control rescreening of smears previously diagnosed as within normal limits by manual screening. The PAPNET System (Neuromedical Systems, Inc., Suffern, NY) is approved for quality control rescreening only.

The AutoPap system is placed in individual laboratories. Its principle is based on high-speed computer processing of cell images. It evaluates conventional smears using a conventional, rule-based algorithm. The device may be adjusted to select a certain percentage of cases to be reviewed.

The PapNet system operates on different principles. It uses neural network software to rescreen slides that have been previously screened by cytotechnologists and classified as negative. It identifies slides that are likely to contain abnormal cells. The abnormal cell images are displayed on a high-resolution monitor for assessment by a cytotechnologist who can decide whether to review the slide under light microscopy. This system requires slides to be sent to a central facility from individual laboratories, which then receive the selected abnormal images saved on disks for final diagnosis by the cytologist.

The aim of the automated screening devices is to reduce human screening errors. Several studies have shown that both systems are instrumental in finding lesions on smears previously classified as normal after primary screening. However, the costs related to the ThinPrep and the computerized systems are significantly higher than with the conventional Pap smear. Future clinical trials will define the role of automated techniques in clinical practice.

Human Papillomavirus Testing

Most cervical carcinomas are associated with the oncogenic types of HPV. Clinical and epidemiologic studies have shown that women infected with HPVs of high oncogenic potential (mainly subtypes 16 and 18) have a markedly increased risk for development of CIN compared with noninfected women (28,30,31). In addition, **low-grade lesions have a higher rate of progressing toward high-grade lesions when HPV 16 or 18 is detected.** The significance of HPV testing lies in its potential to identify individuals infected with high-risk HPVs before high-grade lesions develop.

Several techniques are available to detect and identify HPV. These techniques have varying specificities and sensitivities. The optimal reference method is the *Southern blot. Polymerase chain reaction (PCR)* also has been used in many laboratories. PCR requires very little viral DNA and therefore allows the study of small samples. The method is based on the amplification of a selected region of viral DNA by hybridization with flanking sequences (primers) to the selected fragment. PCR is very sensitive, simple, and rapid; however, sample contamination is a significant problem that can cause false-positive results.

The *hybrid capture system* is a second-generation hybridization assay that uses chemiluminescent detection. The HPV DNA is hybridized with a specific RNA probe cocktail. The DNA–RNA hybrid is captured by an anti-RNA–DNA antibody attached to the sides of the tube. The immobilized hybrid is then detected through a chemiluminescent reaction. This technique allows quantification of the viral load, and therefore increases the specificity of the test for clinically significant disease. The system detects five low-risk and nine high-risk HPV types. Under experimental conditions, this method is as sensitive as PCR, and does not suffer from contamination.

Applications of Human Papillomavirus Testing

Primary Screening Tool The role of HPV testing as a mass screening tool is limited. Especially in the young population, latent HPV infection is very common (up to 60%) and is a marker of sexual activity rather than cervical cancer risk. Clinically significant disease develops in only a small proportion of carriers. Therefore, HPV testing alone leads to many unnecessary colposcopic examinations. However, HPV testing may be indicative of clinically significant disease in older women in whom the prevalence of HPV infection is low.

Triage of ASCUS and LSIL Pap Smears Two kinds of problems exist within the group of Pap smears with mild abnormalities:

1. Low reproducibility due to interobserver disagreement among pathologists.
2. Disagreement over optimal management, mainly because some low-grade lesions regress without treatment, and therefore may not need therapy.

Up to one third of women with an ASCUS or LSIL diagnosis have a high-grade lesion on biopsy. HPV testing has been proposed in this group of patients to determine which subset is at risk for harboring or developing a high-grade lesion. Ninty-three to 100% of patients with high-grade CIN whose original Pap smears showed LSIL were correctly identified in two studies that used hybrid capture for HPV typing (30,31). A negative repeat Pap smear combined with a negative high-risk HPV test conferred a negative predictive value of 95% to 100% (30).

In terms of cost effectiveness, ASCUS triage studies suggest that it is critical to do the HPV testing on the sample obtained at the time of the initial Pap smear rather than scheduling the patient for a second office visit based on the initial Pap smear diagnosis (31,32 and 33). For this purpose, one study used HPV testing (hybrid capture) on the residual cells remaining in the vial after a ThinPrep slide was prepared (32,33). However, in this study, if colposcopy had been done on patients based only on HPV test results, 20% of HSIL and 18% of LSIL would have been missed.

Thus, many advances have been made in cervical/vaginal cytologic analysis in recent years. The aim of these new techniques is to eliminate the probably irreducible false-negative rate of at least 5% in conventional Pap smears. Future studies will define the most cost-effective and sensitive strategies to improve the accuracy of screening for cervical cancer.

Vagina

Tumor-Like Lesions

Vaginal Polyp

This is a benign fibroepithelial lesion, most common in women older than 20 years of age (34). One third of patients are pregnant at the time of diagnosis, and another one third have a prior history of vaginal surgery or instrumentation. Most patients are asymptomatic, but some may present with abnormal bleeding or a vaginal lump. The polyps occur predominantly in the anterior vaginal wall, ranging in size from 0.5 to 4.0 cm. Histologically, they are lined by squamous epithelium and are composed of a myxoid stroma containing atypical stromal cells. The importance of recognizing the atypical stromal cells as part of the benign polyp lies in distinguishing them from sarcomas, especially sarcoma botryoides. Vaginal polyps lack the cambium layer and the stromal undifferentiated small blue cells characteristic of sarcoma botryoides, and occur predominantly in adults.

Vaginal Cysts

These are usually asymptomatic, and most are located in the posterior and lateral vaginal wall. They are classified according to their epithelial lining. The most common type is the *epithelial inclusion cyst*, which is lined by squamous epithelium and is frequently associated with previous surgery. *Müllerian cysts* are lined by an endocervical-type columnar mucinous epithelium. Cilia and squamous metaplasia are common. In contrast to vaginal adenosis, with which they may be confused, they usually present as a single large cyst. *Mesonephric cysts (Gartner duct cysts)* are remnants of the mesonephric duct lined by nonmucinous cuboidal epithelium without cilia or squamous metaplasia.

Postoperative Spindle Cell Nodule

This lesion is a benign submucosal spindle cell lesion, typically discovered within 3 months after a surgical procedure, most commonly a hysterectomy (1). It is characterized by high cellularity and prominent mitotic figures. Postoperative spindle cell nodule is most commonly mistaken for a leiomyosarcoma. Clinical history and immunohistochemistry (negative smooth muscle immunostains) are helpful in the differential diagnosis.

Squamous Lesions

Condyloma Acuminatum

Vaginal condyloma acuminatum is similar in its macroscopic and microscopic appearance to its cervical counterpart, and is described in detail in the cervical section.

Squamous Intraepithelial Lesions

Squamous intraepithelial lesions of the vagina **have been termed *dysplasia* and *vaginal intraepithelial neoplasia (VAIN)*, similar to the terminology used for cervical SIL** (35,36). The microscopic appearance and the grading system based on the severity of the intraepithelial changes are the same as those for the cervix, ranging from VAIN 1 to 3.

Women with VAIN are approximately 10 years older than women with CIN. In half of the cases, VAIN is multifocal, and in more than 90% of the cases, it affects the upper third of the vagina. Most patients with VAIN are asymptomatic. Approximately 80% of VAIN cases are detected in women with prior, concurrent, or subsequent CIN or vulvar intraepithelial neoplasia (VIN). In fact, the most common clinical presentation is through cytologic detection in a patient who has undergone hysterectomy for cervical HSIL. Because the incidence of VAIN is low in the general population (0.2 to 0.3 per 100,000 women in the United States), screening for VAIN by Pap smear should be directed to this high-risk population with a prior history of HPV infection or dysplasia.

Squamous Cell Carcinoma

Primary squamous cell carcinoma of the vagina is rare, accounting for 2% of all female genital tract malignancies (35,37). Most vaginal squamous cell carcinomas are due to recurrence or direct extension from a cervical primary. In patients with a history of a previous preinvasive or invasive cervical or vulvar carcinoma, a 5- to 10-year disease-free interval is necessary to rule out recurrent disease before diagnosing a new vaginal primary (5).

Vaginal squamous cell carcinoma is more common in women older than 60 years of age. Risk factors include genital HPV infection, vaginal trauma, early hysterectomy, and cigarette smoking. Most patients present with vaginal bleeding and discharge. The tumor is commonly located in the upper third of the vagina as an ulcerating, exophytic, or annular/constricting mass. Microscopic features are similar to those of cervical squamous cell carcinoma.

Verrucous and Warty (Condylomatous) Carcinomas These lesions, which are described in the cervical section, rarely occur in the vagina. They are special variants of squamous cell carcinoma associated with localized growth and good prognosis.

Glandular Lesions

Adenosis and Atypical Adenosis

***Vaginal adenosis* refers to the presence of glandular epithelium in the vagina, which is normally lined by squamous epithelium** (1). Vaginal adenosis is a congenital disorder, usually related to *in utero* diethylstilbestrol (DES) exposure. In approximately 65% of the cases, DES exposure can be documented in the first trimester of the pregnancy. DES inhibits the urogenital-derived squamous epithelium from replacing the preexisting müllerian epithelium, which later develops into adenosis.

Most women with adenosis are asymptomatic, but some may present with a mucoid vaginal discharge. Adenosis most commonly involves the upper one third of the anterior vaginal wall and is grossly visible as cysts or granularity of the vaginal mucosa. Microscopically, vaginal adenosis may be of endocervical mucinous or tubal/endometrial type.

Atypical adenosis (1) is characterized most commonly by tuboendometrial type glands, which display varying degrees of cytologic atypia (pleomorphic, enlarged nuclei with prominent nucleoli).

Most cases of adenosis regress. However, because of the risk of development of clear cell carcinoma, these patients should be followed. There is no conclusive evidence that atypical adenosis is a precursor lesion of clear cell adenocarcinoma, but because of the uncertainty as to their natural outcome, these cases should be followed even more carefully.

Adenocarcinoma

Clear Cell Adenocarcinoma

Clear cell adenocarcinoma (1,35) is a form of adenocarcinoma composed of glycogen-containing clear and hobnail cells arranged in a solid, tubulocystic, or papillary pattern. Approximately 60% of patients with clear cell carcinoma have a history of DES exposure. Clear cell carcinoma may appear as a polypoid, papillary, flat, or ulcerated lesion (Fig. 6.23). It may be deep in the vaginal wall. The prognosis depends on the stage of disease.

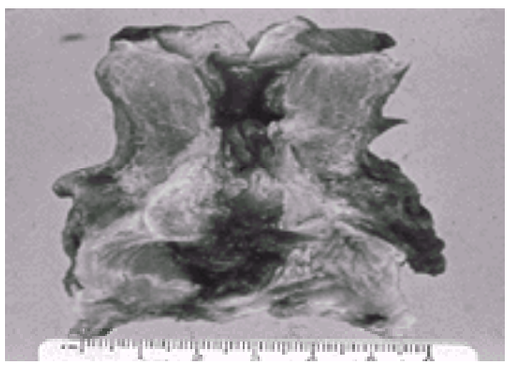


Figure 6.23 Clear cell adenocarcinoma of the vagina. This is a hemorrhagic, friable tumor in the posterior wall of the vagina.

Other types of adenocarcinomas include endometrioid, endocervical mucinous, intestinal-type mucinous, and mesonephric, all of which are rare tumors.

Mesenchymal Lesions

Sarcoma Botryoides (Embryonal Rhabdomyosarcoma)

Sarcoma botryoides, although rare overall, is the most common childhood malignancy of the vagina (38). It is unusual after the first 5 years of life, with a peak incidence at 2 years of age. Most patients present with vaginal bleeding and/or a polypoid mass protruding from the vagina. Grossly, the tumor is pedunculated or sessile, and composed of multiple grape-like masses. Microscopically, the tumor is lined by nonkeratinizing squamous epithelium, beneath which a highly cellular cambium layer is found. Deep to the cambium layer, the stroma is loose and edematous (Fig. 6.24). Within the cambium and loose stroma, rhabdomyoblasts (small blue cells, some of which may have cytoplasmic cross-striations) are found. Immunohistochemically, rhabdomyoblasts are positive for muscle markers such as desmin, myoglobin, and muscle-specific actin.

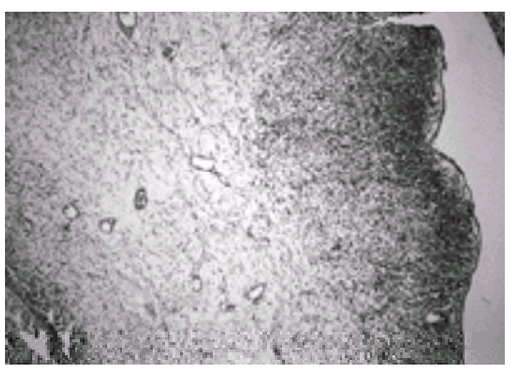


Figure 6.24 Embryonal rhabdomyosarcoma. A hypercellular cambium layer lies beneath the surface epithelium and deep myxoid stroma.

Sarcoma botryoides is a very aggressive tumor. It grows rapidly, primarily by invasion of the neighboring organs. Local resection combined with chemotherapy has led to a significant improvement in survival.

Leiomyosarcoma

Leiomyosarcoma is the most common vaginal soft tissue malignancy in adults (39). It occurs in a wide age range, from 25 to 86 years of age. Leimyosarcoma presents as a bulky submucosal mass. The microscopic appearance is similar to that of its counterpart in the uterine corpus. **Five or more mitotic figures per ten high-power fields, increased cellularity, cellular atypia, and infiltrative growth pattern are the histologic criteria for malignancy.** The histologic grade is the most important predictor of outcome; low-grade tumors have a low rate of recurrence and metastasis after treatment by local surgery alone.

Malignant Melanoma

Although primary malignant melanoma of the vagina comprises less than 1% of all melanomas in women, it is the most common vaginal malignant neoplasm after squamous cell carcinoma (40). Three-fourths of the cases occur in white women older than 60 years of age. The tumors are thought to be related to vaginal nevi or melanosis. Grossly, they appear as blue/black, soft, mucosal or submucosal nodules. Microscopically, they resemble their counterparts in the skin. Most are pigmented, but some may be amelanotic. The Breslow and Clark systems, which are discussed in more detail in the vulvar section, are used as part of staging.

Most melanomas are deeply invasive at the time of diagnosis, which in part accounts for their overall poor prognosis. The tumor size rather than the depth of the tumor (because most are deep at the time of diagnosis) appears to be the most significant factor in determining prognosis (41).

Metastatic Tumors

Metastatic tumors are much more common in the vagina than primary malignant tumors, comprising 80% of vaginal invasive tumors. The most common primary sites include cervix, endometrium, colon, rectum, ovary, vulva, urinary bladder, and urethra. Metastases from melanoma, renal cell carcinoma, and breast carcinoma have also been reported (42).

Vulva

Squamous Lesions

Condyloma Acuminatum

Condyloma acuminatum similar to that in the cervix occurs in the vulva as well as the vagina. Condyloma acuminatum is discussed in detail in the cervical section.

Squamous Intraepithelial Lesions

Squamous intraepithelial lesions of the vulva have been designated *dysplasia/CIS* and *VIN*, similar to the terminology used for the cervix. Microscopic grading is carried out in the same way as for cervical SIL, and depends on the extent of the dysplasia; replacement of the lower third of the squamous epithelium by dysplastic cells is classified as VIN 1, the lower two thirds as VIN 2, and full-thickness involvement as VIN 3. Pure VIN 1 and 2 lesions occur less commonly than VIN 3. Most often, VIN 1 and 2 are seen in association with VIN 3.

Although the dysplasia is full thickness in VIN 3, the architecture of the lesion can show morphologic diversity. Based on these differences in pattern, VIN 3 is divided into three categories:

1. *Warty* VIN—with spiked surface resembling a condyloma (Fig. 6.25)

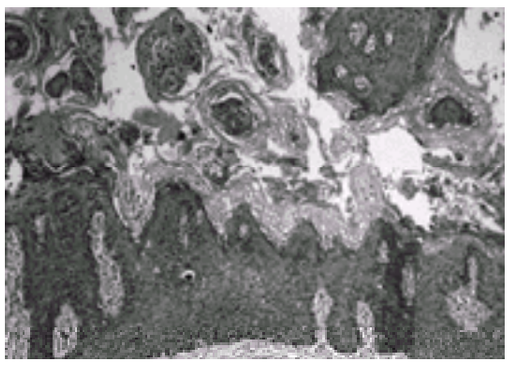


Figure 6.25 Warty vulvar intraepithelial neoplasia. This lesion is characterized by a condylomatous-appearing squamous epithelium with full-thickness epithelial atypia.

2. *Basaloid* VIN—with flat surface and basaloid cell proliferation (Fig. 6.26)

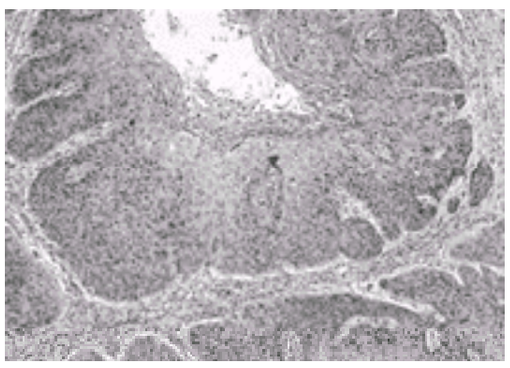


Figure 6.26 Basaloid vulvar intraepithelial neoplasia. The neoplastic squamous lining shows a flat surface. The proliferating atypical cells are small and show peripheral palisading.

3. *Differentiated* VIN—which may look deceptively benign, with the dysplastic cells showing brightly eosinophilic cytoplasm and sometimes squamous pearl formation at the basal layer (Fig. 6.27).

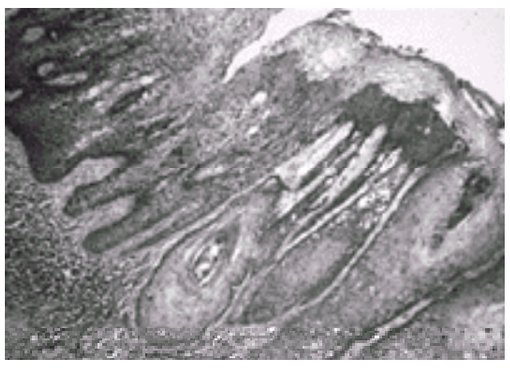


Figure 6.27 Differentiated vulvar intraepithelial neoplasia. The squamous epithelium is thickened and shows irregular, finger-like projections into the underlying stroma. The atypia is more pronounced in the basal layers. The neoplastic epithelial cells are strikingly eosinophilic compared with the basaloid variant.

Vulvar intraepithelial neoplasia is frequently found adjacent to invasive squamous cell carcinoma, suggesting that VIN may develop into invasive carcinoma if left untreated. However, the frequency with which this progression occurs is not known because VIN is usually treated by complete excision (43).

The incidence of VIN has shown a dramatic increase in the last several decades. Most patients with VIN are in their reproductive years, with a previous history of cervical SIL, genital condyloma, or some sexually transmitted disease. **Like cervical SIL, vulvar dysplasia is strongly associated with HPV infection. Most LSIL are HPV 6 and 11 related, and HSIL are HPV 16 and 18 related.**

Squamous Cell Carcinoma

Squamous cell carcinoma is the most common malignant tumor of the vulva, with an increasing incidence (44). **It is suggested that vulvar squamous cell carcinoma occurs in two different patient populations.**

1. The *first group is young women* with a history of cigarette smoking, VIN, and HPV infection.
2. The *second group is older women* without a history of smoking or HPV infection; instead, this group usually has long-standing lichen sclerosus.

Most squamous cell carcinomas occur on the labia, usually the labia majora. They may present as a nodule, ulcer, or a hyperkeratotic white plaque (Fig. 6.28). Microscopically, they resemble squamous cell carcinomas seen at other sites. The most common histologic types are the *warty (condylomatous)* and *basaloid* (relatively small, uniform cells with prominent nuclear hyperchromasia, and without evidence of keratinization) variants. Rarer forms include giant cell carcinoma, lymphoepithelioma-like carcinoma, and spindle cell carcinoma.

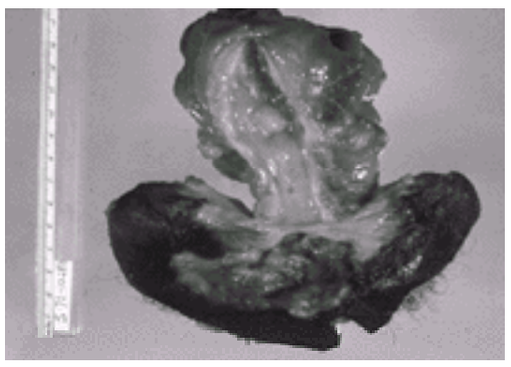


Figure 6.28 Squamous cell carcinoma of the vulva. This radical vulvectomy specimen shows ulcerated and fungating tumor.

The International Federation of Gynecology and Obstetrics defined a subset of stage 1 squamous cell carcinomas as stage 1A, which refers to a tumor with a diameter of 2.0 cm or less and a depth of invasion of 1 mm or less (45). The depth of invasion is measured from the epidermal–dermal junction of the adjacent normal dermal papilla to the deepest point of invasion.

The prognosis of vulvar squamous cell carcinoma depends on the tumor depth, size, vascular invasion, and node involvement. There are differences in opinion as to whether tumor differentiation has a significant impact on prognosis independent of tumor depth and size.

Verrucous Carcinoma

This is a well differentiated variant of squamous cell carcinoma most commonly seen in postmenopausal women (1). It resembles its counterpart in the cervix. The tumor is characterized by localized slow growth. The treatment is wide local excision. Lymph node metastasis is unusual unless the tumor is associated with squamous cell carcinoma of the usual type.

Basal Cell Carcinoma

Basal cell carcinoma, a common skin tumor, occurs uncommonly in the vulvar skin. As in other locations, it can be locally aggressive, but rarely metastasizes.

Glandular Lesions

Hidradenoma Papilliferum

Hidradenoma papilliferum is a benign apocrine sweat gland tumor most common in middle-aged women. It presents as a small, firm nodule in the anogenital area. Histologically, the neoplasm has a complex pattern with acini, tubules, and cysts filled with papillary fronds. It is identical histologically to nipple adenoma of the female breast.

Paget's Disease

Paget's disease is defined by the presence of malignant glandular cells within the vulvar epidermis and/or skin appendages, and thus is a form of *AIS* (1). It is predominantly seen in postmenopausal white women (46). The most common symptoms are pruritus and soreness. The macroscopic appearance is characterized by multifocal, well demarcated and red eczematous patches. Histologically, Paget's cells are large, round, or oval with abundant pale, sometimes vacuolated cytoplasm (Fig. 6.29). Nuclear chromatin is vesicular and the nucleolus is often prominent. The cells are arranged singly or in clusters in the squamous epithelium. The histologic differential diagnosis includes VIN and superficially spreading malignant melanoma. Special stains aid in this distinction. Paget's cells contain cytoplasmic mucin and stain with the mucicarmine stain. They are also positive for an adenocarcinoma immunohistochemical marker, carcinoembryonic antigen (CEA). Malignant melanoma cells, on the other hand, stain with the melanoma-associated marker HMB-45. VIN is negative for mucicarmine, CEA, and HMB-45 immunostains.

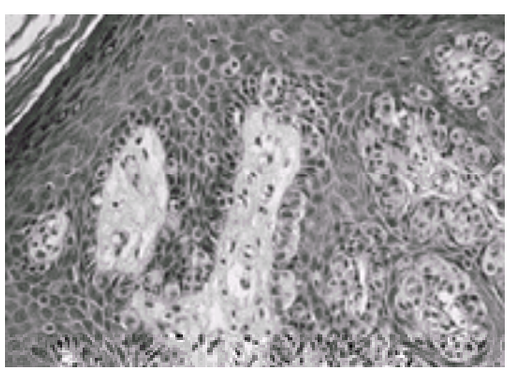


Figure 6.29 Paget's disease of the vulva. This lesion shows intraepidermal proliferation of malignant cells with abundant, pale cytoplasm and prominent nucleoli, arranged singly and in clusters.

Paget's disease may be associated with invasive adenocarcinoma and can occur anywhere along the milk line. The incidence of an underlying adenocarcinoma varies with the location. In vulvar Paget's disease, the frequency is much lower than in the breast. The excised specimen should be thoroughly dissected to search for invasive adenocarcinoma. Because Paget's disease is often multifocal and may extend beyond the clinically visible margins, the recurrence rate is high.

Adenocarcinoma

Primary adenocarcinomas of the vulva are rare. They may arise from the sweat glands, Bartholin's gland, vestibular glands, periurethral glands, mesonephric remnants, cloacal remnants, endometriosis, or ectopic breast tissue. Metastasis should be ruled out when dealing with an adenocarcinoma in this anatomic location.

Bartholin Gland Carcinoma

Bartholin gland carcinomas occur in the postmenopausal years, usually presenting as a deep mass in the posterior part of the labium majus (1). For a tumor to be accepted as a primary Bartholin gland carcinoma, it should arise at the site of the Bartholin gland and be histologically consistent with a primary neoplasm of the Bartholin gland. A wide variety of tumors originate from the Bartholin gland. Adenocarcinoma is the most common histologic type, but squamous cell, adenoid cystic, transitional cell, and adenosquamous carcinomas are also seen.

Mesenchymal Lesions

Various benign soft tissue neoplasms can be encountered in the vulva. Among the more common types are leiomyoma, rhabdomyoma, lipoma, hemangioma, angiokeratoma, neurofibroma, glomus tumor, schwannoma, and granular cell tumor. They present as a slowly enlarging and often well demarcated mass. Histologically, they resemble their counterparts at other sites.

Among the various sarcomas that can occur in the vulva are embryonal rhabdomyosarcoma, leiomyosarcoma, dermatofibrosarcoma protuberans, malignant fibrous histiocytoma, liposarcoma, malignant rhabdoid tumor, malignant peripheral nerve sheath tumor, and angiosarcoma. Sarcomas, like the benign soft tissue neoplasms, resemble their counterparts at other sites where they are more commonly seen.

Aggressive Angiomyxoma

Aggressive angiomyxoma is a benign but locally aggressive soft tissue neoplasm (47). It is most common in the second and third decades of life. The usual presentation is as a rubbery vulvar mass that may clinically simulate a Bartholin gland cyst. On gross examination, the tumor is myxoid with ill-defined margins. Microscopically, it is characterized by a hypocellular, loose, and myxoid stroma, and prominent, sometimes hyalinized blood vessels (Fig. 6.30). No mitotic activity or atypia are present. The spindle and stellate cells in the stroma are myofibroblasts and fibroblasts.

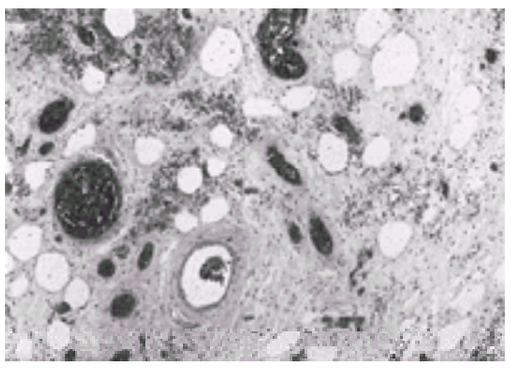


Figure 6.30 Aggressive angiomyxoma. Dilated vessels are seen in a loose stroma that contains spindle cells.

The treatment is wide local excision. Local recurrence is common, and reported in up to half of the cases. This is due to the deep infiltration of the tumor, which makes complete surgical excision difficult.

Melanocytic Lesions

Melanocytic Nevus

Vulvar nevi are uncommon. When they occur, they are frequently found in the labia majora. Most are compound or the intradermal type.

Lentigo Simplex

Lentigo simplex presents as a flat, pigmented lesion less than 0.5 cm in diameter. It is characterized by an increased number of melanocytes and melanin pigment at the dermal–epidermal junction.

Malignant Melanoma

Malignant melanoma is the second most common malignant tumor of the vulva. Most patients are older than 50 years of age. Melanoma is more common in white women. It may present as a flat plaque or as a slightly elevated or nodular, pigmented or nonpigmented vulvar mass. Satellite nodules may be present. Histologically, melanomas are of three types: *superficially spreading, nodular*, and *lentiginous.* The individual malignant cells may be epithelioid (polygonal), dendritic (spindled), or a mix of these cell types. The tumor may be *melanotic* (Fig. 6.31) or *amelanotic.* Malignant melanoma can histologically simulate poorly differentiated squamous cell carcinoma, large cell lymphoma, and Paget's disease. Immunohistochemical stains are of value in this differential diagnosis. Malignant melanoma is positive for S-100 antigen and the melanoma-associated marker HMB-45, whereas lymphoma is positive for lymphoid markers, squamous cell carcinoma for keratin, and Paget's disease for CEA, keratin, and intracytoplasmic mucin.

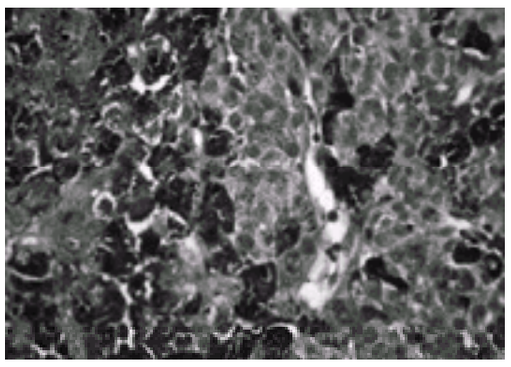


Figure 6.31 Vulvar melanoma. This lesion is characterized by a proliferation of epithelioid cells with eosinophilic cytoplasm and prominent nucleoli characteristic of melanoma. Note the abundant pigment (melanin).

Histologic staging of malignant melanoma provides useful prognostic information (48). Both the level of invasion *(Clark's levels)* and the tumor thickness *(Breslow thickness)* should be measured. For practical purposes, however, most vulvar melanomas are deeply invasive at the time of diagnosis and seldom require meticulous measurement of the depth of invasion. The prognosis is significantly worse than in cutaneous melanomas occurring at other sites.

Metastatic Tumors

Metastatic tumors comprise approximately 10% of vulvar malignant tumors. They present as single or multiple intradermal or subcutaneous nodules, most commonly in the labia majora or around the clitoris. The primary origin is most frequently in the cervix, followed by endometrium and ovary (49). Other common sites include vagina, urethra, kidney, breast, and lung.

Uterine Corpus

Endometrium: Normal Histology and Cycling Changes

The normal endometrium is divided into three layers:

1. *Superficial layer (compacta)*, consisting of surface epithelium and immediately underlying gland necks
2. *Middle layer (spongiosa*, or *functionalis)*, occupying most of the thickness of the endometrium and most responsive to hormonal effects
3. *The deep layer (basalis)*, which reacts very weakly to hormonal stimulation, and is supplied by basal arteries, whereas the outer two layers are supplied by spiral arteries

The endometrium (especially the functionalis layer) responds dramatically to changes in the hormonal milieu and its morphology varies markedly during the normal menstrual cycle (Table 6.5).

Phase of Menstrual Cycle	Endometrial Morphology
Early proliferative	Simple, small, round glands in dense stroma; many mitoses
Late proliferative	Tortuous glands in edematous stroma; many mitoses
Early secretory	Subnuclear glycogen vacuoles in epithelium; mitoses disappear
Mid-secretory	Vacuoles are supranuclear; stroma edematous
Late secretory	Intraglandular secretions, prominent spiral arterioles, predecidualization of stroma around glands
Premenstrual	Neutrophils in stroma, later within glands
Menstrual	Necrosis and hemorrhage, collapsed stroma forms "ball"

Table 6.5 Endometrial Morphology during the Menstrual Cycle

Benign Endometrial Changes

The benign changes that may mimic preneoplastic and neoplastic conditions of the endometrium are physiologically noncycling endometrium and epithelial metaplasias and related changes.

Physiologically Noncycling Endometrium

1. *Atrophy* (prepubertal, postmenopausal): A cystic atrophic pattern (dilated glands with an attenuated lining in a dense stroma) may be confused with simple hyperplasia.
2. *Gestational endometrium:* The changes include markedly decidualized stroma, the *Arias-Stella change* in glands with cellular stratification, hypersecretion and marked enlargement of both cytoplasm and nucleus, and hyperchromatic smudged nuclei (Fig. 6.32). This cellular change may be confused with clear cell carcinoma.

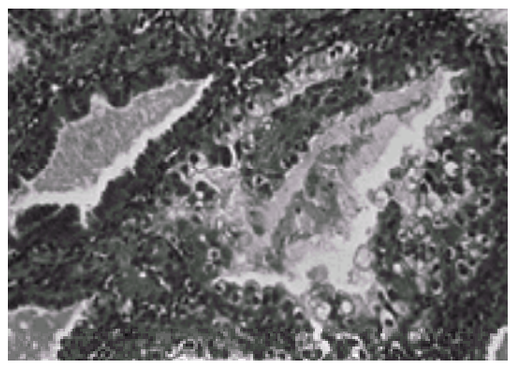


Figure 6.32 Arias-Stella reaction of the endometrium. The glandular lining shows enlarged hobnail cells with clear cytoplasm and "smudged" nuclei.

Epithelial Metaplasias and Related Changes

These encompass a group of nonneoplastic epithelial changes in which the normal endometrial epithelium is focally replaced by another type of nonneoplastic epithelium. Many types exist (e.g., syncytial, tubal, mucinous, squamous); the cause is usually thought to be due to hormonal effect and/or reparative/degenerative changes. These epithelial changes can be seen in endometrial hyperplasia and carcinoma, and may be confused with those conditions.

Endometrial Hyperplasia

Endometrial hyperplasia is classified into *simple, complex*, and *atypical* (the latter can be either complex or, very rarely, simple). All three types of hyperplasia are associated with increased thickness of the endometrium and show increased glandular crowding compared with normal proliferative endometrium (Table 6.6, Fig. 6.33, Fig. 6.34).

	Simple (without Atypia)	*Complex (without Atypia)*	*Atypical (Complex or Simple)*
Histology	Increased number of round glands, which may be cystically dilated ("Swiss cheese"). The stroma participates in the process as the glands are not markedly crowded. No cytologic atypia.	The glands are closely packed and have irregular contours; little stroma remains. No cytologic atypia.	Cytologic atypia: nuclear pleomorphism, loss of polarity, prominent nucleoli, necrotic debris in the gland lumens. Architecture may be either simple or more commonly complex.
Clinical	Premenopausal women/anovulatory bleeding	Perimenopausal and postmenopausal women	Postmenopausal
Premalignant potential*	Slight (<5%)	5%–15%	≥30%

*See references [6–8].

Table 6.6 Features of Endometrial Hyperplasias

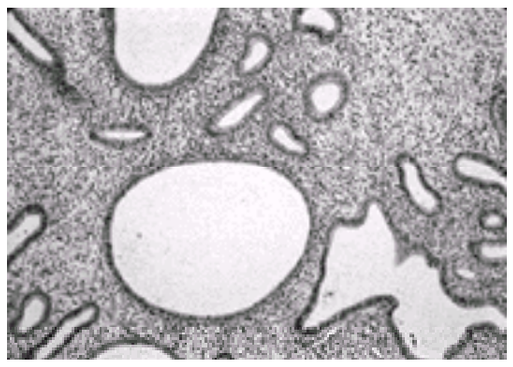


Figure 6.33 Simple endometrial hyperplasia without atypia. An increased number of round glands is seen, some of which are cystically dilated. There are no cytologic atypia.

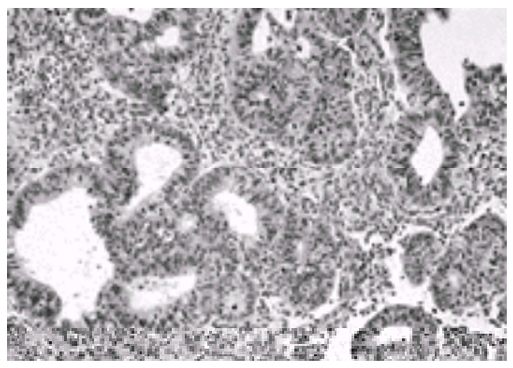


Figure 6.34 Atypical complex hyperplasia. Crowded, irregular glands show little intervening stroma. The glands show rounded, pleomorphic nuclei with prominent nucleoli.

Differential Diagnosis

1. *Chronic endometritis:* This condition can produce glandular irregularity and crowding that mimic hyperplasia. Various metaplastic changes can produce architectural (papillary or surface syncytial change) or cytologic features (eosinophilic or ciliated metaplasia) that can simulate hyperplasia or atypical cytology within a hyperplasia.
2. *Well differentiated adenocarcinoma:* **The most common diagnostic problem that arises when atypical complex hyperplasia is diagnosed is the distinction between atypical hyperplasia and well differentiated adenocarcinoma.** This differential diagnosis is especially difficult in small biopsy specimens. Multiple diagnostic criteria have been proposed, but the most significant are the ones that imply stromal invasion. The signs of stromal invasion are (a) confluent glands (Fig. 6.35), (b) desmoplastic stromal reaction (Fig. 6.36), and (c) stromal necrosis (51). Other criteria listed by Kurman and Norris (54) include the presence of solid sheets of squamous epithelium replacing glands, or complex papillary processes; these are both seen, however, as metaplastic changes in benign endometrium. These patterns, as well as confluent glands, must occupy at least half of a low-power field, according to Kurman and Norris (54). This quantitative criterion may lead to underdiagnosis of adenocarcinoma in small endometrial biopsies and probably is, along with sampling, responsible for the fact that adenocarcinoma is found in 17% (54) to 43% (55) of hysterectomies performed immediately after the diagnosis of atypical hyperplasia.

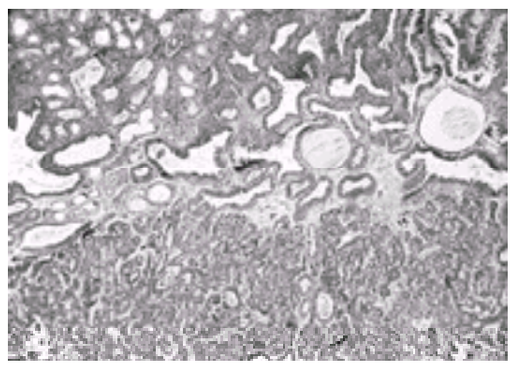


Figure 6.35 Well differentiated endometrioid adenocarcinoma arising in atypical complex hyperplasia. The upper portion of the figure shows complex hyperplasia with closely packed glands with cytologic atypia. In the bottom portion, the glands become confluent, with no intervening stroma, and represent adenocarcinoma.

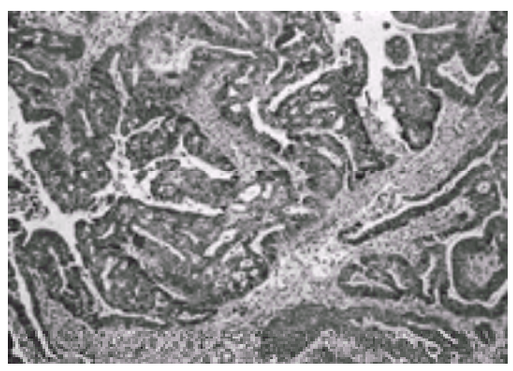


Figure 6.36 Well differentiated endometrioid adenocarcinoma. Glandular nests with extensive cribriforming are surrounded by desmoplastic, loose stroma.

The relationship between atypical complex hyperplasia and well differentiated endometrial adenocarcinoma is further confirmed by the fact that both these lesions express estrogen and progesterone receptors. This finding provides the basis for usefulness of progesterone therapy in these lesions (56). Furthermore, this relationship is stressed in Ferenczy's classification, which regards atypical hyperplasia as endometrial intraepithelial neoplasia.

Endometrial Carcinoma

Histologic Types

Most endometrial adenocarcinomas are of *endometrioid* type. In these tumors, malignant glands are lined by stratified, often elongated nuclei, reminiscent of benign endometrial epithelium. A distinct subtype of endometrioid carcinoma is *villoglandular* carcinoma, in which there are long, slender papillae lined by relatively bland cells with cigar-shaped nuclei. Villoglandular carcinoma is a low-grade tumor with an excellent prognosis; the main reason for recognizing this subtype is that it should not be confused with serous carcinoma of the endometrium, which is also papillary but has a much worse prognosis.

Adenocarcinoma with Squamous Differentiation Focal squamous areas that are identified in an endometrioid carcinoma are classified as histologically benign (adenocarcinoma with squamous differentiation, or adenoacanthoma; Fig. 6.37) or histologically malignant (adenosquamous carcinoma). The latter type has a more aggressive behavior, largely because its glandular elements are almost always poorly differentiated. Importantly, the squamous areas (benign or malignant) are excluded from histologic grading.

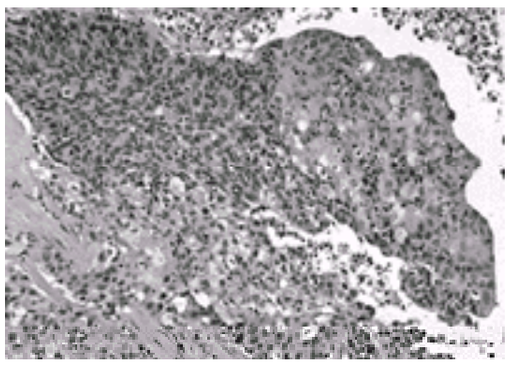


Figure 6.37 Endometrioid adenocarcinoma with squamous differentiation (adenoacanthoma). A solid area of benign-appearing squamous cells is seen in the right half of the field.

Secretory and Ciliary Carcinomas Other subtypes of endometrioid adenocarcinoma include rare *secretory* and *ciliated* carcinomas, which are usually well differentiated and have a good prognosis (especially pure secretory carcinoma). These morphologic patterns can also be seen focally in an otherwise typical endometrioid carcinoma.

Mucinous Adenocarcinoma Mucinous adenocarcinoma (Fig. 6.38) is most often of low grade and stage, and is frequently seen in women treated with tamoxifen. If this pattern is seen in an endometrial biopsy, the question may arise whether the primary tumor is in the cervix or endometrium.

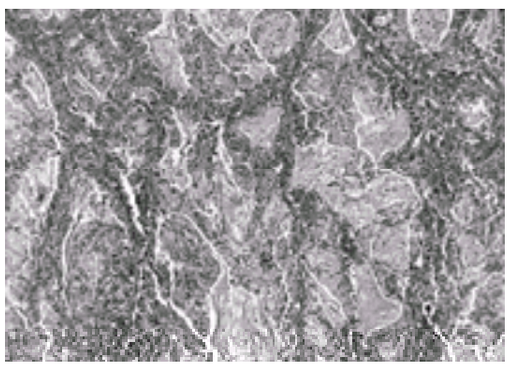


Figure 6.38 Mucinous adenocarcinoma. Confluent and cribriform glands are lined by mucinous epithelium.

Serous Carcinoma This tumor comprises between 5% and 10% of all endometrial carcinomas and is known for its aggressive behavior. It typically affects postmenopausal women. The hallmarks of this carcinoma are a tendency for myometrial invasion, extensive lymphatic space invasion, and early dissemination beyond the uterus (most often in the form of diffuse peritoneal involvement; Fig. 6.39). Even when serous carcinoma is confined to a polyp, recurrence occurs in up to 60% of cases (57). Microscopically, the tumor is composed of complex papillary fronds lined by highly atypical cells with prominent, brightly eosinophilic nucleoli. Exfoliation of cells and psammoma body formation are also seen (Fig. 6.40). Serous carcinoma usually has mutations of the *p53* gene and is estrogen and progesterone receptor negative—the opposite of the pattern for endometrioid carcinoma. Serous carcinoma of endometrium is not graded; it is regarded as a high-grade tumor by definition.

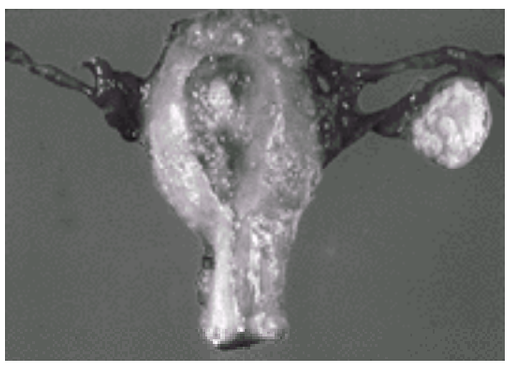


Figure 6.39 Serous carcinoma of the endometrium. The tumor is a polypoid mass arising in an atrophic uterus. Extensive myometrial lymphatic spread and involvement of the ovary were seen.

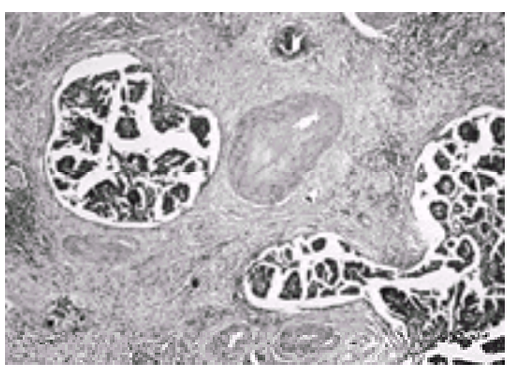


Figure 6.40 Serous carcinoma of the endometrium. This tumor shows extensive lymphatic space invasion deep in the uterine wall.

Figure 6.40 Serous carcinoma of the endometrium. This tumor shows extensive lymphatic space invasion deep in the uterine wall.

Endometrial Intraepithelial Carcinoma This lesion is characterized by replacement of benign (often atrophic) endometrial epithelium by highly malignant cells resembling serous carcinoma (58). It is regarded as a precursor of serous carcinoma and is sometimes seen adjacent to it.

Clear Cell Carcinoma Clear cell carcinoma is less common than serous carcinoma (1% to 5%) but occurs in the same (postmenopausal) patient population. It often presents at a high stage and thus has a poor prognosis. The classic clear cell carcinoma is characterized by clear, glycogen-filled cells with highly pleomorphic nuclei; these cells are often hobnail-like and grow in tubular or papillary arrangements (Fig. 6.41).

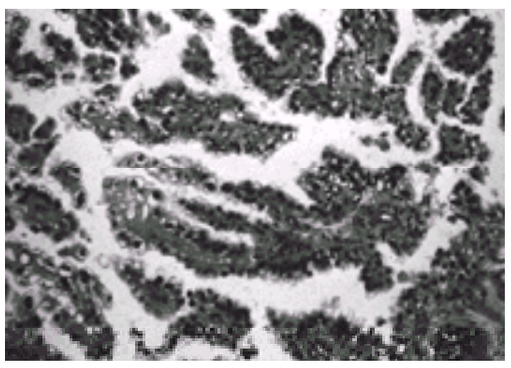


Figure 6.41 Clear cell carcinoma of the endometrium. Papillary fronds are lined by anaplastic hobnail cells with clear cytoplasm.

Squamous Cell Carcinoma Squamous cell carcinoma of the endometrium is very rare. If a cervical carcinoma extending into the endometrium is carefully excluded, true squamous cell carcinoma of the endometrium is associated with cervical stenosis and pyometra.

Undifferentiated Carcinoma This is a tumor that shows no glandular or squamous differentiation. It represents 1% to 2% of all endometrial carcinomas and has epidemiologic features similar to those of endometrioid carcinoma. These tumors often express neuroendocrine markers and have a prognosis similar to, or worse than, grade 3 endometrioid carcinoma. The rare *small cell neuroendocrine-type tumor* may present with precocious distant metastases and is best treated by chemotherapy, as well as total abdominal hysterectomy and bilateral salpingo-oophorectomy.

Mixed Carcinoma This term applies when an endometrial carcinoma shows two or more patterns of differentiation. To qualify for this diagnosis, the minor component should comprise 10% or more of the tumor.

Histologic Grading of Endometrioid Carcinoma

The histologic grade is assigned according to the percentage of solid epithelial growth (not including areas of squamous differentiation).

1. ***FIGO grade 1*—the tumor exhibits good gland formation and has 5% or less of solid growth pattern.**
2. ***FIGO grade 2*—the solid growth pattern occupies between 6% and 50% of the tumor.**
3. ***FIGO grade 3*—tumors display more than 50% solid epithelial growth.**

Severe nuclear atypia raises the grade by one, but the possibility of a nonendometrioid (serous or clear cell) carcinoma should always be considered in this situation.

Pathologic Staging of Endometrial Carcinoma

Endocervical Involvement This may be diagnosed in the endocervical curettage specimen if fragments of carcinoma are seen associated with endocervical tissue. **Endocervical involvement is divided into surface epithelial involvement (replacement) by carcinoma (stage IIA) and cervical stromal invasion (stage IIB). In the new FIGO system, hysterectomy is required for accurate staging.**

Myometrial Invasion The depth of myometrial invasion is expressed as a proportion of the myometrium invaded by the tumor; in the FIGO staging system, this is reported as inner or outer half, and in the Society of Gynecologic Oncologists' system, as inner, middle, or outer third (Fig. 6.42). Thus, it is best for the pathologist to report the deepest invasion and the myometrial thickness at that point. The presence of lymphatic/vascular space invasion is not used to determine the depth of invasion. Care should be taken not to interpret the involvement of adenomyosis by adenocarcinoma as myometrial invasion; the presence of residual endometrial stroma and/or benign basalis glands between the tumor and myometrium is a helpful differentiating feature.

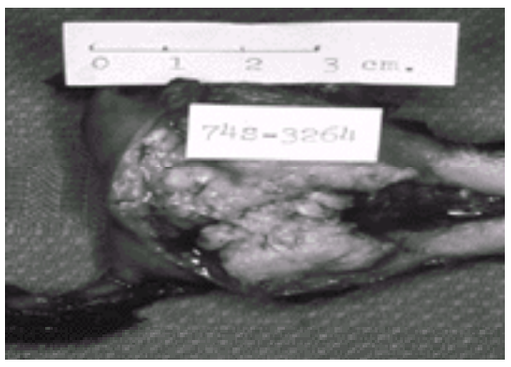


Figure 6.42 Endometrial adenocarcinoma. This is a polypoid exophytic tumor with myoinvasion into the outer third of the myometrium.

Endometrial Stromal Tumors

These tumors include stromal nodule and low-grade and high-grade endometrial stromal sarcomas and comprise approximately 10% of uterine mesenchymal tumors.

Endometrial Stromal Sarcoma

Low-Grade Stromal Sarcoma This tumor microscopically resembles benign endometrial stroma in the proliferative phase, with small uniform cells and small blood vessels that are reminiscent of spiral arterioles (Fig. 6.43). The tumor characteristically shows extensive myometrial (and sometimes parametrial) invasion, mainly in the form of plugs of tumor in the lymphatic or venous channels (Fig. 6.44); grossly, these produce worm-like masses within the myometrium or, in a third of cases, outside of the uterine corpus. A common gross feature is a polypoid exophytic mass in the endometrial cavity, but many tumors are confined to the myometrium.

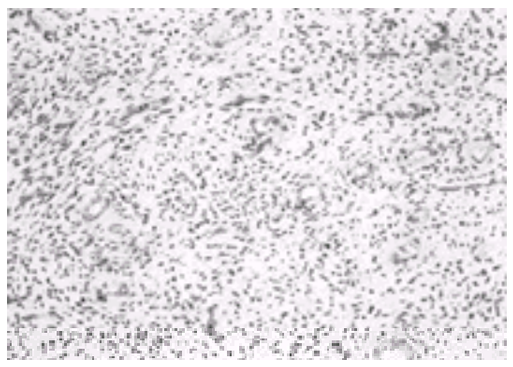


Figure 6.43 Endometrial stromal sarcoma, low grade. The tumor resembles benign endometrial stroma of proliferative phase, with small bland cells and prominent small vessels.

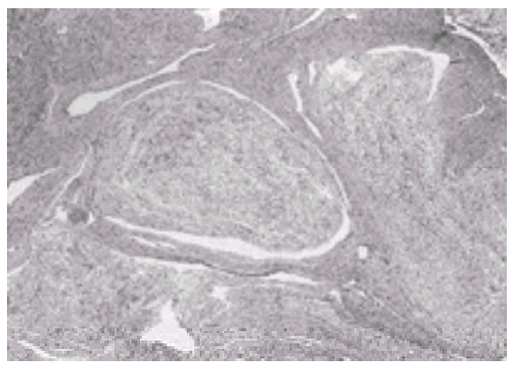


Figure 6.44 Endometrial stromal sarcoma, low grade. This tumor shows deep myometrial invasion.

Benign Stromal Nodule This is microscopically identical to low-grade stromal sarcoma, but has a circumscribed, noninfiltrative border. The difficulty in differential diagnosis may arise in endometrial biopsy/curettings where complete examination of the interface with myometrium is not possible. In these cases, only a hysterectomy may resolve the diagnostic problem. Stromal nodules are clinically benign, whereas low-grade stromal sarcomas may recur locally and metastasize, but can do so many years after initial treatment. These tumors are almost always progesterone receptor rich and often respond to treatment with progestins.

High-Grade Stromal Sarcoma This has an overtly malignant appearance and only slight, if any, resemblance to normal endometrial stroma. It is fortunately very rare, but has a poor prognosis. This aggressive tumor recurs and eventually metastasizes (most often to the lungs) relatively quickly, usually within 2 years of initial presentation.

Undifferentiated Uterine Sarcoma This term refers to very high grade sarcomas that do not bear any similarity to endometrial stroma. These tumors are often polypoid and largely necrotic, and display highly anaplastic spindle cells with very high mitotic counts. Prognosis is extremely poor.

Mixed Epithelial–Stromal Tumors

These lesions are summarized in Table 6.7.

	Adenofibroma	Atypical Polypoid Adenomyoma	Adenosarcoma	Carcinosarcoma
Epithelial component	Benign glands	Crowded atypical glands	Benign glands	Malignant endometrioid, serous, clear cell carcinoma
Stromal component	Benign fibroblastic	Smooth muscle	Malignant endometrial stroma	High-grade sarcoma, homologous or heterologous
Age	Postmenopausal	Premenopausal	Varies	Postmenopausal
Behavior	Benign	Benign	Recurs, rarely metastasizes	Highly malignant

Table 6.7 Clinicopathologic Features of Mixed Epithelial Stromal Tumors of the Uterus

Adenofibroma This benign tumor occurs in postmenopausal women and is a polypoid neoplasm that consists of benign glands and fibrous stroma.

Atypical Polypoid Adenomyoma This occurs in premenopausal women and is a polypoid tumor arising in the lower uterine segment or endocervix. This benign tumor is characterized by an admixture of crowded and sometimes cytologically atypical endometrial glands in the background of interlacing smooth muscle bundles. The architectural and cytologic atypia may cause concern for endometrial hyperplasia or carcinoma invading myometrium.

Adenosarcoma This tumor most often arises in the endometrium and usually is a polypoid mass that fills the endometrial cavity (Fig. 6.45). The tumor may be seen within an otherwise typical endometrial polyp. It consists of benign endometrial glands and a sarcomatous stroma. The endometrial or fibroblastic stroma shows characteristic “cuffing” or relative hypercellularity around epithelium; the stromal cells exhibit cytologic atypia and increased mitotic activity (usually over three to four per ten high-power fields; Fig. 6.46). The stroma may distend the epithelium, producing compressed, narrow glands and leaf-like projections. Sarcomatous overgrowth (when at least 25% of the tumor consists of pure sarcoma), myometrial invasion, and extrauterine spread at the time of diagnosis are all indicators of aggressive behavior. Local recurrence is seen in 25% to 40% of patients, and 5% have distant metastases, which usually consist purely of sarcomatous elements.

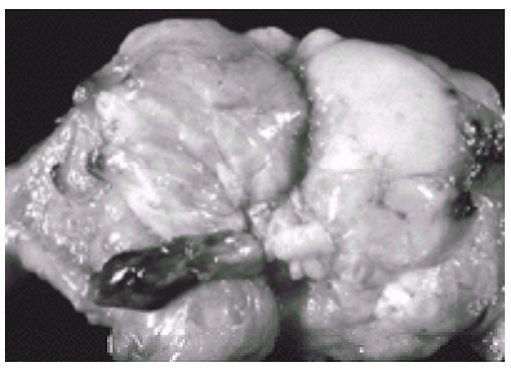


Figure 6.45 Adenosarcoma. Multiple polypoid masses arise in the endometrium.

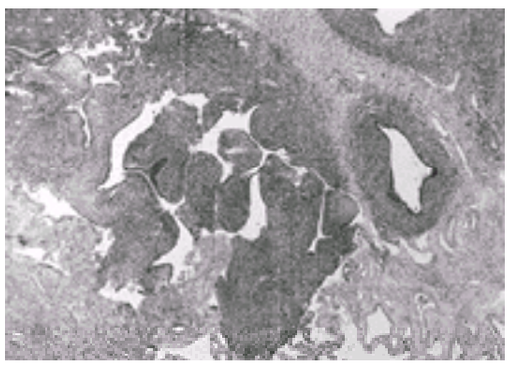


Figure 6.46 Adenosarcoma. Benign endometrial glands are surrounded by cuffs of hypercellular, mitotically active endometrial stroma.

Carcinosarcoma (Malignant Mixed Mesodermal or Müllerian Tumor) This is a mixed epithelial–stromal tumor in which both components are malignant. It is the most common malignant uterine tumor after carcinoma, but constitutes only 2% to 3% of all uterine malignancies. It is often classified incorrectly as a sarcoma, but probably represents a metaplastic carcinoma in most, if not all cases. Most carcinosarcomas occur in postmenopausal women; grossly, they present as polypoid masses filling the endometrial cavity (Fig. 6.47). The epithelial component can be of endometrioid (most common), serous, clear cell, mucinous, undifferentiated, or squamous type. **If the stromal component is of the pure endometrial stromal or fibrosarcomatous type (less commonly, leiomyosarcomatous), these tumors are termed *homologous. Heterologous* carcinosarcomas show stromal differentiation that is “foreign” to uterine tissues (e.g., rhabdomyosarcoma, chondrosarcoma, osteosarcoma, and liposarcoma, in decreasing order of frequency)** (Fig. 6.48). Homologous and heterologous carcinosarcomas have the same prognosis. When the epithelial component is of high-grade or of serous or clear cell type, the prognosis worsens; even tumors confined to a polyp may metastasize in up to 25% of cases (59). High surgical-pathologic stage at presentation, large tumor size, and cervical involvement also worsen the prognosis. Distant metastases may be of sarcomatous, carcinomatous, or mixed type, but initially are usually pure carcinoma.

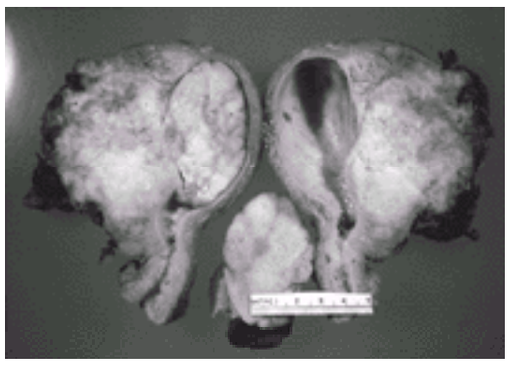


Figure 6.47 Carcinosarcoma. This hysterectomy specimen shows a large, partially necrotic polypoid mass filling the endometrial cavity

Figure 6.47 Carcinosarcoma. This hysterectomy specimen shows a large, partially necrotic polypoid mass filling the endometrial cavity and extensively invading the uterine wall.

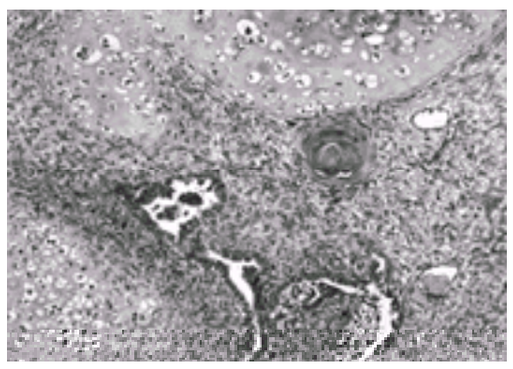


Figure 6.48 Carcinosarcoma. In this lesion, malignant glands lie within sarcomatous stroma, both of homologous and heterologous (malignant cartilage) types.

Smooth Muscle Tumors

Leiomyoma

Leiomyoma is a benign neoplasm of smooth muscle origin and represents the most common tumor of the uterus. These tumors usually present during reproductive years and in perimenopause; an association with low parity has been reported. Leiomyomas are usually multiple, round, sharply circumscribed tumors that can vary in size from several millimeters to 20 cm or more. Grossly, these tumors have a characteristic white, firm, whorled appearance, and often have yellow or gray soft areas corresponding to degeneration. Histologically, the tumors consist of interlacing bundles of bland smooth muscle fibers. Degenerative changes are common, and usually consist of hyalinization, infarction, or cystic change. These changes should not be confused with tumor cell necrosis, which is a feature of malignancy. Mitotic activity is usually low (less than five mitotic figures per ten high-power fields). *Mitotically active leiomyoma* is a cytologically benign tumor with higher-than-usual mitotic activity; these occur in premenopausal women (60). The diagnosis of mitotically active leiomyoma should not be made in a postmenopausal patient. *Cellular leiomyomas* are unusually cellular but have a low mitotic activity and no cytologic atypia. *Bizarre (atypical, symplastic) leiomyomas* contain occasional large cells with bizarre, sometimes multiple nuclei. The chromatin is often smudged. These tumors have fewer than five mitotic figures per ten high-power fields. Bizarre leiomyomas are similar to the mitotically active leiomyomas in that they occur predominantly in premenopausal women, and this diagnosis should be made with caution in a postmenopausal patient (61).

Leiomyosarcoma

Leiomyosarcoma constitutes 1.3% of uterine malignancies and is the most common uterine sarcoma. Most patients are older than 40 years of age, and the tumor is usually single and large. Less often, it may represent one of multiple fibroid nodules that grossly differs from the usual appearance of a leiomyoma (Table 6.8, Fig. 6.49).

	Leiomyoma	Leiomyosarcoma
Number	Usually multiple	More often single
Size	Variable	Large (usually >10 cm)
Cross appearance	Firm, white, whorled cut surface	Soft, fleshy, yellow, with hemorrhage or necrosis
Microscopic border	Circumscribed	Infiltrative
Nature of degenerative changes	Infarction, hyalinization	Tumor cell necrosis

Table 6.8 Pathologic Features of Benign and Malignant Smooth Muscle Tumors of the Uterus

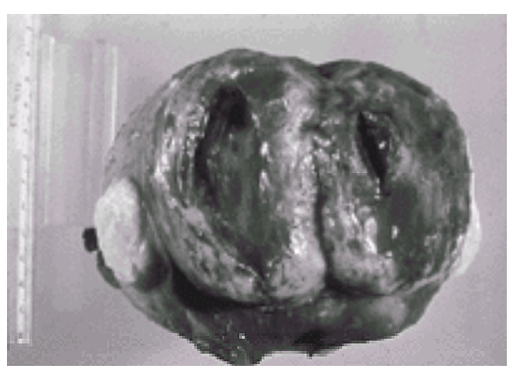


Figure 6.49 Leiomyoma and leiomyosarcoma. The small nodule on the left is well circumscribed, with the bulging, white, firm and whorled cut surface, typical of leiomyoma. The large, soft, hemorrhagic, and fleshy mass represents a leiomyosarcoma.

Microscopically, the tumors are evaluated for the presence or absence of tumor cell necrosis, which is the most important predictor of malignancy. Because benign leiomyomas often undergo infarction with hemorrhage and hyalinization, these latter features should be carefully differentiated from true coagulative tumor cell necrosis. Mitotic activity and cytologic atypia are other important features used in making the diagnosis (Table 6.9, Fig. 6.50).

Mitotic Count (per 10 HPF)	Cytologic Atypia	Cellularity	Tumor Cell Necrosis[a]	Patient Age	Diagnosis
<10	+	Low	-	N/A	Atypical (bizarre) leiomyoma
>10	+	High	Regardless	N/A	Leiomyosarcoma
Regardless	+	High	+	N/A	Leiomyosarcoma
>10 (usually <15)	-	Normal	-	Premenopausal	Mitotically active leiomyoma
>10	-	Regardless	-	Postmenopausal	STUMP[b]

HPF, high-power field; N/A, not applicable; STUMP, smooth muscle tumors of uncertain malignant potential.
[a]Tumor cell necrosis must be differentiated from infarction and hyalinization seen in leiomyoma.
[b]Other combinations of features also may result in a diagnosis of STUMP.

Table 6.9 Differential Microscopic Diagnosis in Smooth Muscle Tumors of the Uterus

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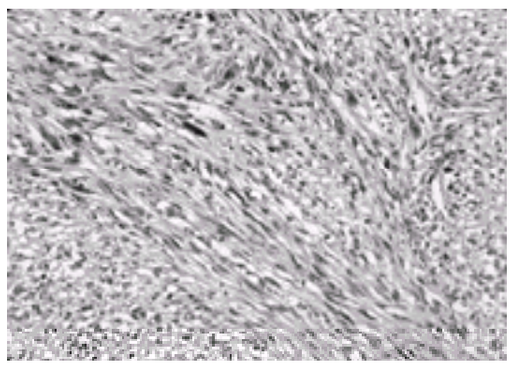

Figure 6.50 Uterine leiomyosarcoma. This is a pleomorphic, cellular, and mitotically active spindle cell tumor; elsewhere there was tumor cell necrosis.

Smooth Muscle Tumors of Uncertain Malignant Potential

Smooth muscle tumors of uncertain malignant potential are smooth muscle tumors that do not meet the necessary diagnostic criteria for leiomyosarcoma, but which exhibit some features that make prediction of behavior difficult. The algorithm for the differential diagnosis of uterine smooth muscle tumors (62) is shown in Table 6.9.

Other Smooth Muscle Tumors

Myxoid Smooth Muscle Tumors These tumors have to be approached with more caution because they may behave aggressively in the absence of high mitotic activity or necrosis. Myxoid leiomyosarcomas, however, are usually obviously invasive even at gross inspection.

Intravenous Leiomyomatosis This is a rare condition characterized by masses of smooth muscle growing in the lumens of veins and apparently arising from the vascular musculature. Grossly, the tumor has cord-like extensions into myometrial, pelvic, and broad ligament veins and may even extend into the inferior vena cava. Prognosis is excellent.

Benign Metastasizing Leiomyoma This is an extremely rare and difficult-to-prove occurrence, in which a benign-appearing smooth muscle tumor appears to have metastasized, usually to the lung, and often 15 to 20 years after the initial surgery. Most cases possibly represent multifocal benign smooth muscle proliferations or an undersampled uterine leiomyosarcoma.

Disseminated Peritoneal Leiomyomatosis This is a rare condition that must be distinguished from multiple metastases of uterine leiomyosarcoma. It occurs in women of reproductive age and is often associated with pregnancy or oral contraceptive use. It is characterized by multiple small (<1 cm) nodules of benign-appearing smooth muscle on pelvic and abdominal peritoneal surfaces.

Other Benign Tumors

Adenomatoid Tumor These benign tumors occur in women of reproductive age and are of mesothelial origin. They are usually found incidentally in uteri removed for other reasons. They are located in the subserosal myometrium and resemble vascular proliferations, but stain for epithelial mesothelial markers.

Ovary

Surface Epithelial Tumors

The ovarian serosa is the direct descendant of the celomic epithelium that, during embryogenesis, covers the nephrogenital ridge, from which the ovary arises. Celomic epithelium gives rise to the müllerian ducts, from which the endocervical epithelium, the endometrium, and the epithelium of the fallopian tube develop. The celomic epithelium also gives rise to wolffian ducts, from which parts of the urogenital system develop. Undifferentiated cells in the ovarian serosa can undergo neoplastic change and differentiate along various müllerian pathways. Differentiation of neoplastic cells along the tubal pathway produces the serous group of neoplasms; differentiation along the endocervical pathway results in mucinous neoplasms, and differentiation along the endometrial line results in endometrioid and probably clear cell tumors. Transitional cell tumors resemble urinary-type transitional epithelium and arise from the surface epithelium by wolffian, rather than müllerian, differentiation.

The surface epithelial tumors are thought to originate from surface epithelial inclusion cysts, which are ubiquitous invaginations and clefts in ovarian surface epithelium. All surface epithelial tumors are divided into benign tumors, tumors of low malignant potential (borderline), and carcinomas.

Serous Tumors

Serous tumors constitute approximately one third of all ovarian tumors; two thirds of serous tumors are benign.

Benign Serous Tumors

Benign serous tumors account for 25% of all benign ovarian tumors and over half of all serous tumors. They are most commonly seen in patients in their fourth and fifth decades and are bilateral in 15% to 20% of cases. The most common varieties of benign serous tumors are cysts *(serous cystadenoma)*, either unilocular or multilocular (Fig. 6.51). The cysts are lined by flattened or cuboidal epithelium, frequently with cilia (similar to the fallopian tube epithelium). Focal papillary projections may be seen grossly. Some tumors have a fibrous cut surface with thick papillae (serous adenofibroma); combined cystic and fibrous tumors are termed *cystadenofibromas.*

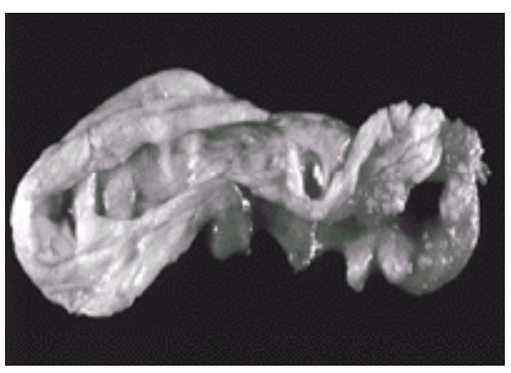

Figure 6.51 Serous cystadenoma of the ovary. This unilocular cyst has a smooth lining, microscopically resembling the fallopian tube epithelium.

Serous Tumors of Low Malignant Potential

These tumors constitute 10% of ovarian serous tumors. The mean patient age is slightly older than that of the patient with a benign serous tumor. These tumors are bilateral in 25% to 30% of cases. Grossly, tumors of low malignant potential or borderline tumors may be similar to benign serous tumors, or may have more abundant and finer papillary projections that sometimes involve the ovarian surface (Fig. 6.52). Solid areas are usually absent. Microscopically, the cysts and papillae are lined by stratified columnar epithelium of varying thickness with characteristic budding and tufting (Fig. 6.53). Stromal invasion is absent; this is the single feature distinguishing borderline tumors from carcinomas. Psammoma bodies are seen in up to 50% of cases.

Figure 6.52 Ovarian serous tumor of low malignant potential. Abundant papillary projections involve the ovarian surface in this case.

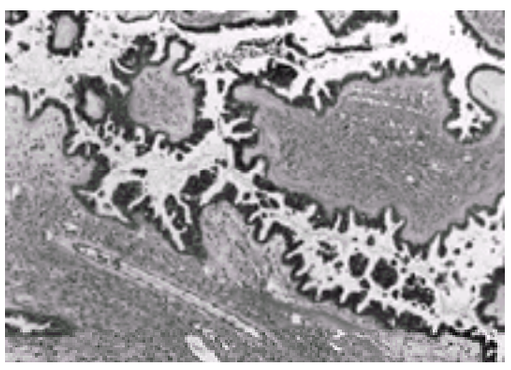

Figure 6.53 Ovarian serous tumor of low malignant potential. Papillae are lined by stratified epithelium with extensive tufting and budding. No stromal invasion seen.

Micropapillary and Cribriform Patterns A distinctive pattern in serous tumors of low malignant potential is a prominent micropapillary or cribriform pattern of growth. Such tumors have been shown to be associated with higher stage, bilaterality, and higher frequency of so-called invasive peritoneal implants (63). It appears that their poorer prognosis is related strictly to invasive extraovarian disease (64).

Microinvasion This is defined by the presence of a few single epithelial cells or papillary clusters in the tumor stroma. Usually these cells have more abundant eosinophilic cytoplasm and may exhibit more atypia. The presence of microinvasion does not adversely affect the prognosis (65,66).

Extraovarian (Peritoneal) Disease In up to 40% of cases, there is extraovarian peritoneal disease. The epithelial extraovarian lesions represent a spectrum of changes. The simplest ones are cystic lesions lined by tubal-type epithelium; these are termed *endosalpingiosis.* Similar lesions but with papillary projections, tufting, cellular stratification, and frequent psammoma bodies resemble the borderline tumor in the ovary. **Frequent coexistence of endosalpingiosis and low malignant potential (borderline) lesions throughout the peritoneum indicates that these lesions may not be genuine "implants" of ovarian tumor of low malignant potential, but arise *in situ*** (67). These lesions determine the outcome of the disease.

Serous peritoneal lesions of low malignant potential are sometimes divided into *nondesmoplastic* and *desmoplastic "implants."* Both of these lesions are superficial on the peritoneal surface and do not deeply involve the underlying tissue. Desmoplastic implants show bland papillary serous proliferation within desmoplastic and reactive stroma and are important to recognize because they present a difficult differential diagnostic problem, raising concern for *invasive carcinoma.* The latter diagnosis can be made if there is destructive stromal invasion into underlying tissue, often by malignant-appearing cells, singly and in clusters. This distinction, although at times difficult, is an extremely important one to make because the presence of invasive carcinoma outside the ovary that is involved by borderline serous tumor worsens the prognosis, whereas the presence of noninvasive implants (desmoplastic or nondesmoplastic) does not (68).

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Up to 10% of patients have lymph node involvement, but the clinical significance of this finding is uncertain (69).

Serous Carcinoma

Serous carcinoma accounts for 40% to 50% of ovarian malignant tumors. It is bilateral in 60% of cases and occurs most commonly in the fifth and sixth decades. Grossly, these tumors may be cystic, or mostly solid (Fig. 6.54). The external surface is smooth or covered with papillary fronds. Microscopically, serous carcinomas exhibit fine papillae (well differentiated carcinoma) that can become fused and form slit-like spaces. Poorly differentiated tumors are predominantly solid, with sheets of anaplastic cells. Grade 2 tumors show a mixture of solid and papillary areas. Nuclear atypia is usually pronounced, and prominent, brightly eosinophilic nucleoli are characteristic. Psammoma bodies are seen often, most commonly in grade 1 tumors.

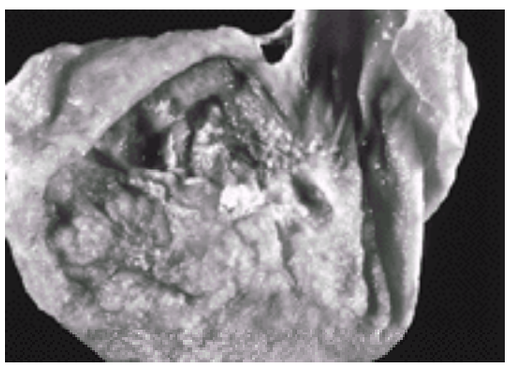

Figure 6.54 Serous carcinoma of the ovary. This partially cystic tumor exhibits papillary and solid areas.

Rare serous carcinomas are composed predominantly of psammoma bodies that constitute 75% or more of the tumor. These tumors are termed *psammocarcinomas* and have a good prognosis (70).

Mucinous Tumors

Mucinous tumors comprise 12% to 15% of all ovarian tumors; 75% of mucinous tumors are benign, 10% are borderline malignancy, and 15% invasive carcinoma. Mucinous neoplasms are the largest of all ovarian tumors, reaching 20 to 30 cm (Fig. 6.55). As with serous tumors, mucinous tumors occurring in young patients are usually benign or of low malignant potential, with the proportion of carcinomas rising with increasing age. Mucinous tumors are divided into two types: intestinal type (with goblet cells and, usually, neuroendocrine cells), and endocervical (müllerian) type, characterized by a mucinous lining resembling that of the endocervix.

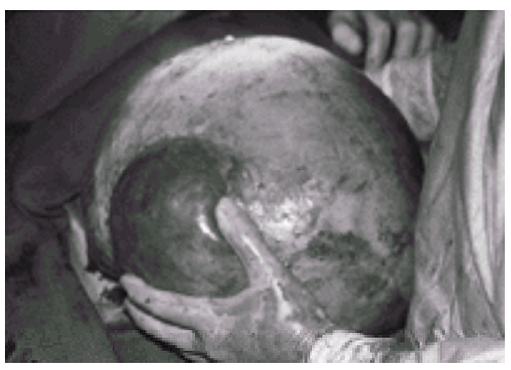

Figure 6.55 Mucinous intestinal tumor of low malignant potential. This unilateral cystic mass has attained a very large size.

Benign Mucinous Tumors

Benign mucinous tumors are most common in the third to fifth decades. Bilaterality is very rare (2% to 3%). Being notoriously large, they often present with acute torsion.

Grossly, benign mucinous tumors *(mucinous cystadenomas)* are multiloculated, cystic masses that contain thick mucinous material. Microscopically, the cysts are lined by a single layer of columnar cells with mucin-containing cytoplasm and small, basally located nuclei. Rarely, a mucinous cystadenoma can be accompanied by an incidental Brenner tumor in the wall of the cystic tumor.

Mucinous Tumors of Low Malignant Potential (Borderline)

Borderline mucinous tumors are characterized by papillary projections with cell stratification and mild to moderate nuclear atypia (Fig. 6.56). As in serous borderline tumors, destructive stromal invasion is absent; other criteria such as cell stratification more than four layers thick and significant cytologic atypia do not reliably predict aggressive behavior (71). Microinvasion (<5 mm focus of stromal invasion or of confluent glandular pattern) does not adversely affect the prognosis (72). Extensive histologic sampling is required to exclude invasive carcinoma because these tumors may be very heterogeneous. An intraoperative diagnosis of mucinous borderline tumor therefore never rules out the possibility of invasive carcinoma on permanent sections.

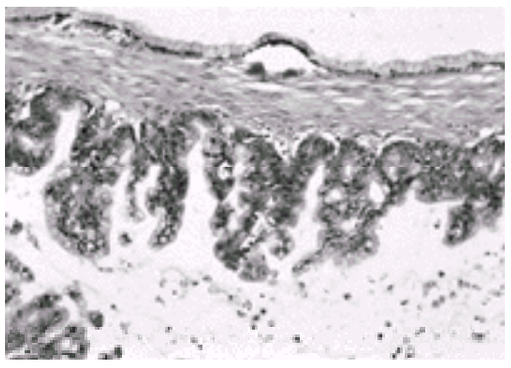

Figure 6.56 Mucinous tumor of low malignant potential, intestinal type. The mucinous tumor shows a benign component *(top)* with a single layer of goblet cells, and areas with borderline features *(bottom)* exhibiting papillary projections with stratification and atypia. No stromal invasion is seen.

Mucinous borderline tumors are subdivided into *intestinal* and *endocervical* types. These two types have several differences in presentation and clinical implications (71,73) (Table 6.10).

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	Mucinous Borderline Tumor of Endocervical Type	Mucinous Borderline Tumor of Intestinal Type
Average age (yr)	33	45
Bilateral (%)	15	7
Average size (cm)	8.5	18
Extraovarian involvement (%)	Discrete tumor implants, peritoneum and lymph nodes, 15	Pseudomyxoma peritonei, 8
Endometriosis (%)	23	2
Prognosis	Excellent, even when high stage or with microinvasion	Tumor-related death—0%; with pseudomyxoma peritonei, 30%; 5-yr survival

Table 6.10 Two Types of Mucinous Tumors of Low Malignant Potential (Borderline)

Pseudomyxoma Peritonei

This is a condition associated with mucinous intestinal tumors of the ovary and is characterized by masses of mucus in the pelvis and abdomen. Microscopic examination shows pools of mucin with variable numbers of free-floating strips of atypical mucinous epithelium (Fig. 6.57). The tumors most commonly associated with pseudomyxoma peritonei are mucinous tumors of low malignant potential, but malignant and benign mucinous tumors have also been reported (74). **When pseudomyxoma peritonei is associated with mucinous borderline tumors (intestinal type) of the ovary, and especially if ovarian tumors are bilateral, a similar tumor is likely to be found in the appendix. In these cases, the ovarian tumors may be metastatic from the appendix** (75,76). **Thus, an intraoperative diagnosis of a mucinous intestinal borderline tumor should always prompt an appendectomy.** When mucinous intestinal tumor of low malignant potential is associated with pseudomyxoma peritonei, the prognosis is guarded, with an approximately 50% 5-year survival rate (77).

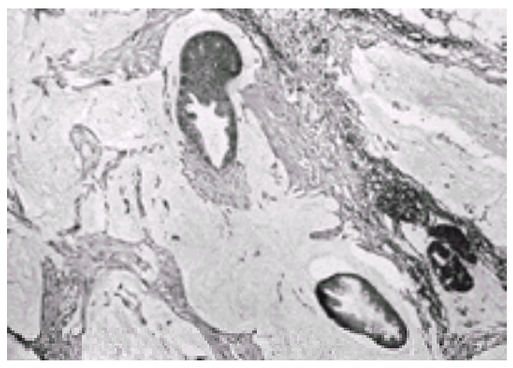

Figure 6.57 Pseudomyxoma peritonei. The tumor involving the pelvis shows pools of mucin with floating nests of stratified mucinous epithelium (mucinous borderline tumor, intestinal type).

Mucinous Carcinoma

Mucinous carcinomas occur at a slightly older age than borderline mucinous tumors (mean age, 53 to 54 years) and constitute 10% of all ovarian cancers. A small proportion of these tumors are bilateral (8% to 10%), but in these cases a metastasis from a gastrointestinal primary should be ruled out because such metastasis may closely mimic a primary mucinous tumor of the ovary.

Grossly, mucinous carcinoma may present as a focal solid area in an otherwise cystic benign or borderline mucinous tumor. At the time of diagnosis, most mucinous carcinomas are confined to the ovary. Mucinous carcinomas, unlike serous tumors, which have most morbidity and mortality associated with intraperitoneal disease, may present with late extraperitoneal metastases (lung).

Endometrioid Tumors

Of endometrioid tumors, benign tumors are the least frequent (<1% of all benign ovarian tumors); 2% to 3% of ovarian borderline tumors and 25% of carcinomas are endometrioid. All endometrioid tumors are more common in postmenopausal women. Endometriosis can be seen either in the same ovary or elsewhere. Although endometriosis is considered benign ectopic tissue, transition to endometriosis is seen in up to 10% of endometrioid carcinomas. Endometrial hyperplasia can be observed in endometriosis (78), as well as focal cytologic and architectural atypia, so-called *atypical endometriosis;* the premalignant potential of these lesions has been suggested (79).

Benign and Borderline Endometrioid Tumors

The rare benign tumors usually have a pattern of adenofibroma; in this tumor, benign glands are scattered in a fibrous background. Criteria for the diagnosis of borderline endometrioid tumors are not well established, but include more gland crowding and a greater degree of complexity than usually seen in an adenofibroma. Destructive stromal invasion with desmoplastic stromal reaction is diagnostic of malignancy; pronounced cribriform architecture is also an indication of stromal invasion.

Endometrioid Carcinoma

Most (80%) ovarian endometrioid tumors are malignant, and they represent the second most common ovarian carcinoma (25%). A third of these tumors are bilateral.

Grossly, endometrioid carcinomas are usually at least partially solid. Histologically, they are identical to endometrial endometrioid carcinomas. Endometriosis of the same ovary can be seen in up to 42% of cases, and pelvic endometriosis in up to 28% (80).

A concomitant endometrial carcinoma is present in up to 20% of cases; this occurrence presents a dilemma in determining whether these tumors are synchronous separate primaries or metastases from one organ to another. When the tumor is confined to both organs, the prognosis is very good (81), favoring the independent primary hypothesis. Criteria for this distinction are presented in Table 6.11.

	Ovarian Primary Favored	Endometrial Primary Favored	Independent Synchronous Primaries
Precursor lesion	Endometriosis of ovary present	Atypical endometrial hyperplasia present	Ovarian endometriosis and endometrial hyperplasia may be present
Size of tumors	Ovarian tumor larger	Endometrial tumor larger	—
Histologic features	Both tumors similar	Both tumors similar	Tumors dissimilar
Myometrial invasion	None or superficial	Deep	None or superficial
Myometrial lymphatic invasion	Absent	Present	Absent
Ovarian involvement	Single, unilateral ovarian tumor	Multiple, bilateral, superficial masses	Single, unilateral ovarian tumor
DNA ploidy, molecular studies	Similar findings	Similar findings	Dissimilar findings

From Scully RE, Young RH, Clement PB. Atlas of tumor pathology: tumors of the ovary, maldeveloped gonads, fallopian tube, and broad ligament. Third series. Washington, DC: American Registry of Pathology, 1996.

Table 6.11 Endometrioid Carcinoma with Ovarian and Uterine Involvement

Clear Cell Tumors

Benign and Low Malignant Potential Tumors

Benign clear cell tumors are very rare and usually take the form of adenofibroma, in which there are scattered glands lined by hobnail cells with clear cytoplasm. Clear cell tumors of low malignant potential exhibit more cytologic and architectural atypia, although precise criteria are not well established.

Clear Cell Carcinoma

These tumors comprise approximately 10% of all ovarian carcinomas and usually affect perimenopausal and postmenopausal patients. Disseminated disease is common. Clear cell carcinoma is the most common ovarian tumor to be associated with hypercalcemia and with endometriosis.

Grossly, these are solid or partially cystic tumors that are bilateral in up to 40% of cases. Histologically, clear cell carcinoma of the ovary is identical to that of the uterus; hobnail cells with glycogen-rich, clear cytoplasm and highly pleomorphic nuclei are characteristic.

Transitional Cell Tumors

Benign Transitional Cell (Brenner) Tumor

Brenner tumors are relatively rare, representing less than 2% of all ovarian tumors, and are most common in the fifth to sixth decades. Brenner tumor is usually an incidental finding and frequently accompanies a mucinous cystadenoma, and, less frequently, serous cystadenomas and dermoid cysts.

Grossly, these tumors are usually small, solid, and firm, with a gray-white, whorled cut surface. Microscopically, they are composed of nests of transitional (urothelial-like) epithelium scattered in dense fibrous stroma. The epithelial islands may be solid or partially cystic and may contain mucin-secreting cells.

Intermediate Transitional Cell Tumors

These tumors are subdivided into *proliferating Brenner tumors and Brenner tumors of low malignant potential* (82). Both subtypes are usually unilateral, multilocular cystic tumors exhibiting papillary projections into the cyst lumen. Histologically, both tumors show noninvasive papillary fronds lined by multilayered transitional epithelium of low-grade (proliferating Brenner tumor) or high-grade (Brenner tumor of low malignant potential) cytology. Both tumors are rare, and their prognosis is not entirely certain but appears to be excellent.

Malignant Transitional Cell Tumors

Malignant transitional cell tumors are divided into malignant Brenner tumors and transitional cell carcinomas. The mean age of the patients is 55 years. Grossly, both types are partially solid, partially cystic tumors with papillary areas. Histologically, both tumors show invasive transitional-type epithelium (transitional cell carcinoma).

Malignant Brenner Tumors These are defined by coexistence of a benign Brenner tumor component and a transitional cell carcinoma. These tumors have a good prognosis when confined to the ovary.

Transitional Cell Carcinoma If a benign Brenner tumor component is not identified, the tumor is classified as transitional cell carcinoma. Transitional cell carcinoma usually presents at an advanced stage and behaves more aggressively than a malignant Brenner tumor; however, these tumors (or mixed carcinomas comprising a 50% or more transitional cell component) appear to be more sensitive to chemotherapy than other ovarian carcinomas and may have a better prognosis (83). However, this has not been confirmed by other studies (84).

Mixed Carcinomas

Tumors exhibiting admixture of two or more distinct carcinoma patterns with at least 10% of each component qualify for inclusion in this category. The presence of a serous carcinoma as one of the patterns significantly worsens the prognosis (85).

Undifferentiated Carcinoma

According to the WHO classification, tumors with no or only minor areas of differentiation are included in this category. Up to 14% of ovarian carcinomas are undifferentiated. One fifth of the tumors are bilateral; most patients present with disseminated disease.

Sex Cord–Stromal Tumors

These neoplasms account for 8% of all primary ovarian tumors, and contain derivatives of the sex cords of embryonic gonad (*granulosa cells* and *Sertoli cells*) and of ovarian stroma (*theca, lutein*, and *Leydig cells*) (Table 6.12). Because the undifferentiated gonadal mesenchyme is able to produce structures of both male and female gonads, tumors recapitulating both cell types can arise in the ovary. Although most tumors in this category consist of cells of ovarian origin (*granulosa* and *stromal cell tumors*), rare tumors *(Sertoli cell tumors)* show testicular cell differentiation. Still less common tumors contain a mixture of ovarian and testicular type cells *(gynandroblastoma).*

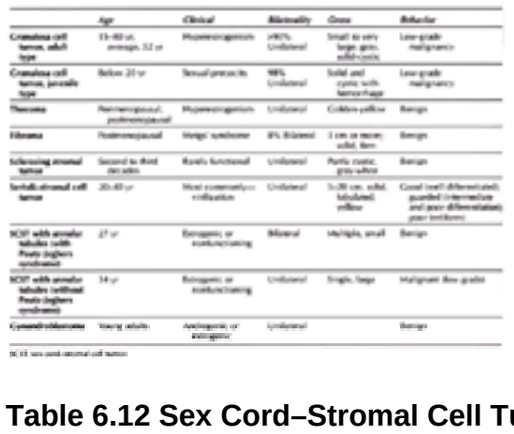

Table 6.12 Sex Cord–Stromal Cell Tumors

Granulosa Cell Tumors

Adult Granulosa Cell Tumors

These tumors constitute 1% to 2% of all ovarian neoplasms; they are the most common malignant tumors of the sex cord–stromal tumor category. These tumors occur in women from 15 to 80 years of age; the mean age is 52 years. Most patients present with postmenopausal bleeding; premenopausal patients may present with menstrual abnormalities. A common manifestation of adult granulosa cell tumor is hyperestrogenism: over a third of patients have endometrial hyperplasia, and 10% have endometrial carcinoma.

Grossly, these tumors are usually unilateral (>90%), solid and/or cystic, gray-yellow, and focally hemorrhagic. Size varies from microscopic to very large. Ninety percent of tumors are confined to the ovary at presentation.

Microscopically, adult granulosa cell tumors exhibit a variety of patterns, the most classic consisting of small cavities lined by granulosa cells and filled with fluid and degenerating desquamated cells. These structures are termed *Call-Exner bodies* and recapitulate a developing follicle; this pattern has been termed *microfollicular* (Fig. 6.58). Other patterns, which may be pure or coexist, are macrofolli cular, trabecular, insular, “watered silk,” and diffuse. The appearance of the nuclei is the best key for the diagnosis because they are very characteristic: uniform, pale, with longitudinal grooves (“coffee bean”). Cytologic atypia and mitotic figures are uncommon. Theca cells (lipid-rich luteinized cells in the tumor stroma) are responsible for estrogen production by the tumor; a tumor with a significant proportion of theca cells is sometimes termed *granulosa-theca cell tumor.*

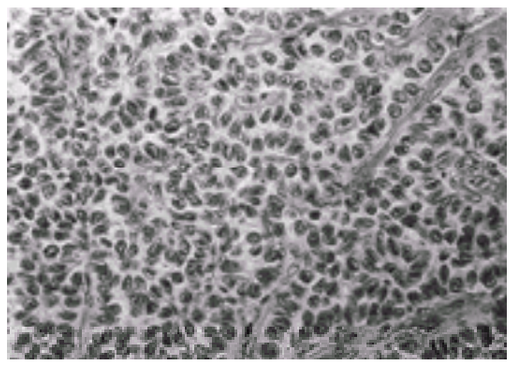

Figure 6.58 Granulosa cell tumor, adult type. This lesion is characterized by a microfollicular growth pattern with Call-Exner bodies; nuclei show the classical longitudinal groove (“coffee bean”).

These tumors usually behave as tumors of low malignant potential, with local and distant recurrences that may be seen many years after the initial surgery. Extension beyond the ovary at presentation portends a poor prognosis.

Juvenile Granulosa Cell Tumors

This tumor is seen predominantly in patients younger than 20 years of age. Most of these tumors result in sexual pseudoprecocity. Microscopically, they show a macrofollicular (cystic) pattern with cysts lined by pleomorphic, hyperchromatic, immature-appearing granulosa cells with frequent mitoses. Nuclear grooves are not seen. Despite more malignant cell features, this type of granulosa cell tumor behaves less aggressively than the adult type.

Thecoma

This benign unilateral tumor occurs after puberty but most commonly in perimenopausal and postmenopausal women and is known for estrogen production (approximately 15% of patients have endometrial hyperplasia and 25%, endometrial carcinoma).

These tumors have a characteristic gross appearance—the cut surface is golden-yellow. Rarely, a thecoma may become largely calcified; this is seen in young women. Histologically, thecomas consist of diffuse sheets of bland, lipid-rich cells reminiscent of theca interna cells separated by fibrous bands.

Fibroma

Fibromas constitute approximately 5% of ovarian tumors and occur most often in postmenopausal women. These unilateral solid tumors can be diagnosed only if they measure at least 3 cm (Fig. 6.59). This tumor is rarely associated with *Meigs' syndrome*, which consists of an ovarian fibroma, ascites, and pleural effusion. Rarely, fibromas are associated with Gorlin's syndrome *(basal nevus syndrome)*, in which keratocysts of the jaw and cutaneous basal cell carcinomas are seen.

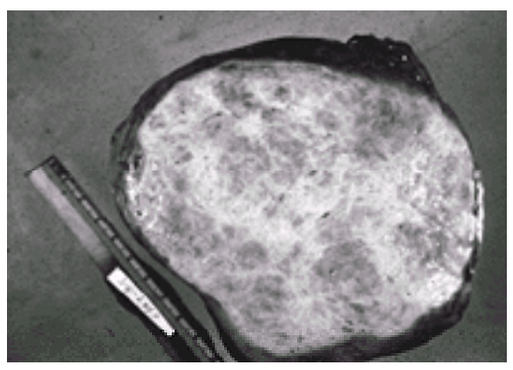

Figure 6.59 Ovarian fibroma. The ovary is enlarged, with a firm, white-gray cut surface.

Grossly, fibromas are solid and firm; microscopically, they are composed of bundles of bland spindle cells. Because tumor cells in fibromas may contain lipid, the distinction between fibroma and thecoma is often difficult, and a designation of *fibrothecoma* may be used for a tumor with mixed features.

Cellular Fibroma and Fibrosarcoma

These cellular tumors are both rare. The main distinguishing feature is said to be mitotic activity (fewer than three mitoses per ten high-power fields in cellular fibroma, four or more in fibrosarcoma).

Sclerosing Stromal Tumor

Unlike fibromas and thecomas, these unilateral benign tumors occur in women in their second and third decades. Grossly, these tumors are partly cystic, and gray-white with yellow flecks. Microscopically, they show a lobulated pattern with varying cellularity.

Sertoli-Stromal Cell Tumors

These rare tumors occur in women between 20 and 40 years of age. Well differentiated tumors occur in slightly older patients than intermediate and poorly differentiated tumors. They recapitulate testicular structures at different stages of development. These neoplasms have been known for their virilizing properties, but some tumors have no endocrine function and still others present with symptoms of estrogen production (86). Sertoli–stromal tumors are almost always unilateral.

Well differentiated Sertoli-Leydig cell tumors are composed of hollow tubules lined by mature Sertoli cells and recapitulating mature seminiferous tubules of the testis; large, eosinophilic, lipid-containing Leydig cells are seen in the stroma. These tumors do not recur or metastasize.

Sertoli-Leydig cell tumors of intermediate differentiation are the most common and differ from the well differentiated type by the Sertoli cell component, which consists of poorly formed masses and cords of more pleomorphic cells resembling sex cord in the testes of embryos (Fig. 6.60). Leydig cells are easily seen in the stroma.

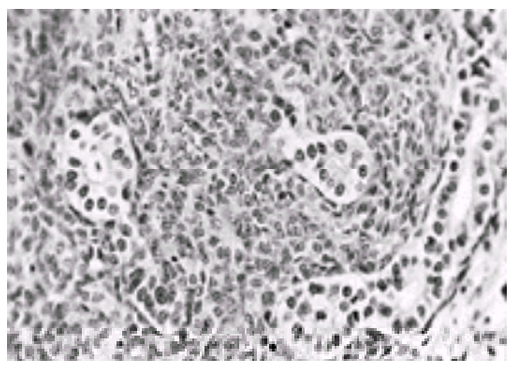

Figure 6.60 Sertoli-Leydig cell tumor of intermediate differentiation. Hollow tubules lined by Sertoli cells lie in a densely cellular stroma.

Poorly differentiated (sarcomatoid) Sertoli-Leydig cell tumors represent a diffuse, sarcoma-like growth of pleomorphic spindle cells with abundant mitoses. These cells focally aggregate into cords or trabeculae.

Retiform Sertoli-Leydig cell tumors constitute approximately 15% of all SertoliLeydig cell tumors and are usually seen in teenagers (87). The tumors are composed of tubular and papillary structures resembling rete testis. These tumors are considered of intermediate or poor differentiation and have a poor prognosis; virilization is less common in this subtype.

All Sertoli-Leydig cell tumors can exhibit a variety of heterologous elements, including mucinous epithelium, cartilage, and skeletal muscle. The nonepithelial heterologous elements appear to affect the prognosis adversely. Intermediate and poorly differentiated tumors are usually cured by surgery; if they recur, they do so within the first few years. Prognostically unfavorable findings are tumor rupture, extraovarian spread at diagnosis, retiform pattern, and heterologous mesenchymal differentiation.

Sex Cord Tumor with Annular Tubules

These tumors may be functional (estrogenic) or nonfunctional. They are usually unilateral, and their behavior may be malignant. A third of these tumors arise in patients with *Peutz-Jeghers syndrome.* In patients with this syndrome, the ovarian tumors are usually bilateral, small, multifocal, and show calcifications. When associated with Peutz-Jeghers syndrome, these tumors behave in a uniformly benign fashion, and in some cases are associated with minimal deviation adenocarcinoma of the cervix. Up to 15% of tumors not associated with Peutz-Jeghers syndrome behave in a malignant fashion; these are usually solitary and large (88). Microscopically, the tumor shows round tubules that contain dense hyaline material.

Gynandroblastoma

This is an extremely rare tumor composed of a mixture of ovarian and testicular-type cells (well differentiated Sertoli-Leydig cell tumor and granulosa cell tumor).

Unclassified Sex Cord–Stromal Tumors

These tumors comprise 10% of sex cord–stromal tumors and 17% of sex cord–stromal tumors during pregnancy. There is no clearly identifiable ovarian or testicular differentiation.

Steroid (Lipid) Cell Tumors

These tumors consist of luteinized cells resembling Leydig or adrenal cortical cells. These cells may produce estrogen, progesterone, androgen, adrenal cortical hormones, or adrenocorticotropic hormone.

Stromal Luteomas

These benign tumors are commonly associated with stromal hyperthecosis and occur in postmenopausal women. Production of estrogen is common, but virilization may rarely occur. They are unilateral, yellow-brown, and small (<3 cm). Microscopically, the tumor is composed of luteinized cells with lipofuscin pigment.

Leydig Cell Tumors

Most of these tumors arise in the ovarian hilum. Leydig cell tumors are also unilateral and occur in postmenopausal women. Virilization is common. Histologically, these tumors are similar to stromal luteomas, but the diagnostic feature is the presence of intracytoplasmic *crystals of Reinke.*

Steroid Cell Tumors, Not Otherwise Specified

Steroid cell tumors, not otherwise specified comprise most steroid cell tumors (Fig. 6.61). They may occur at any age and usually present with virilization. Crystals of Reinke are not seen in these tumors. Large size (>7 cm), high mitotic activity, necrosis, hemorrhage, and cytologic atypia predict an aggressive behavior (89).

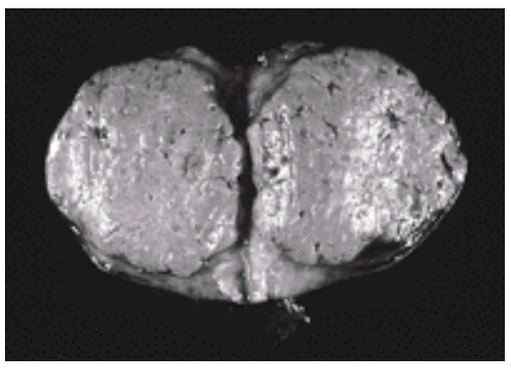

Figure 6.61 Steroid cell tumor, not otherwise specified. This tumor is a solid, golden-yellow mass.

Germ Cell Tumors

Germ cell tumors are thought to derive from primitive germ cells. These tumors often show a mixture of different cell types, and thus thorough sampling is needed for accurate assessment of the prognosis. Up to 60% of ovarian tumors occurring in the first two decades of life are germ cell tumors; of these, one third are malignant.

Dysgerminoma

This ovarian counterpart of testicular seminoma is the most common malignant ovarian germ cell tumor and comprises 1% to 2% of all ovarian tumors. It is most common in the second and third decades, but can occur up to middle age. It is bilateral in 10% of cases.

Grossly, a dysgerminoma is solid, well circumscribed, and gray, tan, or yellow (Fig. 6.62). Microscopically, the tumor consists of uniform round cells with distinct cell borders and clear cytoplasm. The nucleus typically shows one or two central eosinophilic nucleoli. A sprinkling of mature T lymphocytes is common, and a granulomatous reaction may be seen. Scattered single giant (syncytiotrophoblastic) cells may be seen; these cells stain positively with human chorionic gonadotropin (hCG) immunostain. The presence of these cells does not adversely affect the prognosis. Histologic appearance does not predict the behavior of this tumor. Recurrence is more common in young patients (<20 years), in large tumors (>15 cm), in tumors that rupture during surgery, and in tumors with minimal lymphocytic infiltrate.

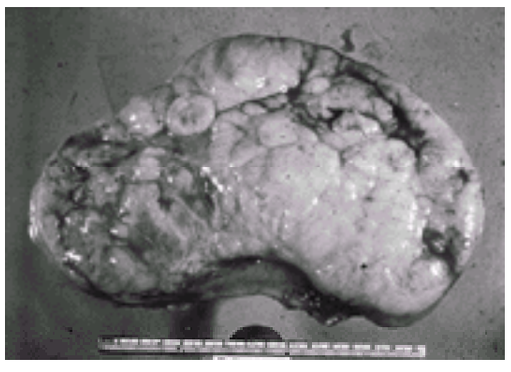

Figure 6.62 Dysgerminoma. This solid tumor has a gray, fleshy, and lobulated cut surface.

Yolk Sac Tumor (Endodermal Sinus Tumor)

Yolk sac tumors comprise approximately 20% of malignant germ cell tumors; they are common in the first two decades of life. Schiller called this tumor *endodermal sinus tumor* because of its resemblance to yolk sac–derived endodermal sinuses of rodents. Grossly, these are large, always unilateral, solid and cystic, white-gray tumors. A dermoid cyst is seen in the same ovary in 15% and in the contralateral ovary in 5% of cases.

Microscopically, many patterns are described. The most common is the reticular (microcystic) pattern in which thin septa are lined by atypical cells with hyperchromatic nuclei. *Schiller-Duval bodies* are identified in typical cases and represent a small cystic space with a central glomerulus-like projection with a fibrovascular core (Fig. 6.63). Intracytoplasmic hyaline globules that stain positively with a-fetoprotein immunostain are commonly seen.

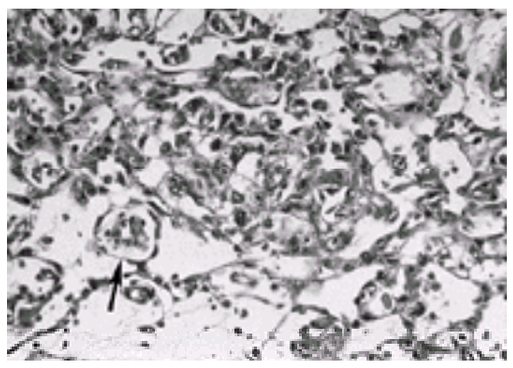

Figure 6.63 Yolk sac tumor. Microcystic spaces are lined by highly pleomorphic cells. A Schiller-Duval body (glomeruloid structure) is seen on the left *(arrow)*.

Embryonal Carcinoma

These tumors are vanishingly rare in the ovary but may be encountered in mixed malignant germ cell tumors. Microscopically, the tumor is characterized by masses of immature cells with overlapping pleomorphic nuclei and high mitotic activity. Multinucleated syncytiotrophoblastic giant cells are common and stain positively for hCG, but should not be interpreted as choriocarcinoma. a-Fetoprotein immunostain may also be positive.

Choriocarcinoma

These tumors are extremely rare in their pure form, and most are likely of gestational rather than germ cell origin (90). Most tumors occur in children and young women. hCG secretion is responsible for the clinical presentation. Both syncytiotrophoblast and cytotrophoblast must be present for the diagnosis. The presence of focal choriocarcinoma in a mixed germ cell neoplasm significantly worsens the prognosis.

Teratoma

Mature Teratoma

Mature teratoma is the most common germ cell tumor (and the most common tumor) of the ovary, comprising over 20% of all ovarian neoplasms and occurring at any age, with a peak incidence in the first two decades of life. These tumors are also known as dermoid cysts. As this name implies, they are commonly cystic. Bilaterality is not uncommon (20%), and large size is characteristic. Grossly, the cysts contain sebaceous/fatty material and hair. The cyst usually shows a solid protuberance containing bone, teeth, and cartilage (Fig. 6.64).

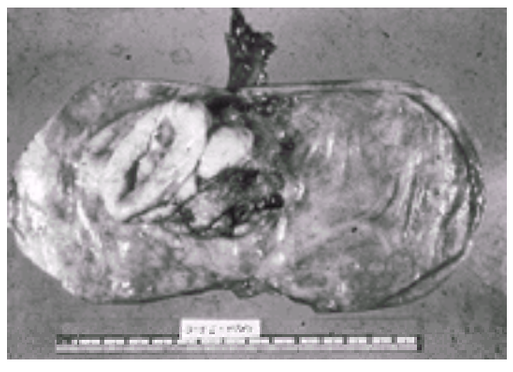

Figure 6.64 Mature teratoma. This cystic neoplasm contains hair and sebaceous material. The solid white area represents mature cartilage.

Microscopically, a mature teratoma may consist of representative structures of all three germ layers, with mostly ectodermal elements. Ectoderm is represented most commonly by skin with sebaceous and sweat glands, and hair follicles. Bronchial and intestinal tissue represent the most common endodermal elements; muscle, bone, and cartilage represent the mesoderm. Mature brain tissue is often seen.

Struma Ovarii This is a mature teratoma in which thyroid tissue is the dominant component of the tumor. Rarely, papillary thyroid carcinoma may arise in struma ovarii.

A malignant tumor developing from one of the components of a mature teratoma is a rare occurrence (2%). The most common type of malignancy is a squamous cell carcinoma. Melanomas, sarcomas, and other tumors have been reported.

Carcinoid Tumors These tumors may arise in mature teratomas and appear as a yellow nodule in a wall of an otherwise ordinary cystic teratoma. One third of the patients present with carcinoid syndrome. Microscopically, the tumor cells are arranged in nests (insular pattern) and ribbons; the nuclei are bland, without prominent nucleoli. The immunostains for neuroendocrine markers (chromogranin, synaptophysin) are positive. *Strumal carcinoid* is a tumor showing an admixture of thyroid tissue and carcinoid tumor.

Immature Teratoma

This tumor is rare, comprising only approximately 3% of all ovarian teratomas. Most of the patients are young. Grossly, an immature teratoma is a large, unilateral, predominantly solid and focally cystic tumor.

An immature teratoma must contain immature (embryonal) tissues in addition to mature tissue such as that seen in a mature teratoma. These immature elements are usually composed of immature neuroepithelial solid nests and tubules, which may constitute only a minute part of the tumor; thus, thorough sampling is required for accurate grading. The currently used grading system (91) defines *grade 1 tumors* as having immature elements limited to no more than one low-power field in any one slide. In *grade 2 tumors*, the areas occupied by immature elements should not exceed three low-power fields, and *grade 3 tumors* show immature elements in more than three low-power fields. Grade 2 and 3 tumors are regarded as high-grade immature teratomas, and usually are treated with chemotherapy. Because extraovarian tumor implants may be either completely mature (and behave accordingly) or have varying amounts of immature elements, separate grading is performed on all implants.

Gonadoblastoma

Gonadoblastoma is a rare lesion found in patients with abnormal gonadal development; most of these patients have a Y chromosome. The uterus is hypoplastic in most cases. The tumor may be found microscopically within a streak gonad, or form a large solid tumor mass. Microscopically, it consists of aggregates of germ cells admixed with sex cord elements resembling immature Sertoli and granulosa cells. Hyaline eosinophilic bodies are seen in the centers of sex cord–like cells; this material may become calcified. Sometimes the entire tumor is extensively calcified. The tumor is benign unless a dysgerminoma or other malignant germ cell tumor develops in it.

Other Tumors

Small Cell Carcinoma with Hypercalcemia

This highly malignant tumor occurs in young women (average age, 24 years) and is accompanied by elevated serum calcium levels in two thirds of cases. Grossly, the tumors are unilateral, large, and solid, with necrosis and hemorrhage. Diffuse growth of immature small cells with high mitotic activity is seen microscopically (Fig. 6.65); formation of follicle-like microcysts is common. The cellular origin of this neoplasm is still unclear (92). The prognosis is ominous, and no therapeutic regimen has proven effective.

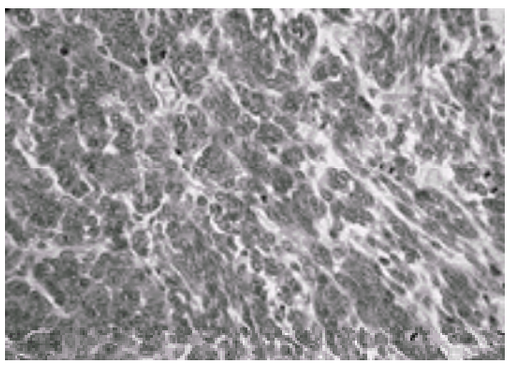

Figure 6.65 Small cell carcinoma with hypercalcemia. This lesion shows sheets of immature small cells with high mitotic rate.

Tumors Metastatic to the Ovary

The ovary is a frequent site of metastases from other organs; metastatic tumors comprise 5% of all ovarian malignancies. The most common sites of origin are endometrium, gastrointestinal tract, and breast. Most ovarian metastases are bilateral.

Gastrointestinal Tract Primary

Krukenberg Tumor This is a term reserved for signet ring cell carcinoma diffusely infiltrating the ovarian stroma (Fig. 6.66). Most of these tumors arise in the stomach, and, much more rarely, from elsewhere in the gastrointestinal tract, or other organs. This tumor causes diffuse bilateral ovarian enlargement with retention of normal ovarian contours.

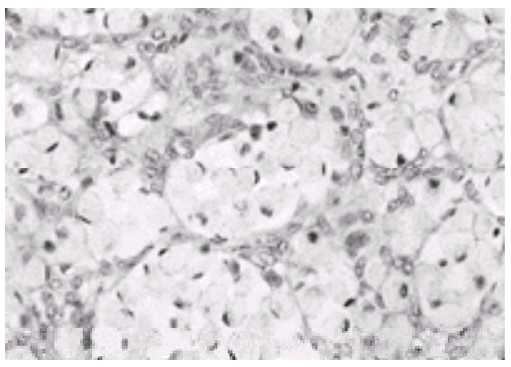

Figure 6.66 Krukenberg tumor. This metastatic gastric carcinoma shows diffuse infiltration of the ovarian stroma by signet ring cells. Both ovaries were diffusely enlarged.

Metastases from colonic adenocarcinoma are the most common tumors to mimic closely a primary ovarian carcinoma. Grossly, they are indistinguishable from primary ovarian carcinoma; microscopically, they most commonly mimic ovarian endometrioid carcinoma (93).

Other metastatic mucinous tumors from the gastrointestinal tract, such as pancreatic adenocarcinoma, often mimic a primary mucinous tumor of the ovary. The metastases commonly show a mixture of areas resembling a mucinous cystadenoma, borderline mucinous tumor, and well differentiated mucinous carcinoma. Most of these metastases are bilateral, compared with only 10% of primary mucinous ovarian tumors (94).

Gynecologic Tumors

Cervical carcinomas rarely involve the ovaries; of these, adenocarcinoma is more common. It may be difficult to determine the primary if cervical and ovarian mucinous adenocarcinomas coexist. If the ovary contains a squamous cell carcinoma, and an origin from a mature teratoma is excluded, a search for cervical or other potential sources must be undertaken. Fallopian tube tumors involve the ovary by direct extension or surface implantation.

Other Tumors

Ovarian metastases in patients with breast cancer are quite common, with an incidence ranging from 6% to 40% of cases in autopsy series. In most cases, the ovarian involvement is bilateral, and the ovaries are diffusely enlarged without a visible, discrete tumor mass. *Renal cell carcinoma* metastatic to the ovary may lead to an erroneous diagnosis of a primary ovarian clear cell carcinoma. *Lymphomas* of the ovary are most often metastatic and bilateral. Burkitt's lymphoma is known commonly to involve the ovaries.

Tumor-Like Lesions

Follicular cyst is lined by granulosa and theca cells and results from anovulation. These cysts are thus more common in menarchal and perimenopausal patients. Follicle cysts may cause pain or may even rupture; they may also cause symptoms secondary to autonomous estrogen production by the cyst lining. Grossly, follicle cysts are unilocular, have a smooth lining, and rarely exceed 8 cm in diameter.

Corpus luteum cyst is a cystic corpus luteum that measures more than 3 cm. The cyst is filled with blood and the lining is bright yellow. Microscopically, the cyst wall is lined by a thick layer of large, luteinized granulosa cells, beneath which the theca cells are located. These often bleed and are operated on as surgical emergencies.

Polycystic ovarian disease causes bilateral ovarian enlargement. The etiology is anovulation resulting in the formation of multiple follicle cysts. Grossly, the ovaries are rounded, with multiple small cysts beneath a thickened fibrotic cortex (Fig. 6.67).

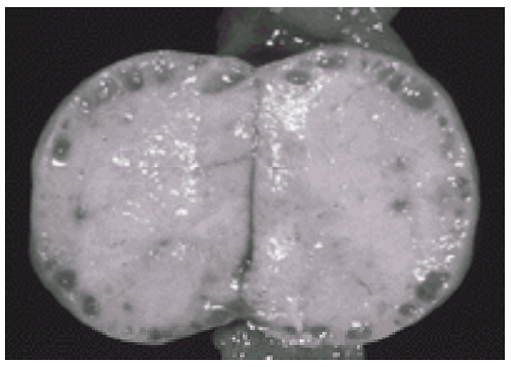

Figure 6.67 Polycystic ovarian disease. Both ovaries are enlarged and contain multiple subcortical follicle cysts.

Stromal hyperthecosis is a diffuse bilateral process in which the ovarian stroma is hyperplastic, with luteinized cells scattered throughout. Postmenopausal women with this disorder may present with hyperestrogenism, and premenopausal women with virilization. Grossly, both ovaries are enlarged; the cut surface is white or yellow.

Stromal hyperplasia is a proliferative process involving just the ovarian stroma, without the associated scatter of luteinized cells. This condition usually affects perimenopausal and postmenopausal patients. Grossly, there are multiple white to yellow nodules that may become confluent; microscopically, the nodules consist of ovarian stromal cells.

Massive ovarian edema produces tumor-like enlargement of one or, rarely, both ovaries. The patients are young (6 to 33 years) and may present with acute abdominal pain. The cut surface of the ovary is opaque and gelatinous, with edematous, hypocellular stroma.

Endometriosis of the ovary may result in the formation of endometriotic cysts (endometriomas) that have a fibrotic wall with irregular, brown lining and contain thick brown (chocolate-colored) material. Nodules in the wall of an endometriotic cyst should be carefully sampled because they can harbor a malignant tumor. Microscopically, endometrial-type epithelium lines the cyst; underlying the epithelium there is endometrial stroma; fresh and/or old hemorrhage is a constant finding.

Pregnancy-Associated Conditions

Pregnancy Luteoma This represents single or multiple, red-brown nodules of luteinized cells producing ovarian enlargement during pregnancy or postpartum. This enlargement is usually an incidental finding during cesarean section. The condition may be bilateral and may cause virilization in the mother as well as in female infants.

Hyperreactio Luteinalis This is bilateral ovarian enlargement seen during pregnancy or in patients undergoing ovulation induction. Patients with high levels of hCG (hydatidiform mole, choriocarcinoma, multiple gestation) have an increased incidence of this condition. Grossly, both ovaries are massively enlarged, with multiple, tense, thin-walled cysts lined by theca interna cells (Fig. 6.68).

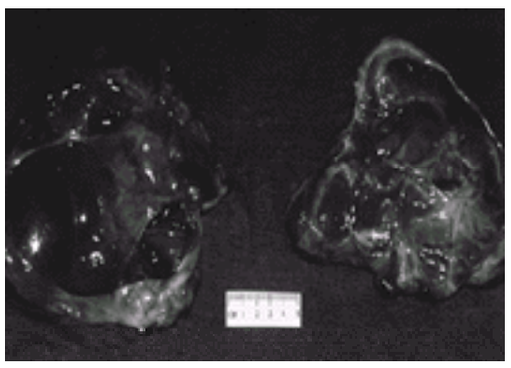

Figure 6.68 Hyperreactio luteinalis. Both ovaries are enlarged and contain multiple, tense, thin-walled cysts.

Solitary Luteinized Follicle Cyst of Pregnancy and the Puerperium This represents a large unilateral cyst lined by luteinized cells with bizarre nuclei.

Fallopian Tube

The normal fallopian tube serves to ensure transport of the ova and spermatozoa and is where fertilization occurs. Thus, any pathologic process in the fallopian tube may result in infertility. Only a few primary neoplasms arise in the fallopian tube; secondary tumors are much more common.

Benign Tumors

Adenomatoid Tumor This is the most common benign tumor of the fallopian tube. These tumors are usually small (<1 cm) and are located just beneath the serosal surface. The cut surface is white-gray; the tumor may grow from the serosa toward the tubal lumen, sometimes resulting in obstruction. Histologically, the tumor cells form clefts or gland-like spaces. An immunohistochemical profile of these cells proves the mesothelial origin of the tumor.

Malignant Tumors

Carcinoma *In Situ* This exceedingly rare diagnosis is reserved for flat mucosal lesions of the fallopian tube that are not apparent on gross examination. Microscopically, the tubal epithelium is focally replaced by overtly malignant cells. This diagnosis should be made with caution because reactive changes of tubal epithelium, usually secondary to salpingitis, may show striking stratification, atypia, and even mitotic figures.

Primary Tubal Adenocarcinoma

This is one of the rarest malignant tumors of the female genital tract. Only tumors that exclusively or predominantly involve the fallopian tubes are classified as primary tubal carcinomas. Ideally, a transition from *in situ*/dysplastic tubal mucosa to adenocarcinoma should be seen.

Grossly, these tumors may be bilateral in 3% of cases (95), and produce a fusiform swelling of the fallopian tube that may simulate hydrosalpinx. A papillary, friable tumor is discovered on opening. Primary tubal adenocarcinoma involves the ampullary portion of the fallopian tube twice as often as the isthmic portion. Microscopically, most tumors are of the serous papillary type, with rare endometrioid, transitional cell, and clear cell carcinomas reported.

Other Malignant Tumors

Other primary malignant tumors of the fallopian tube are vanishingly rare and include carcinosarcoma and leiomyosarcoma.

Metastatic carcinoma involving the fallopian tube is much more common than primary carcinoma, and usually originates from endometrium or ovaries. Lymphatic spread is seen more often than direct extension.

Gestational Trophoblastic Disease

Gestational trophoblastic disease is a heterogeneous group of lesions, some of which are true neoplasms, whereas others represent an abnormality in placental development. In normal pregnancy, the trophoblast is transformed from the covering of the blastocyst to placental tissue. During this process, trophoblast invades the uterine tissues and enters the maternal circulation.

Trophoblast is classified morphologically into three types: cytotrophoblast, intermediate trophoblast, and syncytiotrophoblast. *Cytotrophoblast* consists of small, primitive cells with a single nucleus and high mitotic rate. *Syncytiotrophoblast* represents very large, multinucleated cells with abundant, deeply eosinophilic cytoplasm; these cells are found on the surface of the chorionic villi; before the formation of chorionic villi, syncytiotrophoblast has the ability to invade vessels. *Intermediate trophoblast* has characteristics intermediate between the two other types of trophoblast; these cells infiltrate the myometrium and have the ability to invade vessels. Immunohistochemical stains can be used to differentiate between the three types of trophoblast: all three types of trophoblast stain with keratin; syncytiotrophoblast also stains with hCG and, increasingly throughout gestation, with human placental lactogen (hPL); intermediate trophoblast stains strongly with hPL and weakly with hCG, and cytotrophoblast reacts with neither hCG nor hPL.

Hydatidiform Mole

Hydatidiform mole is noninvasive abnormal placental tissue characterized by edematous chorionic villi and trophoblast proliferation. Hydatidiform moles are subdivided into complete and partial hydatidiform moles. Complete hydatidiform mole is the most common precursor of choriocarcinoma; this event is almost never seen in partial hydatidiform mole (96). DNA ploidy is a helpful adjunct modality for differential diagnosis of difficult cases of molar pregnancy and can be performed either on fresh or archival (formalin-fixed, paraffin-embedded) tissue (97). Fluorescent *in situ* hybridization is another technique that has the advantage of examining the DNA content in tissue sections (98).

Complete Hydatidiform Mole

Complete hydatidiform mole is the most common form of gestational trophoblastic disease. It is characterized by a diploid karyotype (46XX or 46XY) that results from a single sperm fertilizing an empty ovum; thus, complete mole is of paternal origin only. In complete hydatidiform mole, all or most chorionic villi are markedly edematous, resulting in a classic gross picture of voluminous tissue with transparent, grape-like vesicles (Fig. 6.69). Villous swelling results in formation of so-called cisterns, or acellular, fluid-filled spaces seen microscopically within the chorionic villi. Trophoblastic hyperplasia is usually pronounced and completely encircles the surface of the villi (Fig. 6.70).

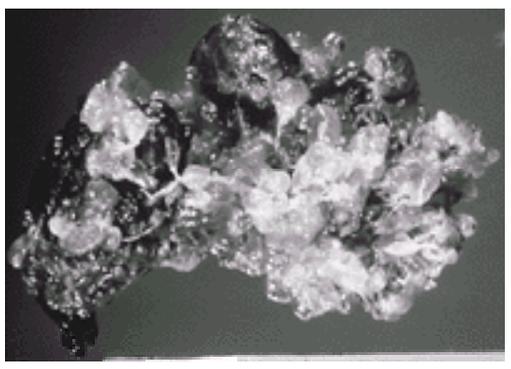

Figure 6.69 Complete hydatidiform mole. This lesion comprises placental tissue with multiple, grape-like, thin-walled vesicles. No embryo is present. (Figure courtesy of C. C. Sun, MD, University of Maryland Medical Center, Baltimore, Maryland.)

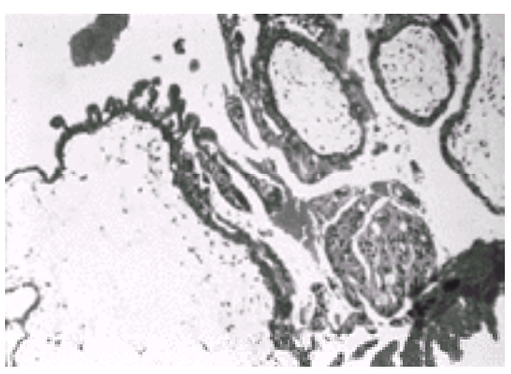

Figure 6.70 Complete hydatidiform mole. This lesion is characterized by markedly swollen chorionic villi with cistern formation and prominent circumferential trophoblast hyperplasia. (Figure courtesy of C. C. Sun, MD, University of Maryland Medical Center, Baltimore, Maryland.)

Partial Hydatidiform Mole

Partial hydatidiform mole has a triploid karyotype (69XXX, 69XXY, or 69XYY), resulting from a normal egg having been fertilized by two sperm. Partial hydatidiform mole consists of two populations of chorionic villi (one edematous and the other of normal morphology); this admixture may be evident grossly. A fetus is nearly always present but may be difficult to detect because of its early demise. Trophoblastic hyperplasia is less marked and more focal than in complete moles (Table 6.13).

	Complete Mole	Partial Mole
Clinical	Spontaneous abortion	Missed or spontaneous abortion
Karyotype	Diploid	Triploid
Villous edema and trophoblastic proliferation	Diffuse	Focal
Fetus	Absent	Present
Risk of persistent gestational trophoblastic disease	18%	5%
Risk of choriocarcinoma	2%–4%	Virtually none

Table 6.13 Features of Complete and Partial Hydatidiform Moles

Invasive Hydatidiform Mole

Invasive mole is the most common form of persistent gestational trophoblastic disease after hydatidiform mole. In this condition, the hydropic chorionic villi invade the myometrium and its blood vessels and, rarely, metastasize. The diagnosis of invasive mole can be made only on demonstration of molar villi in direct contact with myometrium; thus, this diagnosis cannot be made on an endometrial curettage specimen unless it contains fragments of invaded myometrium. Extrauterine spread is seen in 20% to 40% of cases and usually occurs in the lung, vagina, and vulva. Because without pathologic examination the distinction between an invasive mole and choriocarcinoma cannot be made, the term *persistent gestational trophoblastic disease* is used. Of the 20% of patients with persistent gestational trophoblastic disease after a complete molar pregnancy, only 3% to 4% have choriocarcinoma (99).

Choriocarcinoma

Choriocarcinoma is a highly malignant tumor arising from any gestation, but most often from a hydatidiform mole. It consists of a biphasic proliferation of cytotrophoblast and syncytiotrophoblast; no chorionic villi are seen in this tumor (Fig. 6.71). Hemorrhage and extensive necrosis are the rule, so that very little viable tumor may be left to examine; thus, extensive histologic sampling is required to make the diagnosis (Fig. 6.72). The lungs are the most common site of distant metastases (>90% of patients with metastatic disease), but brain and liver may also be involved. Vaginal involvement is reported in up to 30% of patients.

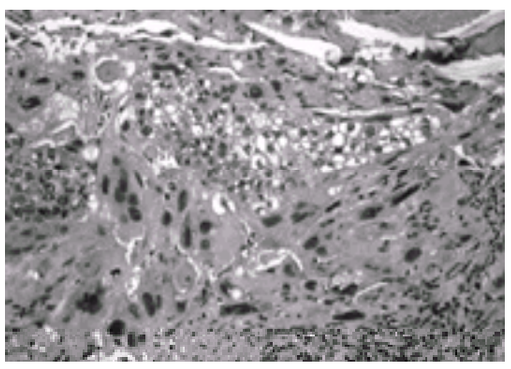

Figure 6.71 Choriocarcinoma. Large bizarre cells that represent syncytiotrophoblast are admixed with smaller uniform cells (cytotrophoblast).

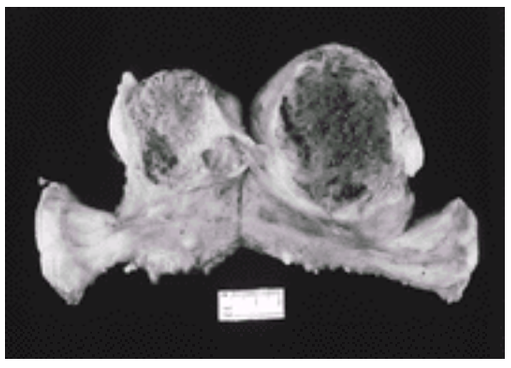

Figure 6.72 Choriocarcinoma. A hysterectomy specimen (rarely seen today) with hemorrhagic and necrotic tumor within the uterine wall.

Placental Site Trophoblastic Tumor

Placental site trophoblastic tumor is the least common form of gestational trophoblastic disease. It deeply invades the myometrium and consists of only one type of trophoblast—intermediate trophoblast (Table 6.14, Fig. 6.73). The tumor recapitulates myometrial invasion by the nonneoplastic trophoblast in the implantation site; it may produce diffuse uterine enlargement or be well circumscribed. When there is transmural invasion of the uterine wall, perforation may result; this complication may also result from endometrial curettage. The behavior of this tumor is unpredictable; although most tumors are cured by curettage, some behave in a malignant fashion and are unresponsive to chemotherapy, unlike choriocarcinoma. There are no known reliable histopathologic features that help predict the behavior of this tumor.

	Choriocarcinoma	Placental Site Trophoblastic Tumor
Clinical	Persistent gestational trophoblastic disease after hydatidiform mole	Missed abortion
Type of trophoblast	Syncytiotrophoblast and cytotrophoblast	Intermediate trophoblast
Behavior	Highly malignant, chemoresponsive	Unpredictable—benign, persistent, or highly aggressive; poor response to chemotherapy

Table 6.14 Features of Choriocarcinoma and Placental Site Trophoblastic Tumor

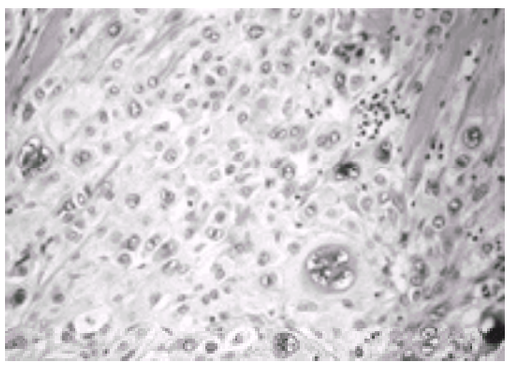

Figure 6.73 Placental site trophoblastic tumor. Large pleomorphic cells (intermediate trophoblast) diffusely infiltrate the myometrium.

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7 Epidemiology and Biostatistics

Daniel W. Cramer

Epidemiology and biostatistics apply to gynecologic oncology in defining cancer occurrence and survival, identifying risk factors, and implementing strategies for treatment or prevention. In this chapter, some key principles of epidemiology and biostatistics are considered under the headings of descriptive statistics, etiologic studies, statistical inference and validity, and cancer risk and prevention. Readers should refer to standard statistical and epidemiologic texts for more detailed discussion and computational formulas (1,2,3,4 and 5).

Descriptive Statistics

Cancer is described in populations by statistics related to its occurrence and survival from it. Descriptive statistics about cancer in the United States can be obtained from the National Cancer Institute through its website: http://www-seer.ims.nci.nih.gov/; descriptive statistics about cancer in the world can be obtained from the International Agency for Research on Cancer through its website: http://www-dep.iarc.fr/.

Incidence

The incidence rate (IR) is defined as the number of new cases of disease in a defined population within a specified time period.

IR = New cases/Person-time

The fact that time is a component of the denominator should help clinicians avoid the misapplication of this term to *prevalence*, another measure of disease occurrence.

Cancer Incidence and Mortality **Cancer incidence or mortality is usually stated as cases (or deaths) per 100,000 population per year, or as cases per 100,000 person-years.** Incidence or mortality is measured in a specific population over a specific period. For example, state cancer registries count the number of new cancer cases diagnosed or cases dying among residents over a year and divide that figure by census estimates of the total population in the state.

Crude Incidence or Mortality **Crude incidence or mortality is the total number of new cancers (or deaths) that occur over a specified time in the entire population.**

Age-Specific Incidence or Mortality **Age-specific incidence (or mortality) is the number of new cancers (or deaths) that occur over a specified time among individuals of a particular age group divided by the total population in that same age group.** Age-specific incidence or mortality rates are the best way to describe the occurrence of cancer in a population and are commonly graphed in 5-or 10-year groups. Annual age-specific incidence and mortality curves for the common gynecologic cancers in the United States based on all women in the Surveillance, Epidemiology, and End Results Survey (SEER) area for 1991 to 1995 (6) are shown in Fig. 7.1 and Fig. 7.2.

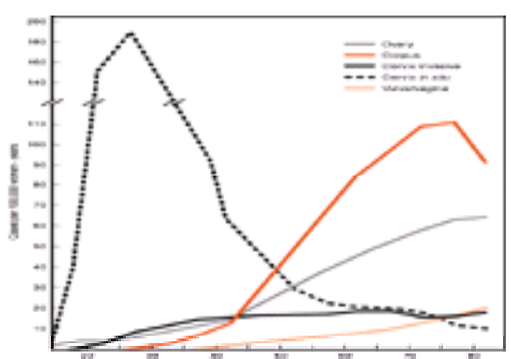


Figure 7.1 Age-specific incidence curves for the gynecologic cancers in women in the United States, 1991 to 1995 (6).

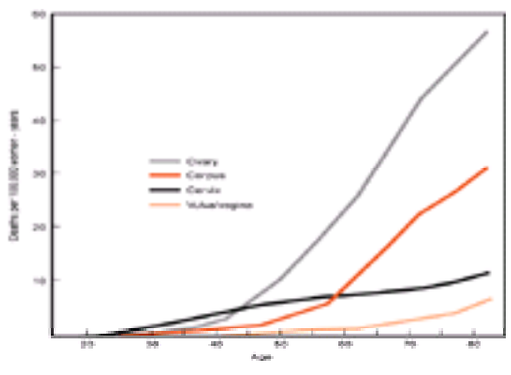


Figure 7.2 Age-specific mortality curves for the gynecologic cancers in women in the United States, 1991 to 1995 (6).

Figure 7.2 Age-specific mortality curves for the gynecologic cancers in women in the United States, 1991 to 1995 (6).

In situ cervical cancer has a sharp peak at approximately 190 cases per 100,000 women-years at ages 25 to 29 years, whereas invasive disease shows a more gradual rise and plateau after 50 years of age at approximately 16 cases per 100,000 women-years. Cancer of the corpus (largely endometrium) rises during the perimenopause and peaks at approximately 110 cases per 100,000 women-years after 70 years of age. Cancer of the ovary also displays an increase during the perimenopause and also peaks after age 70 years at approximately 60 cases per 100,000 women-years. Vulvar and vaginal cancers rise slowly throughout a woman's life and peak after 80 years of age at approximately 25 cases per 100,000 women-years. Cancer mortality curves display similar age patterns, but ovarian cancer is revealed as the most lethal of the gynecologic cancers.

Cumulative Incidence or Mortality **Cumulative incidence (or mortality) may be thought of as the proportion of people who develop disease (or die from it) during some period of observation.** Cumulative "incidence" is technically a misnomer because it does not contain time in the denominator but, rather, is expressed as a percentage. The cumulative IR (CIR) may be crudely approximated from age-specific IRs by the following formula:

$$\mathrm{CIR} = \Sigma \mathrm{IR}_i(\Delta \mathrm{T}_i)$$

where IR_i is the age-specific rate for the "i" age stratum and DT_i is the size of the age interval of the "i" stratum (usually 5 years). Cumulative incidence, summed over the age range 0 to 85 years, yields the "lifetime risk" for cancer occurrence or death. Lifetime risks that a woman in the United States will have or die from cancer of the cervix, corpus, or ovary are shown in Table 7.1 and confirm that a U.S. woman has a greater risk of acquiring cancer of the cervix or corpus than ovarian cancer, but a higher risk of dying from ovarian cancer than either cervical or endometrial cancer.

	Risk of Acquiring			Risk of Dying		
	All	White	Black	All	White	Black
Cervix	0.8%	0.7%	1.2%	0.3%	0.2%	0.5%
Corpus	2.7%	2.8%	1.8%	0.5%	0.5%	0.6%
Ovary	1.8%	1.8%	1.3%	1.3%	1.2%	1.6%

Table 7.1 Lifetime Risk of Acquiring or Dying from Gynecologic Cancers in White and Black U.S. Women (6)

Age-Adjusted Incidence or Mortality **Age-adjusted incidence or mortality (AAI) is obtained by summing weighted averages of the incidence or mortality rates for each age stratum.** The weight is derived from the age distribution of a standard population:

$$\mathrm{AAI} = \frac{\Sigma \mathrm{IR}_i(\mathrm{W}_i)}{\Sigma \mathrm{W}_i}$$

where IR_i is the IR in the "i" age stratum, and W_i is the number of people in the "i" stratum in the standard population. Age-adjusted rates are better than crude rates for summarizing age-specific incidence or mortality when comparing cancer occurrence among populations that may differ in their age structure. An "old" population would have a higher crude incidence of ovarian cancer and a lower crude incidence of carcinoma *in situ* of the cervix than a "young" population, even though both populations might have identical age-specific incidences for each disease. Cancer rates adjusted to the "world population standard" are shown in Table 7.2.

Region	Breast	Colon	Lung	Stomach	Cervix	Corpus	Ovary
World	33.2	13.3	10.8	11.6	13.4	3.9	6.8
Northern Africa	25.0	4.2	2.6	2.6	11.3	1.6	2.8
Southern Africa	31.1	8.4	7.7	6.3	43.4	7.4	5.3
Eastern Africa	19.0	4.2	2.8	5.3	37.4	3.0	7.8
Western Africa	19.0	3.9	3.9	6.6	26.2	2.9	6.4
Northern America	89.3	37.9	37.9	4.0	9.9	15.0	11.2
Central America	23.3	7.9	7.9	12.2	44.4	7.7	7.0
South America	46.4	14.5	7.3	14.0	33.9	9.0	7.4
Eastern Asia	14.4	12.9	13.9	21.8	6.7	2.0	3.3
Southeast Asia	22.3	8.9	9.3	5.3	18.9	3.9	6.2
Western Asia	24.3	7.6	9.3	6.6	9.9	6.9	6.3
Northern Europe	69.0	26.0	20.1	8.0	12.4	9.9	11.9
Eastern Europe	36.0	18.5	10.3	16.8	13.7	9.9	11.3
Western Europe	67.4	29.0	8.3	8.3	10.9	11.9	10.0
Southern Europe	49.5	20.2	7.3	10.0	10.4	9.9	8.0
Australia-New Zealand	71.7	34.8	16.1	4.9	11.2	9.3	9.9
Micronesia	37.5	9.9	18.4	5.3	13.3	11.9	9.4
Polynesia	26.9	11.9	16.8	9.3	21.9	13.3	9.7

[a] Age adjusted to the world standard in cases per 100,000.
From Parkin DM, Whelan SL, Ferlay J, Raymond L, Young J, eds. Cancer incidence in five continents, vol. VII. Lyon, France: IARC Scientific Publications No. 143, 1997.

Table 7.2 Age-Adjusted Incidence Rate[a] for the Gynecologic Cancers in Comparison with Other Major Cancers

Worldwide, cervical cancer is the most important of the gynecologic cancers and is second only to breast cancer in overall occurrence. Cervical cancer is most frequent in southern Africa and Central America and least frequent in North America and parts of Asia. Cancer of the corpus is least frequent in Africa and Asia and most frequent in North America. Ovarian cancer is least frequent in Africa and Asia and most frequent in northern Europe.

Prevalence

Prevalence (P) is the proportion of people who have a particular disease or condition at a specified time. Prevalence can be calculated by multiplying incidence times the average duration of disease:

$$\text{Prevalence} = \text{Incidence} \times \text{Average duration of disease}$$

More commonly, prevalence is derived from cross-sectional studies in which the number of individuals alive with a particular condition is identified from a survey and stated as a percentage of the total number of people who responded to the survey. Other examples of studies that yield prevalence data are those based on autopsy findings and screening tests. The frequency of previously unidentified cancers found in a series of autopsies yields data on the prevalence of occult cancer. The first application of a screening test in a previously unscreened population yields the prevalence of preclinical disease.

Cancer Survival

When the proportion of patients surviving cancer is plotted against time, the pattern often fits an exponential function (Fig. 7.3). To say that survival is exponential means that the rate of death is constant over time. This can also be demonstrated by plotting the logarithm of the probability of survival against time and demonstrating a straight line. Summary measures for a survival curve commonly include median survival time or the point at which 50% of the patients died (2 years in the figure) and the probability of survival at 1, 2, and 5 years (85%, 50%, and 15%, respectively, in the figure).

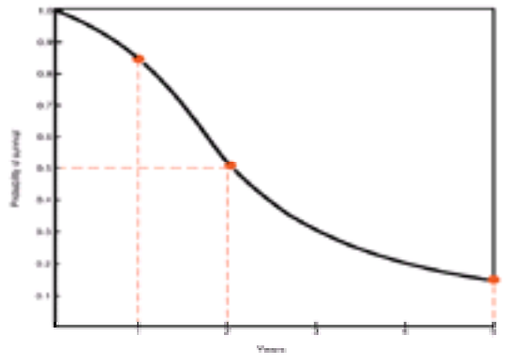


Figure 7.3 Idealized plot of exponential survival curve. One-year survival, median survival, and 5-year survival points are illustrated. (Redrawn with permission from Cramer DW. Epidemiologic and statistical aspects of gynecologic oncology. In: Knapp RC, Berkowitz RS, eds. *Gynecologic oncology.* New York: MacMillan, 1986:201–222, with permission.)

Relative Survival **Relative survival is defined as the ratio of the observed survival rate for the patient group to the survival rate expected for a population with similar demographic characteristics.** Five-year relative survival rates are frequently cited as the proportion of patients with cancer who are potentially cured, and are shown in Table 7.3 by type and stage of gynecologic cancer for U.S. women.

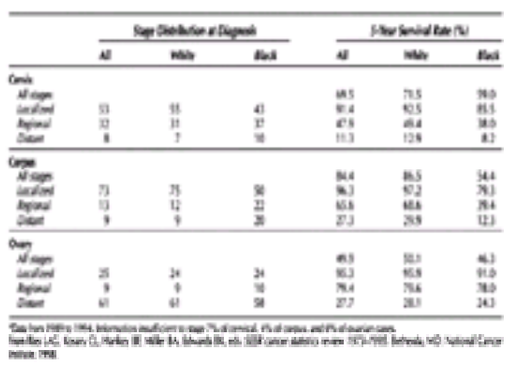


Table 7.3 Stage at Diagnosis for the Gynecologic Cancers[a] and 5-Year Survival Rates for U.S. Women

Stage at presentation and survival are most favorable for cancer of the corpus and least favorable for cancer of the ovary. In general, African Americans tend to be diagnosed at more advanced stages and have poorer survival compared with whites.

Etiologic Studies

This section discusses the design of etiologic studies, including case–control and cohort studies, and clinical trials as special types of cohort studies. In contradistinction to purely descriptive studies, which largely address how cancer varies by age, race, and geography, etiologic studies describe the relationship between personal factors, such as diet or reproductive history, and cancer occurrence or survival. This relationship is often described by epidemiologic parameters known as relative risk and attributable risk.

Relative risk (RR) **is the risk of disease or death in a population exposed to some factor of interest divided by the risk in those not exposed.** A number greater than 1 may indicate that exposure increases the risk of disease.

Attributable risk **is the risk of disease or death in a population exposed to some factor of interest minus the risk in those not exposed.** A number greater than 0 may indicate that exposure increases the risk of disease.

Case–Control Study

In the case–control study, diseased and nondiseased populations are selected and existing or past characteristics (exposures) are assessed to determine the possible relationship between exposure and disease. The investigator starts with diseased cases and nondiseased control subjects who are then studied to determine whether they had a particular exposure. The odds that the cases were exposed (a/b) is compared with the odds that the control subjects were exposed (c/d) in a measure called the exposure odds ratio (Fig. 7.4).

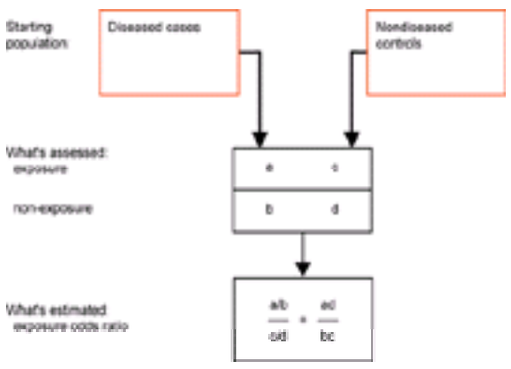


Figure 7.4 Case-control study design.

Exposure Odds Ratio **The odds of exposure among cases divided by the odds of exposure among the control subjects is the *exposure odds ratio* and is equivalent to the relative risk.** If an entire population could be characterized by its exposure and disease status, the exposure odds ratio would be mathematically identical to the relative risk obtained in a cohort study. Because it is practical to study only subsets of cases and control subjects, the exposure odds ratio in the sampled population approximates the relative risk, as long as the cases and control subjects actually sampled have not been preferentially selected on the basis of their exposure status.

Attributable risk cannot be directly calculated in a case–control study, but may be estimated by the formula:

$$\text{Population attributable risk} = \frac{\text{RR-1}}{\text{RR}} \times (\text{Proportion of controls exposed})$$

Cohort Studies

In a cohort study, the groups to be studied (the cohorts) are defined by characteristics (or exposures) that occur before the disease of interest, and the study groups are followed to observe the risk of disease in the cohorts. The investigator starts with exposed and nonexposed individuals who are followed over time to identify the number of diseased cases that develop. The initial sizes of the cohort and the number of years cohort members are followed determine the person-time contributed by the cohorts. The investigator then calculates the rates of disease in exposed and nonexposed subjects and determines the relative or attributable risk. For rare exposures, an investigator may use the general population as the unexposed group and calculate a parameter equivalent to the relative risk, known as the standardized morbidity ratio (Fig. 7.5).

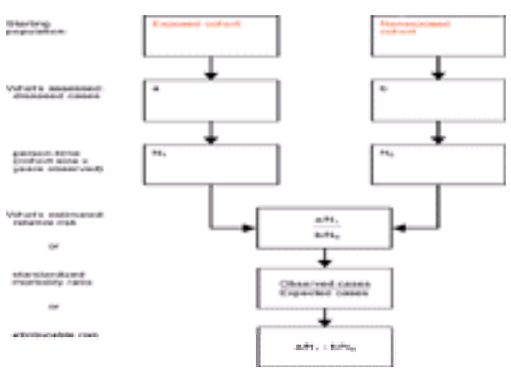


Figure 7.5 Cohort study design.

Standardized Morbidity or Mortality Ratio **The standardized morbidity or mortality ratio (SMR) is the observed number of exposed cohort members in whom disease developed divided by the number expected if general population disease rates had prevailed in the cohort.**

Cohort studies are further distinguished by when the exposure and outcome occurred or will occur in relation to when the investigator begins the study.

Retrospective Cohort Study **In a retrospective cohort study, the exposures and outcomes have already occurred when the study is begun.** For example, studies of second cancers after therapeutic radiation are based on follow-up of women irradiated for cervical cancer 10 to 30 years previously. Medical records and death certificates are used to determine those who subsequently died of cancers other than cervical.

Prospective Cohort Study **In a prospective cohort study, the relevant exposure may or may not have occurred when the study is begun, but the outcome has not yet occurred.** After the cohort is selected, the investigator must wait for the disease or outcome to appear in the cohort members. The Nurse's Health Study is a good example of a prospective cohort study.

Clinical Trial **A clinical trial is a special type of prospective cohort study in which the investigator assigns a therapy or preventive agent in randomized fashion to minimize the possibility of bias accounting for different outcomes subsequently observed between treatment cohorts.** Obviously, such studies cannot be used to assess a harmful effect of an exposure except as might occur as an unintended side effect of the therapy. Clinical trials are the only satisfactory way to assess the effect of different cancer therapies on disease recurrence or death because, in theory, they are able to overcome many of the biases that may affect case–control or cohort studies, as discussed in the next section.

Statistical Inference and Validity

Clinicians should understand issues affecting statistical significance and validity to evaluate studies that claim that some new exposure causes cancer or some new therapy is superior to standard treatment.

Statistical Inference

Statistical inference is a process of drawing conclusions from data by hypothesis testing during which a decision is made either to reject or not reject a null hypothesis. Hypothesis testing involves the following steps:

1. Observations are made and summarized by some statistical parameter such as a mean, a proportion, a rate ratio, and so forth.
2. A research question is stated in terms of a null hypothesis claiming no difference between the observed parameter and some theoretical value.
3. A statistical test is chosen based on the study design and nature of the parameters being studied.
4. The test statistic is calculated and its associated p value is read from the appropriate statistical table.
5. A *p* value less than the traditional 5% leads to the decision to reject the null hypothesis, whereas a value above 5% leads to the decision not to reject the null hypothesis. Errors are possible with either decision.
6. A confidence interval on the parameter may be constructed from the test results and defines the range in which the true value of the parameter is expected to fall.

Type I Error

The degree of conflict between the parameter observed and that assumed by the null hypothesis is summarized by the *p* value, alpha, or type I error and indicates the probability of incorrectly rejecting the null hypothesis.

Type II Error

A type II or beta error indicates the probability of failing to reject the null hypothesis when, in reality, it is false. To calculate a beta error, an "alternate hypothesis" must be stated. In planning a clinical trial, an investigator often calculates the power (1 minus the beta error) that a study will have to detect an association, given a certain study size and certain assumptions about the nature of the association. Small clinical trials that find no significant difference among therapies may be cited as evidence of "no effect of therapy," when the statistical power may have been well below the accepted target of 80% for a meaningful difference in response rates.

Statistical Distributions and Tests

There are no simple rules for determining which statistical test is appropriate in every situation. The choice depends on whether the variable is qualitative (nominal) or quantitative (numerical), what assumptions are made about the distribution of the parameter being measured, what is the nature of the study question, and the number of groups or variables being studied. For example, a *chi-square test* is used to test the null hypothesis that proportions are equal or that nominal variables are independent. The unpaired *t test* is used to compare two means from independent samples, whereas the paired *t* test compares the difference or change in a numerical variable for matched or paired groups.

Validity

Validity means freedom from bias. *Bias* refers to a systematic error in the design, conduct, or analysis of a study that results in a mistaken conclusion and is commonly divided into observation bias, selection bias, and confounding.

Observation Bias

Observation bias or misclassification occurs when subjects are classified incorrectly with respect to exposure or disease. If misclassification was equally likely to occur whether the subject was a case or control subject or an exposed or nonexposed cohort member, then the observation bias is nondifferential and causes the relative risk to be biased toward the null value, one. Alternatively, if misclassification was more likely to occur for cases than control subjects or for exposed than nonexposed cohort members, then a falsely elevated (or reduced) relative risk might occur (e.g., if cases preferentially recalled or admitted to a particular exposure compared with control subjects). Criteria for exposure or disease should be clearly defined to minimize observation bias. Ideally, researchers recording disease status in a cohort study or exposure status in a case–control study should be unaware of the subject's study group. A desirable attribute of a clinical trial is *double blindness*, where neither the subject nor investigator knows which specific treatment the subject is receiving.

Selection Bias

Selection bias is an error due to systematic differences in the characteristics of subjects selected for study and those who are not. For example, a selection bias might occur in a case–control study if exposed cases did much better or worse than nonexposed cases. If the case group consisted of long-term survivors, they might have a different frequency of the exposure than recently diagnosed individuals. Selection bias may also occur in the process of selecting control subjects; for example, control subjects might be selected from hospitalized patients in a disease category that may, itself, relate to the exposure. Selection bias is less likely to occur in cohort studies or in population-based case–control studies, where most cases in a particular area are studied and control subjects are selected from the general population.

Confounding

Confounding occurs when some factor not considered in the design or analysis accounts for an association because that factor is correlated with both exposure and disease. Potential confounders for any cancer study are age, race, and socioeconomic status. Confounding may be controlled during the design of a study by matching cases to control subjects on key confounding variables or during the analysis phase of the study by stratification or multivariate analysis. *Stratifying* means examining the association of interest within groups that are similar with respect to a potential confounder, whereas *multivariate analysis* is a statistical technique that controls for a number of confounders simultaneously.

In a clinical trial, confounders are dealt with by randomization; that is, subjects are allocated to treatment groups by chance such that prejudices of the investigator do not influence allocation of treatment. The initial table in a clinical trial usually shows how the treatment groups compared by age, race, or other important variables.

Other Criteria for Judging an Epidemiologic Study

In addition to validity, other criteria applied to judging an epidemiologic study include consistency, whether a dose response is present, and whether the association has biologic credibility.

Consistency

Measurements that are in close agreement when repeated are said to be *consistent*. In the context of an epidemiologic association, relative risks that are consistent among studies provide evidence for a causal association, especially when different study methods have been used. Consistency can be assessed in a formal manner by performing a study called a meta-analysis. **In a *meta-analysis*, results from independent studies examining the same exposure (or treatment) and outcome are combined so that a more powerful test of the null hypothesis may be conducted.** As part of the meta-analysis, a test for heterogeneity is performed to indicate whether the results for the individual studies are compatible with the overall estimate of the association. In a meta-analysis of 37 studies completed before 1994 assessing the association between unopposed estrogen and endometrial cancer, the relative risk was elevated in 35 of the studies, significantly so in 33 (7).

Dose Response

Dose response refers to a relationship between exposure and disease such that a change in the duration, amount, or intensity of an exposure is associated with an increase or decrease in disease risk. A dose response was observed in studies of unopposed estrogen and endometrial cancer (7).

Biologic Credibility

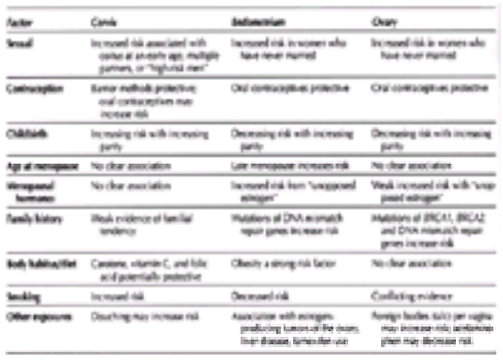
An association has *biologic credibility* if it is supported by a framework of diverse observations from the natural history or demographics of the disease and from relevant experimental models. The search for biologic credibility is, perhaps, a process that is easier to illustrate than to explain. Continuing the theme of unopposed estrogen and endometrial cancer, the following observations suggest biologic credibility for this association:

1. Administration of unopposed estrogen may cause endometrial hyperplasia (8).
2. Endometrial cancer may develop in women with excessive endogenous estrogen from granulosa tumors (9).
3. Endometrial cancer may develop women with decreased degradation of estrogen secondary to liver failure (10).
4. Women who are obese have excessive peripheral conversion of androstenedione to estrone and are at increased risk of endometrial cancer (11,12).
5. The perimenopause is characterized by anovulatory cycles with unopposed estrogen and is a period during which the incidence of endometrial cancer increases rapidly.

These observations not only support a causal association between unopposed menopausal estrogen and endometrial cancer but suggest that the risk of endometrial cancer may be largely mediated through states that lead to an excess of estrogen relative to progesterone.

Cancer Risk and Prevention

This section discusses what is known about risk factors for the gynecologic cancers and how this information may be applied to cancer prevention. Table 7.4 summarizes major epidemiologic risk factors for cervical, endometrial, and ovarian cancer.



Factor	Cervix	Endometrium	Ovary
Sexual	Increased risk associated with coitus at an early age, multiple partners, or "high-risk men"	Increased risk in women who have never married	Increased risk in women who have never married
Contraception	Barrier methods protective; oral contraceptives may increase risk	Oral contraceptives protective	Oral contraceptives protective
Childbirth	Increasing risk with increasing parity	Decreasing risk with increasing parity	Decreasing risk with increasing parity
Age at menopause	No clear association	Late menopause increases risk	No clear association
Menopausal hormones	No clear association	Increased risk from "unopposed estrogen"	Weak increased risk with "unopposed estrogen"
Family history	Weak evidence of familial tendency	Mutations of DNA mismatch repair genes increase risk	Mutations of *BRCA1*, *BRCA2*, and DNA mismatch repair genes increase risk
Body habitus/diet	Carotene, vitamin C, and folic acid potentially protective	Obesity a strong risk factor	No clear association
Smoking	Increased risk	Decreased risk	Conflicting evidence
Other exposures	Douching may increase risk	Association with estrogen-producing tumors of the ovary, liver disease, tamoxifen use	Foreign bodies (talc) per vagina may increase risk; peritoneal plica may decrease risk.

Table 7.4 Risk Factors for Gynecologic Cancers

Cervical Cancer

Invasive squamous cell carcinoma of the cervix is the end stage of a process beginning with atypical transformation of cervical epithelium at the squamocolumnar junction, leading to cervical intraepithelial neoplasia (CIN) of advancing grades and eventual invasive disease. Thus, risk factors for cervical cancer are those associated with atypical transformation and those that influence persistence and progression of disease.

Factors associated with atypical transformation largely relate to sexual practices and include an early age at first intercourse and intercourse with multiple sexual partners or with "high-risk" men (13). Early age at first intercourse may be important because adolescence is a period of heightened squamous metaplasia, and intercourse at this time may increase the likelihood of atypical transformation (14). The woman who has had intercourse with multiple partners or with a "high-risk" man who has himself had contact with multiple partners increases the likelihood of her exposure to sexually transmitted agents that may be the cause of atypical transformation. Although many sexually transmitted pathogens have, at one time or another, been linked to cervical cancer, certain subtypes of the human papillomavirus (HPV) have emerged as the most likely infectious agents (15). The link with genital infection means that a woman can decrease her risk of cervical cancer by safe sexual practices and use of barrier methods of contraception (16).

There may also be risk factors of a nonsexual nature that include douching and smoking. Douching with coal tar substances, as was the practice earlier in the 20th century, was a strong risk factor for cervical cancer and suggests that chemical carcinogenesis of the cervix can occur (17). Although coal tar douches are no longer available, douching should be discouraged among adolescents at the stage of active squamous metaplasia. Smoking also has been associated with cervical cancer, even after adjustment for a number of confounding factors (18). This association has biologic credibility because potentially mutagenic substances are secreted in the cervical mucus of smokers (19).

Besides factors that affect the risk for cervical cancer by initiating atypical transformation, others may modulate risk for cervical cancer by affecting the likelihood that a preinvasive lesion will persist or progress. A factor indisputably related to the progression of CIN is the frequency of cervical cytologic screening. **Population studies have demonstrated a correlation between cytologic screening and declining mortality from cervical cancer (20). Case–control studies demonstrate that women who have had Papanicolaou (Pap) smears at least every 3 years have one-tenth the risk of developing invasive disease compared to women who have never had a Pap test** (21). Other factors that relate to disease progression may include oral contraceptive use and diet. Long-term oral contraceptive use has been reported to increase the risk of high-grade intraepithelial lesions and invasive cervical cancer (22), and a link to adenocarcinomas of the cervix has also been postulated (23). Butterworth et al. attributed the potential harmful effects of oral contraceptives on the cervix to folate deficiency and recommended supplementation (24). Other studies suggest the importance of vitamin C, the carotenoids, and vitamin E (25). Finally, progression of CIN is also likely to be greater in immunosuppressed women such as those with human immunodeficiency virus infection (26), or after kidney transplantation (27).

Endometrial Cancer

Risk for adenocarcinoma of the endometrium is largely mediated by states that lead to an excess of estrogen over progesterone, either through increased production or decreased degradation of estrogen or through exogenous intake of unopposed estrogen. Factors that lead to increased production of estrogen include estrogen-producing tumors of the ovary (9). More commonly, obesity leads to increased production through the peripheral conversion of androstenedione (11). Alternatively, protective factors are those associated with decreased estrogen production. Surgical castration at an early age with retention of the uterus is a strong protective factor (28). Leanness and regular exercise lower estrogen levels and protect against endometrial cancer (29). Smoking also lowers estrogen and protects against endometrial cancer, but obviously cannot be encouraged as a preventive measure (30). Endometrial cancer as a consequence of decreased degradation of estrogen is illustrated by case reports of endometrial cancer in women with cirrhosis of the liver (10).

Endometrial cancer as a consequence of exogenous estrogen is demonstrated by the impressive evidence that unopposed estrogen administered for the menopause increases the risk of endometrial cancer in a dose–response fashion (7). Tamoxifen, with its estrogen antagonist effects in the breast and agonist effects in the uterus, has also been shown to increase the risk for endometrial cancer in a clinical trial (31). Alternatively, menopausal estrogen taken with a progestin has not been shown to increase risk (32), and past use of combination birth control pills has been reported to decrease the risk of endometrial cancer (33). Clinical trials have suggested very low rates of hyperplasia occurring with a continuous regimen of 0.625 mg of conjugated estrogen and 2.5 mg of medroxyprogesterone acetate (34).

It is not clear how genetic risk factors for endometrial cancer fit into the "estrogen excess" model, but it is known that endometrial cancer may occur in families with hereditary nonpolyposis colorectal cancer associated with the DNA mismatch repair genes (35).

Ovarian Cancer

Consistently observed risk factors for ovarian cancer include a protective effect of pregnancy and a protective effect of oral contraceptive use. A popular theory to account for these findings is that these events lead to a break in monthly ovulations, and that it is the repeated disruption and healing of the surface of the ovary (incessant ovulation) that is the cause of ovarian cancer (36). Not readily explained by this model, however, are the facts that the peak occurrence of ovarian cancer is well beyond the cessation of ovulation. In addition, very low rates of the disease are observed in Japan, where there are both low birth rates and little use of oral contraceptives.

An alternative theory to incessant ovulation is that ovarian cancer may arise from excessive gonadotropin stimulation of the ovary (37). Classic animal models for ovarian cancer involved disruption of ovarian–pituitary feedback either by prematurely destroying oocytes using radiation or chemical toxins (38,39) or by transplanting the animal's ovary to its spleen, leading to enhanced metabolism of ovarian hormones before they could exert feedback inhibition (40). A role for gonadotropins was indicated by observations that ovarian tumors did not develop in rodents who were hypophysectomized before the experimental treatment or who were given estrogen, which inhibited gonadotropin release (41,42). More recently, it has been shown that gonadal stromal tumors invariably develop in mice with a targeted deletion of the gene for the gonadotropin downregulator, a-inhibin (43). Again, a critical role for gonadotropins was demonstrated by cross-breeding experiments showing the tumors did not develop in mice with the a-inhibin gene deletion who were also incapable of secreting gonadotropins because of gonadotropin-releasing hormone deficiency (44). Most of these experimental tumors were stromal in origin and their relevance to the epithelial types observed in women has been debated. However, monthly ovulators, in contrast to rodents, have inclusion cysts and an abundant stromal–epithelial admixture, which might lead to epithelial proliferation as the principal manifestation of ovarian stromal stimulation in humans.

Epidemiologic data support the relevance of these models to human ovarian cancer. Ovarian cancer IRs rise sharply between ages 45 and 54 years and remain elevated for the remainder of a woman's life, paralleling gonadotropin levels over this period. The strong protective association between oral contraceptives and ovarian cancer (45) duplicates the modifying effects of exogenous estrogen in the animal models. Another pharmacologic agent that, surprisingly, may lower gonadotropins and protect against ovarian cancer is *acetaminophen* (46,47). Also relevant to the animal models are cohort studies that demonstrate that ovarian cancer occurs after radiation for cervical cancer after a 10- to 15-year lag period (48,49). Besides radiation, other chemical toxins in human beings might include tobacco smoke (50), caffeine (51), tannic acid (52), the mumps virus (53), and milk sugar or galactose (54,55), although the epidemiologic data linking these factors to ovarian cancer are weak or mixed.

The theory that ovarian cancer arises as a consequence of high levels of gonadotropins does not explain observations that use of talc in genital hygiene may increase the risk for disease (56), suggesting that foreign body carcinogenesis of the ovary may also occur. Parmley and Woodruff (57) proposed that epithelial ovarian cancers might be ovarian mesotheliomas that arise from transformation of the surface lining of the ovary exposed to pelvic contaminants. Besides talc, another pelvic “contaminant” might be the menstrual products that are believed to flow out of the fallopian tubes during menstruation to explain endometriosis (58). Indeed, prior endometriosis is a risk factor for ovarian cancer (59), especially the endometrioid and clear cell types (60). **The pelvic contamination theory might also explain why tubal ligation might decrease risk for ovarian cancer by closing the female tract** (61). Thus, it would appear that in addition to agents affecting the ovarian–pituitary axis, factors related to pelvic contamination with talc or menses need to be considered in the pathogenesis of ovarian cancer.

Finally, there are a number of genetic risk factors emerging for ovarian cancer. Having a mother or sister with the disease may increase a woman's risk for ovarian cancer by approximately twofold to threefold (62). Specific genetic factors include mutations of the *BRCA1* and *BRCA2* as well as the DNA mismatch genes (63). Although a genetic factor is more likely to be found in families where a number a relatives have been affected with breast or ovarian cancer, mutations may be found in a surprising number of women with “sporadic” ovarian cancer—10% in one series (64) and up to 40% among women with a Jewish ethnic background (65).

Other Gynecologic Neoplasms

Other than clear cell adenocarcinomas of the vagina associated with maternal use of diethylstilbestrol (66), vaginal carcinoma is primarily a disease of women older than 50 years of age, with an age incidence distribution nearly identical to that of vulvar carcinoma. Like cervical neoplasms, vulvar and vaginal carcinomas may be preceded at an earlier age by an *in situ* phase, but the natural history of these lesions is debated. Vulvar and vaginal cancers frequently occur in the same patient and in association with epithelial neoplasms of other anogenital sites, including the cervix, the anus, and even the urethra and bladder (67,68,69 and 70). Thus, risk factors known to exist for cervical neoplasms may be pertinent for vulvar and vaginal neoplasms, including HPV and smoking (71,72). Further study of dietary factors, especially the carotenoids, would be worthwhile.

Trophoblastic neoplasms include complete and partial hydatidiform moles, invasive moles, and choriocarcinoma. The epidemiology of hydatidiform mole is probably better understood than that of other trophoblastic diseases, but it is likely to be relevant because of the association between molar pregnancy and subsequent invasive mole or choriocarcinoma. The prevalence of molar pregnancy varies from 1 per 100 deliveries in Asia, Indonesia, and other Third World countries to 1 per 1,000 to 1,500 in the United States (73). Clearly, the risk of having a molar pregnancy increases with maternal age (74,75), but it is less certain whether adolescents are also at increased risk (76). The peculiar cytogenetic patterns of complete and partial hydatidiform moles are discussed in Chapter 15 and may indicate the importance of aberrant germ cells in the origin of these disorders.

Berkowitz et al. (77) suggested that **deficiency of the vitamin A precursor, carotene, or of animal fats necessary for its absorption might be a factor in the cause of this disease.** Vitamin A deficiency causes fetal wastage and aberrancy of epithelial development in female animals and degeneration of seminiferous epithelium with poor gamete development in male animals (78,79 and 80). In addition, regions where molar pregnancy is common have a high incidence of night blindness (81).

Cancer Prevention

Cancer prevention may occur at the level of primary prevention (the identification and modification of risk factors for disease), secondary prevention (the detection of the disease at earlier, more treatable stages), or tertiary prevention (effective treatment of clinical disease). This section addresses primary and secondary measures of prevention.

Methods of primary prevention are by no means certain, but suggestions include:

1. *For cervical cancer*, avoidance of tobacco, use of barrier methods of contraception, and a diet high in folates, b-carotene, and vitamins C and E may be beneficial.
2. *For endometrial cancer*, maintenance of ideal body weight, avoidance of a high-fat diet, and avoidance of unopposed estrogen therapy during menopause may be beneficial.
3. *For ovarian cancer*, use of oral contraceptives if not medically contraindicated and avoidance of talc in genital hygiene may be beneficial. Women known to carry a predisposing mutation should consider prophylactic oophorectomy after they have completed childbearing.

Secondary Prevention

Cancer deaths may also be prevented by detecting disease at a stage when it is more curable. The secondary prevention of cervical cancer has been successful, and screening programs for the other gynecologic cancers may eventually be devised. To be successful, a screening program must be directed at a "suitable" disease with a "suitable" screening test (82). A suitable disease must be one that has serious consequences, as most cancers do. Treatment must be available so that when such therapy is applied to screen-detected (preclinical) disease, it will be more effective than when applied after symptoms of the disease have appeared. Also, the preclinical phase of the disease must be long enough that the chances are good that a person will be screened. There must also be a suitable screening test as defined by simplicity, acceptability to patients, low cost, and high validity, as outlined in Table 7.5.

	True Disease Status		
Status Determined by Screening	Positive	Negative	Total
Positive	a (true positives)	b (false-positives)	a + b (all screened positives)
Negative	c (false-negatives)	d (true negatives)	c + d (all screened negatives)
Total	a + c (all diseased)	b + d (all nondiseased)	N (all subjects)
Measure	Definition	Formula	
Sensitivity	True positives / All diseased	$\frac{a}{a+c}$	
Specificity	True negatives / All nondiseased	$\frac{d}{b+d}$	
Predictive value of a positive screen	True positives / All screened positives	$\frac{a}{a+b}$	

Table 7.5 Measures of Validity for a Screening Procedure

Sensitivity **The sensitivity of a test is defined as the proportion of people with a true-positive screening result of all those who have the disease.**

Specificity **The specificity of a test is defined as the proportion of people with a true-negative screening result of all those who do not have the disease.**

Predictive Value **The predictive value of a positive test is a function of sensitivity, specificity, and disease prevalence.** This function implies that a positive screening test is more likely to indicate disease in a high-risk population than in a low-risk population (Table 7.4).

Screening Strategies

For cervical cancer, the 1982 Canadian Task Force report (83) suggested that as women accumulated a history of negative annual Pap smears, the interval between screenings may be safely lengthened to 3 years. In 1988, the American College of Obstetricians and Gynecologists issued a consensus report with the American College of Surgeons and the United States National Cancer Institute (84), which recommended annual Pap smears for sexually active women until three normal smears had been obtained. However, annual physical examinations, including breast examinations, were recommended for all women, once they became sexually active. Although some discretion is permitted in low-risk patients, such as those who are monogamous, the risk of cervical cancer relates to the sexual behavior of both sexual partners. Therefore, to be at low risk, the woman must not only be monogamous, she must have a monogamous partner. A full discussion of these recommendations is presented in Chapter 8.

Endometrial biopsies in perimenopausal or postmenopausal women are appropriate for those at risk for endometrial cancer, including those who are obese, have unopposed estrogen, use tamoxifen, or who come from families with both colon and endometrial cancer. No effective screening strategy exists for ovarian cancer.

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8 Preinvasive Disease

Michael Campion

Cervix

Cervical cancer remains worldwide the second most common cancer among women, accounting for 15% of all female cancers. It is the most common cancer among women in many developing countries, constituting 20% to 30% of female cancers. In developed Western countries, it accounts for only 4% to 6% of female cancers (1,2,3 and 4). This difference largely reflects the impact of mass screening using cervical cytologic methods (5).

The primary goal of cervical screening is to prevent cervical cancer. This is achieved by the detection, eradication, and follow-up of preinvasive cervical lesions (6,7 and 8). The ability to detect preinvasive cervical disease, coupled with comparatively easy access to the cervix for screening and assessment, have contributed greatly to the understanding of cervical carcinogenesis and to the definition of the precursor lesions to cervical cancer.

Classification of Preinvasive Cervical Disease

The proposal that invasive squamous carcinoma of the cervix arises through progression of a preinvasive lesion as opposed to a *de novo* event was initially postulated by Schauenstein in 1908 (9). The term “carcinoma *in situ*” was later introduced to describe cancerous changes confined to the epithelium (10).

The “Dysplasia” Terminology

Although referred to earlier by Papanicolaou (11), in 1956 Reagan et al. (12,13) described cytologic differences between “carcinoma *in situ*” and a group of “less anaplastic” lesions, for which he introduced the term *dysplasia.* In 1975, the World Health Organization defined dysplasia as a “lesion in which part of the epithelium is replaced by cells showing varying degrees of atypia.” Dysplastic changes were graded as mild, moderate, and severe, but precise guidelines for these subdivisions were not defined and grading always remained highly subjective (14,15,16 and 17).

A dual terminology for epithelial abnormalities of the cervix developed, leading to irrational treatment policies. If a diagnosis of “dysplasia” was made, this was considered a nonspecific change and the patient was subjected to a cone biopsy. If the diagnosis of “carcinoma *in situ*” was made, this was considered a “preinvasive cancer” and the patient underwent an obligatory hysterectomy (16,17 and 18).

Cervical Intraepithelial Neoplasia

Invasive squamous cell carcinoma of the cervix was demonstrated to be the end result of progressive intraepithelial dysplastic atypia occurring within the metaplastic epithelium of the cervical transformation zone (19). The classification of lesions from mild dysplasia to carcinoma *in situ* did not truly reflect either the morphologic or biologic continuum of preinvasive cervical disease. The diagnosis was highly subjective and nonreproducible. After pioneering research into the natural history of cervical cancer precursors, Richart (20), in 1966, proposed the term *cervical intraepithelial neoplasia (CIN)* to describe the biologic spectrum of cervical preinvasive squamous disease. **Three grades of CIN were described, specifically, CIN 1 (mild dysplasia), CIN 2 (moderate dysplasia), and CIN 3 (severe dysplasia/carcinoma *in situ*).** This system was consistent with biologic evidence that strongly implied a single process of cervical squamous carcinogenesis (21,22,23 and 24).

A quarter of a century of experience with the CIN terminology, coupled with advances in the understanding of the role of human papillomavirus (HPV) in the causation of cervical neoplasia, have led recently to further reclassification of the terminology for reporting cytologic abnormalities consistent with preinvasive disease (25,26,27,28 and 29). The CIN grading is very subjective. No reproducible cytologic or histologic distinction at the lower end of the CIN continuum exists between CIN 1 and HPV infection alone. Both interobserver and intraobserver consistency in diagnosis are poor. Separating CIN 2 from CIN 3 is again highly nonreproducible and achieves no useful clinical purpose. In reality, the two critical points in the assessment of the cervical epithelium are (a) do the changes represent a cancer precursor, and (b) is the lesion invasive cancer?

The Bethesda System

In 1988, in an effort to standardize the reporting of cervical cytology in the United States, the Bethesda system was introduced (25). The rationale for the introduction of a new cervical cytologic classification is discussed in detail later in this chapter. **The Bethesda system introduced the cytologic terms *low-grade* and *high-grade* squamous intraepithelial lesions (LSIL and HSIL). LSIL includes HPV infection alone and CIN 1; HSIL includes CIN 2 and 3.** Although this system does not replace the histologic terms *CIN* and *dysplasia*, the clinical relevance of the LSIL and HSIL diagnoses to management decision making has inevitably led to their wide acceptance. **The clinical terminology is often further modified to describe histologically proven HPV infection/CIN 1 as a low-grade lesion (LGL) and CIN 2 to 3 as a high-grade lesion (HGL)** (Fig. 8.1).

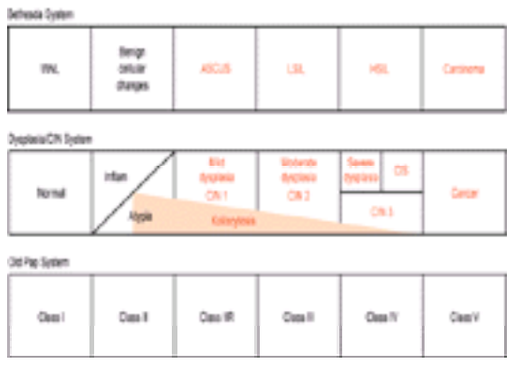

Figure 8.1 Comparison of the terminology for cervical preinvasive squamous disease. Top: The Bethesda System; **(middle)** the dysplasia/cervical intraepithelial neoplasia classification; **(bottom)** the old Papanicolaou classification. (Courtesy of Dr. M. Henry, U.S. Naval Hospital, Bethesda, MD.)

In prospective studies (30,31,32 and 33), approximately 50% of HGLs arise in women with an LGL diagnosed on enrollment. Another 25% are preceded by equivocal LGLs. The remaining 25% are divided almost equally between cytologically normal women with HPV infection detected at the time of enrollment and women with no evidence of HPV infection at enrollment. The latter group may be etiologically distinct and especially informative regarding molecular pathogenesis.

Understanding the Cervical Transformation Zone

Embryogenesis

The cervix and vagina are derived from the mullerian ducts and are initially lined by a single-layer, mullerian-derived columnar epithelium. At 18 to 20 weeks of gestation, this columnar epithelium lining the vaginal tube is colonized by the upward growth of stratified squamous epithelium derived from cloacal endoderm. The vaginal muscularis is derived from mullerian mesoderm, but the squamous epithelium is of cloacal origin.

Original Squamocolumnar Junction

The junction in fetal life between the stratified squamous epithelium of the vagina and ectocervix, and the columnar epithelium of the endocervical canal is called the original squamocolumnar junction (34). Original squamous epithelium extends from Hart's line or the mucocutaneous, vulvovaginal junction to the original squamocolumnar junction. The position of the original squamocolumnar junction is variable, lying on the ectocervix in 66%, within the endocervical canal in 30%, and on the vaginal fornices in 4% of female infants (35). **The position of the original squamocolumnar junction determines the extent of cervical squamous metaplasia** (35,36). **Squamous metaplasia is a pivotal process in cervical carcinogenesis.** Embryogenesis, in determining the distribution of native squamous and columnar epithelia, is an important early influence in determining future risk of neoplastic transformation (Fig. 8.2).

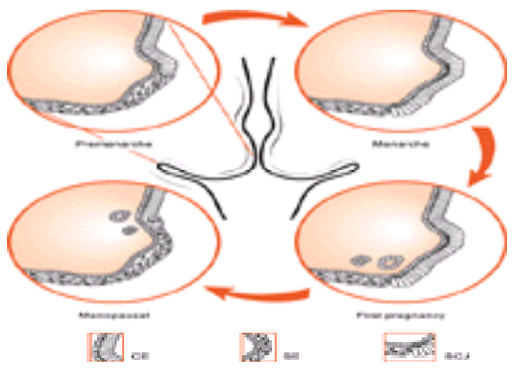

Figure 8.2 Location of squamocolumnar junction at various times in a woman's life. CE, columnar epithelium; SE, squamous epithelium; SCJ, squamocolumnar junction.

New Squamocolumnar Junction

The volume of the cervix alters throughout a woman's life in response to hormonal stimulation. Increased estrogen secretion, particularly with puberty and with the first pregnancy, causes an increase in cervical volume and an eversion of endocervical columnar epithelium to an ectocervical location. This eversion of columnar epithelium onto the ectocervix is called an *ectropion.* An ectropion is often mistakenly referred to as an *erosion.* An erosion is a breach in an epithelial surface or ulcer and is an inappropriate descriptor for an ectropion.

The estrogen surge of puberty results in the establishment of lactobacilli as part of the normal flora of the vagina. These microorganisms produce lactic acid, reducing the vaginal pH to 4 or less. Everted endocervical columnar epithelium is exposed in the postpubertal years to the harsh acidity of the vaginal environment. Damage to the everted columnar epithelium caused by vaginal acidity results in proliferation of a stromal reserve cell underlying the columnar epithelium. This results in replacement of the columnar epithelium with an immature, undifferentiated, stratified, squamous, metaplastic epithelium. Immature squamous metaplasia then undergoes a maturation process, producing a mature, stratified squamous metaplastic epithelium distinguishable only with difficulty from the original squamous epithelium. **The original linear junction between squamous and columnar epithelium is replaced by a zone of squamous metaplasia at varying degrees of maturation. At the upper or cephalad margin of this zone is a sharp demarcation between epithelium, which appears morphologically squamous using the magnified illumination of a colposcope, and erythematous, villous epithelium, which appears colposcopically columnar. This colposcopic junction is called the *new squamocolumnar junction*.**

The Transformation Zone

The transformation zone is defined as that area lying between the original squamocolumnar junction and the colposcopic new squamocolumnar junction (22,23). The initial clinical assessment for most women is in the postpubertal years. Mature squamous metaplastic epithelium has often replaced the distal or caudad limit of the columnar epithelium. The original squamocolumnar junction is most often seen clinically as a squamosquamous junction separating original squamous and metaplastic epithelia. As the transformation zone matures, this junction becomes impossible to delineate. Only the presence of nabothian follicles and gland openings hints at the original columnar origin of mature squamous metaplasia. **Cervical neoplasia almost invariably originates within the transformation zone.** Understanding squamous metaplasia is the key to understanding the concepts of the cervical transformation zone and cervical carcinogenesis (Fig. 8.3).

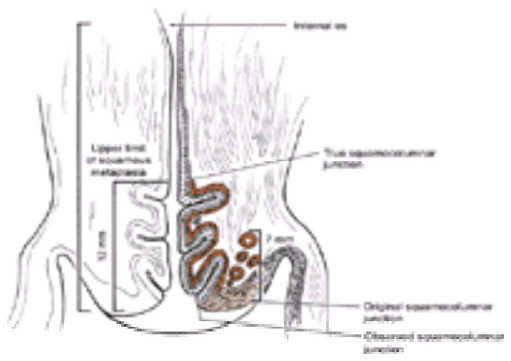

Figure 8.3 The anatomy of the transformation zone.

Cervical squamous metaplasia is a dynamic process of squamous maturation whereby columnar epithelium is replaced by squamous epithelium in response to chronic injury caused by the vaginal acidity. Squamous metaplasia is a permanent process but is not continuous. It occurs in “spurts,” with greatest activity during fetal life, after puberty, and during the first pregnancy. The process begins with proliferation of activated reserve cells under the surface of tips of columnar villi. This produces a six- to eight-cell, multilayered, undifferentiated, immature squamous metaplastic epithelium.

During the maturation phase, the columnar villi fuse, losing the distinctive appearance of columnar epithelium and producing a myriad of cytologic, colposcopic, and histologic appearances. The process is unidirectional but intermittent and may arrest at any stage. The process fluctuates in response to hormonal influences but ultimately produces a mature, glycogenated squamous epithelium. The presence of a subepithelial inflammatory infiltrate in biopsy specimens of immature squamous metaplasia may lead to a histologic misdiagnosis of *chronic cervicitis*. The presence of such inflammatory white cells is a normal part of the metaplastic process and is not a response to an infectious organism. A histologic diagnosis of “chronic cervicitis” is often misleading and should not be accepted as a satisfactory explanation for an abnormal Papanicolaou (Pap) smear (Fig. 8.4).

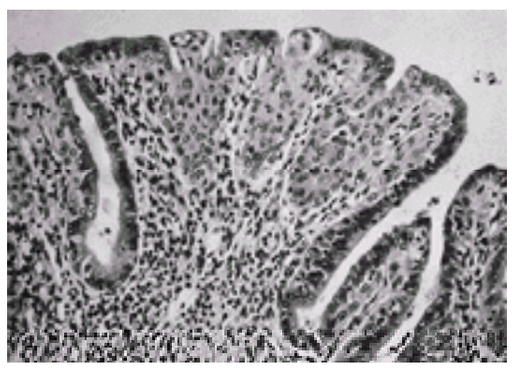

Figure 8.4 Histology of immature squamous metaplasia (chronic cervicitis).

If the new squamocolumnar junction is seen in its entirety in the absence of premalignant disease, the incidence of squamous disease above or cephalad to the new squamocolumnar junction is virtually nil. Thus, if the new squamocolumnar junction is seen in its entirety, the colposcopic examination of the cervix is described as *satisfactory*. If the new squamocolumnar junction is not seen in its entirety, the colposcopic examination is described as *unsatisfactory*. The transformation zone further defines the distal limit of high-grade glandular intraepithelial neoplasia, the precursor lesion to invasive adenocarcinoma of the cervix.

Upper Limit of Squamous Metaplasia

The new squamocolumnar junction is an unstable boundary. Serial colposcopic assessments of the cervix frequently show the new squamocolumnar junction to have moved cephalad. Careful colposcopic assessment of columnar villi immediately above the new squamocolumnar junction reveals opaque, opalescent tips and early villous fusion (Fig. 8.5). Histologic study of colposcopically directed biopsy specimens reveals reserve cell hyperplasia and early immature squamous metaplasia occurring in epithelium, which appears colposcopically columnar. This early immature squamous metaplasia can extend as far as 10 mm above the new squamocolumnar junction.

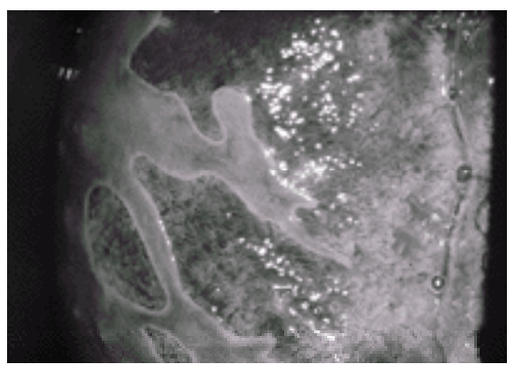

Figure 8.5 Colposcopy of immature squamous metaplasia.

The immature metaplastic epithelium cephalad to the new squamocolumnar junction is not included in the modern definition of the transformation zone but represents the epithelium at greatest risk for future neoplastic transformation. During dynamic phases of metaplasia, occurring particularly with puberty and the first pregnancy, the immature metaplastic cells are actively phagocytic (35). The most critical phase is the initiation of squamous metaplasia at puberty and in early adolescence.

Age of coitarche is an important epidemiologic variable in determining risk of cervical neoplasia (37,38). **The lifetime risk for development of cervical cancer is increased 26-fold if age at first intercourse is within 1 year of menarche, as opposed to 23 years of age or older** (38). Potential carcinogens in the vaginal environment at times of active metaplasia can deviate early metaplastic transformation along a neoplastic pathway. The duration of this metaplastic instability can be very short, and the timing of exposure of the cervix to a potential mutagen significantly influences the risk of subsequent neoplasia (39). Mature metaplastic epithelium exposed to the same mutagen is at less risk of neoplastic transformation.

Human Papillomaviruses and Cervical Neoplasia

In 1995, the World Health Organization's International Agency for Research on Cancer convened a consensus panel (IARC Working Group, 1995) to examine the evidence implicating specific sexually transmitted types of HPV in the causation of cervical neoplasia (40). Extensive molecular biologic and epidemiologic research confirms certain HPV types to be carcinogenic in humans (41,42,43,44,45,46 and 47). Cervical infection by specific HPV types is a precursor event in the genesis of cervical cancer (47). The magnitude of the association between HPV and cervical cancer is higher than the association between smoking and lung cancer. Cervical cancer has a specific and exclusive viral etiology, with the strength of the association similar to that for the association between the chronic carrier state of hepatitis B infection and the development of hepatocellular carcinoma (40). This is in contrast to the various statistical but spurious associations between cervical cancer and other sexually transmitted pathogens.

Taxonomy and Biology

Papillomaviruses are small, nonenveloped, double-stranded DNA viruses encased in a 72-sided icosahedral protein capsid. The HPV genome consists of circular, double-stranded DNA of approximately 7,900 nucleotide base pairs. Papillomaviruses are a divergent group of evolutionarily related viruses with similar biologic characteristics but enormous differences in species specificity, site of predilection, and oncogenic potential (48). Over 70 types of HPV have been sequenced (49,50 and 51). In addition to papillomaviruses that infect only humans, there is a large number of other species-specific papillomaviruses affecting other mammalian species, including cattle, horses, sheep, dogs, rabbits, monkeys, pigs, and deer.

The genome is usually maintained as a viral episome, independent of the host cell genome, in the nucleus of infected cells. In some high-grade CIN lesions, and more frequently in cervical cancer, HPV genomes are covalently bonded or integrated into the host chromosomes (52). This integration event occurs at random within the host cell genome but is highly specific in relation to the viral genome, involving the *E1* and *E2* genes with important consequences for regulation of viral gene expression (53,54) (Fig. 8.6). The late genes, *L1* and *L2*, the sequences of which are highly conserved among all papillomaviruses, encode the common capsid proteins. These viral proteins reflect late gene expression of the virus and are exclusively present in productive infections occurring in differentiated keratinocytes (55).

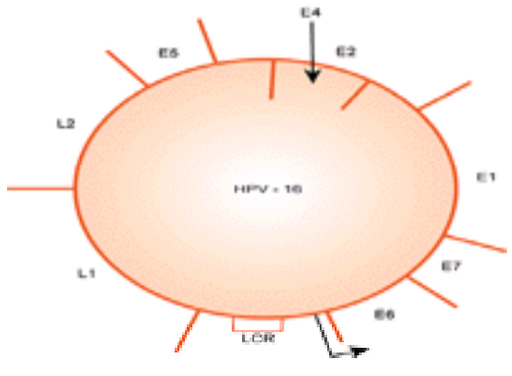

Figure 8.6 Schematic representation of the human papillomavirus genome.

The *E6* and *E7* genes code for multifunctional proteins that interfere with cell growth. The proteins encoded by the *E6* and *E7* genes of high-risk HPV types, particularly HPV 16 and 18, are directly involved in cellular transformation in the presence of an active oncogene (56). E6 and E7 proteins can immortalize primary keratinocytes from cervical epithelium and can influence transcription from viral and cellular promoters (57). The activity of these viral oncoproteins results in genomic instability, leading to the malignant phenotype. **E6 proteins of high-risk HPV types bind the tumor suppressor protein p53** (58). This induces degradation of p53, removing the p53-dependent control of the host cell cycle (59,60,61 and 62). **The *E7* gene product is a nuclear phosphoprotein that associates with the product of the retinoblastoma gene (pRb), which is a tumor suppressor gene important in the negative control of cell growth** (63). The binding of high-risk HPV E7 protein releases the E2F transcription factors bound to pRb, leading to activation of genes involved in the progression of cells through G_1 into the S phase of the cell cycle. **Degradation of p53 by E6 and the functional inactivation of pRb by E7 represent the main mechanisms whereby expression of HPV E6 and E7 oncoproteins subverts the function of the negative regulators of the cell cycle, which are vital in the maintenance of the stability of the cellular genome.**

The HPV *E5* gene product is a small protein bound to the cellular membrane that synergizes with epidermal growth factor in stimulation of epithelial cell proliferation (51). The products of the *E2* gene are involved in transcriptional regulation of the HPV genome. The process of HPV integration into the cellular genome, which occurs in some high-grade CIN lesions and most invasive cervical cancers, disrupts the *E2* gene. This results in increased levels of *E6* and *E7* expression, correlating with increased immortalization activity (64,65 and 66).

Human Papillomavirus Type–Specific Disease Pattern

Differing genomic nucleotide sequences of specific HPV types are responsible for the specific anatomic tropism of each HPV type. The genital HPV types transfect the mucous membranes of the genital tract most efficiently, but may also be present in the keratinized epithelium of the vulva, perineum, penis, and anorectal areas. Genital HPV types are also occasionally associated with oropharyngeal, conjunctival, and subungual lesions. Approximately half of the known HPVs have been isolated from genital epithelia. **The genital HPV types are divided into groups based on the frequency of association with malignant tumors and presumed oncogenic potential. Four viral types are considered to be high-risk (HPV's 16, 18, 45, and 56); eleven are of intermediate risk (HPVs 31, 33, 35, 39, 51, 52, 55, 58, 59, 66, and 68), and eight are of low risk (HPVs 6, 11, 26, 42, 44, 54, 70, and 73)** (67,68,69,70,71 and 72).

Low-risk HPV types, particularly HPVs 6 and 11, are associated with condylomata acuminata of the genital tract in both sexes. HPV 6 and 11 are also detected in low-grade cervical lesions (exophytic condylomata acuminata, subclinical HPV infection, and CIN 1). It was previously believed that these HPV types caused most low-grade cervical lesions, but HPVs 6 and 11 are found alone in only 15% of such lesions. “Mixed infection” with both “low-risk” and “high-risk” HPV types occur in 2% to 10% of women with CIN (30,32,73). Using more reliable HPV detection techniques, not a single cervical cancer has been shown to be associated with low-risk HPV types, and HPVs 6 and 11 in particular. These viruses do not appear to induce malignant transformation; they are unable to integrate into the human genome. The E6 and E7 proteins of “low-risk” HPV types only weakly bind p53 and pRB and thus do not immortalize keratinocytes *in vitro.*

Human papillomavirus 16 is the HPV type universally detected with greatest frequency in high-grade intraepithelial neoplasia and invasive cancers. HPV 16 is associated with 50% of cervical squamous cancers (72,74,75) **and over 30% of adenocarcinomas** (76). **It is present in over 80% of high-grade cervical, vaginal, vulvar, perianal, and penile preinvasive lesions.** It is detected in over 30% of low-grade cervical lesions, 40% of subclinical vulvar HPV infections, and 10% of genital condylomata acuminata, particularly the recalcitrant lesions (67,68,69,70 and 71). HPV 18 is the second most common (25%) HPV type in invasive cervical cancer, but is uncommon (5%) in low-grade cervical lesions. The association of HPV 18 with aggressive adenocarcinomas, particularly in younger women, and the underrepresentation of this viral type in preinvasive lesions have raised concerns that HPV 18 may be associated with “rapid-transit” cancers that escape reliable cytologic detection (77,78). Although this remains a controversial issue, epidemiologic and molecular data support the hypothesis (79,80). HPV 18 DNA is detected 2.6 times more frequently in invasive cervical cancers occurring within 1 year of a negative smear (78). Viral DNA integration occurs more frequently (96%) in cancers associated with HPV 18, 45, and 56 than in those associated with HPV 16, 31, 33, and 35 (53). Human keratinocyte grafts transfected with HPV 18 produce tumors in nude mice earlier than HPV 16–transfected grafts (65). The average age of patients with HPV 18–containing cancers is 8 to 12 years younger and recurrence rates are higher (45% vs. 16%) than for patients with HPV 16–containing cancers (81). A study by Hildesheim et al. (82) from the U.S. National Cancer Institutes did not support a strong association between HPV 18 and rapid-onset cancer, although a nonsignificant 1.6-fold increase in risk was reported.

Human Papillomavirus and Cervical Cancer: A Causal or Casual Association

Although the true prevalence of cervical HPV infection is unknown, it is the most common sexually transmitted infection, with over 60% of sexually active women younger than 35 years of age exposed (83). The basal cells of the cervical epithelium are inoculated with the virus at sites of microtrauma. Transcription and translation of viral DNA and synthesis of viral-specific proteins follow. Regulatory proteins control viral gene expression and transforming proteins induce conducive host cell functions. The virus often colonizes diffusely within the commonly derived cervical and lower genital tract epithelium.

Specific HPV types can infect the developing immature metaplastic cells of the cervical transformation zone. Mature squamous metaplastic epithelium is at minimal risk of neoplastic transformation. Exposure to specific high-risk HPV types, in the presence of cofactor activity, may deviate the metaplastic process along a neoplastic pathway (64,66,84). Disease expression begins at the new squamocolumnar junction. The initial abnormality produced is usually a low-grade cervical lesion. Such lesions represent a heterologous mixture of genuine cancer precursors and benign HPV infections (70,71 and 72).

There are no reliable morphologic predictors of clinical behavior. On colposcopic assessment, the occurrence of the lesion in immature components of the transformation zone and the size of the lesion may correlate with risk of progression. **Virologic probes to detect high-risk HPV types have been demonstrated to differentiate lesions at increased risk for progression to high-grade disease** (85,86,87,88 and 89). **Persistence of high-risk HPV types is a major risk factor for the development of high-grade CIN** (29,32,33). **Most HPV infections are transient, usually disappearing within several months to 2 years** (29). **Persistence of HPV infection is more common among older women** (29) **and when associated with oncogenic HPV types and high levels of HPV DNA** (89). **Only persistent HPV infection of the cervical epithelium appears to trigger neoplastic progression. The reported progressive potential of LGLs is small but definite, varying from 12% to 33% depending on selection criteria, cytologic or colposcopic surveillance, and the inclusion of biopsy in patient selection and follow-up** (18,19,85,88).

High-grade lesions are a homologous population of aneuploid lesions, mostly associated with oncogenic HPVs, and are genuine cancer precursors. Most cervical abnormalities do not transform to invasive cancer. The transit time to invasive cancer is variable, taking as little as 12 to 18 months or as long as several decades.

Cervical neoplasia can be viewed as the result of a complex interplay between a “seed,” that is, high-risk HPV types, and a “soil,” that is, the immature, metaplastic epithelium of the cervical transformation zone (Fig. 8.7). Modern epidemiologic research parallels the convincing laboratory evidence supporting a central, causal role for specific HPV types in the etiology of cervical neoplasia. HPV is necessary for tumor induction, maintenance, or both. The persistence of viral DNA in malignant tumors and derived cell lines and the active transcription of viral DNA in premalignant and malignant cells strongly suggest a role in maintenance of the malignant state. HPV infection alone is necessary but not sufficient to induce carcinoma in an immunocompetent host. HPV infection with oncogenic viral types is much more common than cervical neoplasia, indicating the necessity of cofactors in the process of cervical carcinogenesis.

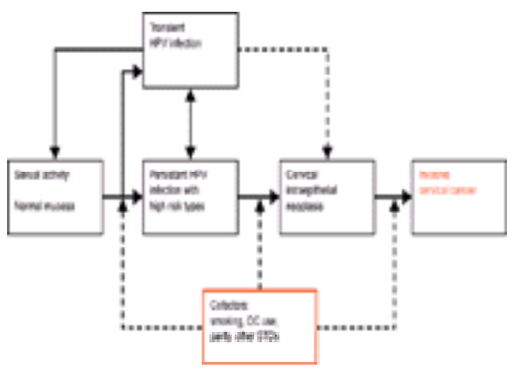

Figure 8.7 “Seed, soil, and nutrient” model for cervical carcinogenesis.

Cofactor Interaction with Human Papillomavirus

Plausible cofactors in cervical and lower genital tract carcinogenesis include the use of tobacco products, infection by other microbial agents, specific vitamin deficiencies, hormonal influences, and immunosuppression.

Cigarette Smoking **Cigarette smoking has been demonstrated to be a risk factor for cervical and vulvar carcinoma** (90,91,92,93,94,95 and 96). **The detection of breakdown products of cigarette smoke, including nicotine, cotinine, hydrocarbons, and tars, in cervical secretions of smokers and the demonstration of mutagenic activity of these products in cervical cells similar to that observed in lung cells, point to an important role for these compounds in cervical carcinogenesis** (94,95).

Cigarette smoking influences epithelial immunity by decreasing the numbers of antigen-presenting Langerhans cells in the genital epithelium (97,98). Cervical HPV infection and CIN are associated with diminished numbers of intraepithelial Langerhans cells (97,98). Such local immunologic depletion could favor virus persistence, contributing to malignant transformation. Cigarette smoke concentrates have been demonstrated *in vitro* to transform HPV-16–immortalized endocervical cells (99), although no increased risk of adenocarcinoma has been identified in association with use of tobacco products. Passive exposure to the cigarette smoke of others has also been shown to increase the risk of cervical cancer (96). The increased risk is as strong as that observed in association with personal cigarette smoking. The high levels of nitrosamines inhaled in passive smoking may be relevant.

Infection by Other Microbial Agents Genital HPV infection and cervical neoplasia are more common among individuals who have had multiple sexual partners or whose partner has had multiple sexual partners (90,100,101). An increased incidence of other sexually transmitted diseases has been reported in association with genital HPV infection and cervical neoplasia. Disruption of epithelial integrity and reparative metaplasia associated with acute cervicitis due to *Chlamydia trachomatis, Neisseria gonorrhoeae*, herpes simplex virus (HSV), or *Trichomonas vaginalis* may increase susceptibility to genital HPV infection. No clear picture has emerged from epidemiologic studies addressing these associations. The concept that HSV and HPV may act as syncarcinogens (102) has not been supported by epidemiologic studies. However, there is experimental evidence that segments of HSV-2 can transform HPV-immortalized cells (103).

Sex Hormonal Influences Condylomata acuminata increase rapidly in size and number in pregnancy. This could suggest that maternal estrogen status is permissive for HPV replication, although it may reflect the immunosuppressive effect of pregnancy. Increased detection of HPV DNA in cervical cytologic samples in pregnancy, including detection of oncogenic HPV types in up to 27% of pregnant women, suggests hormonally induced active viral replication (104,105). CIN and cervical cancer are more frequently found in women with increased parity (106), and in women on oral contraceptives independent of sexual activity (90). There has been no demonstrable clinical value to ceasing oral contraceptives in the management of HPV associated disease.

Exogenous and Endogenous Immunosuppression Iatrogenic induction of immunosuppression in renal transplant recipients increases the rate of CIN to 16 times that of the general community (107). The risk of CIN and cervical cancer is increased in human immunodeficiency virus–infected women, and failure rates of treatment for preinvasive lesions are increased (108). Systemic immune suppression from diseases such as Hodgkin's disease, leukemia, and collagen vascular diseases are associated with an increased incidence and recalcitrancy of HPV-associated disease.

Most cancers have a multifactorial etiology. The consistent association between genital HPV infection and cervical neoplasia argues that specific HPV types play the pivotal role in cervical carcinogenesis. The development of HPV vaccines is an important research initiative. Therapeutic vaccines against HPVs are based on the E6 and E7 proteins of the high-risk HPV types (109). **Prophylactic vaccines directed against the late proteins, L1 and L2, afford complete protection against papillomavirus infection in animals** (110). Such vaccines may eventually prevent HPV infection.

Screening for Cervical Neoplasia

Incidence and mortality rates for cervical cancer in the United States have steadily decreased since the 1950s (111). **Although the incidence of cervical cancer in Western countries was beginning to decline before the introduction of screening efforts, the significant decreases in cervical cancer incidence and mortality can be largely attributed to the success of widespread screening** (112,113,114,115,116,117,118 and 119). **The Pap smear is widely recognized as the most cost-effective cancer screening test yet devised and serves as a model for screening for other malignancies.**

A cohort effect for cervical cancer incidence and mortality has been clearly demonstrated (120). Women who entered their early reproductive years at times of great social upheaval, such as during World Wars I and II, remained at high risk for cervical neoplasia all their lives. Women in their early reproductive years in the two decades after the end of World War II, a period of reversion to very traditional sexual and social mores in many Western countries, appear to have been at low risk for development of cervical cancer. Reports of an increasing incidence of cervical cancer in young women in many Western countries since the 1970s suggest the effects of the introduction of risk factors to younger generations with different timing and levels of impact in different countries (121,122 and 123). Increases in cervical cancer incidence and mortality in young women occur against a background of dramatic increases in the diagnosis of preinvasive cervical disease.

Test Performance Characteristics of Cervical Cytologic Screening

The expectation of women, particularly in the United States and other developed countries, is that the Pap smear is an almost infallible screening test. From the inception of cervical screening, it has been accepted that Pap smear screening decreases the incidence and mortality of cervical cancer and that strict adherence to accepted screening protocols prevents the development of most, but not all, cervical cancers. However, the accuracy of the Pap smear was never tested in a prospective, double-blinded study and there has been no objective statistical analysis of the optimal performance of the test. Only relatively recently has the accuracy of the Pap smear been questioned (124), although it has long been apparent that it has a definite false-negative rate for invasive cancer and its precursors (125,126,127,128,129,130,131,132,133,134,135 and 136).

Sensitivity of Cervical Cytologic Screening

The sensitivity of cervical cytologic methods in the detection of cervical neoplasia is reported to range from 50% to 98% (137,138 and 139). Much of this discrepancy arises from the choice of illogical standards of reference. Many authors compare detection rates of an initial smear with the results of subsequent smears from the same patient. Such studies give insight into the reproducibility of the test but cannot be used to infer true sensitivity. Validity requires an independent standard of reference, preferably histologic study of colposcopically directed biopsies. Sensitivity levels reported by experts under research conditions are not reproduced in routine clinical practice. **Reasonable test performance using a competent laboratory results in false-negative rates of 15% to 30% for HGLs (CIN 2 to 3)** (124,138,139). **False-negative rates for invasive cervical cancer can be even higher, approaching 50% in some series, because of obscuring effects of blood, inflammatory exudate, and necrotic debris. In Western countries, although many women in whom invasive cancer develops have never been screened, up to 50% have been screened but still develop cancer** (129,131,133,135,136). This occurs more frequently among younger women with invasive cancer and reflects the inherent suboptimal sensitivity of cytologic screening (Fig. 8.8).

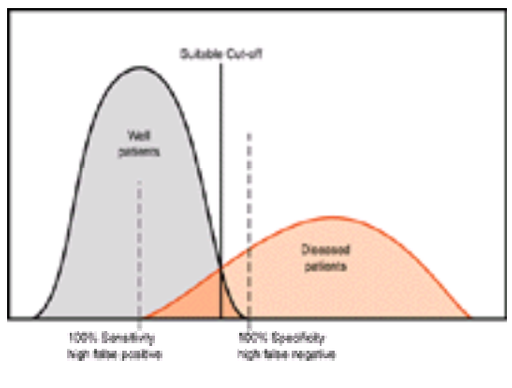

Figure 8.8 Sensitivity and specificity of screening test as reciprocal ratios.

A false-negative cytologic result occurs when the smear report does not predict the presence of any grade of cervical neoplasia. This consists of “true” false-negative results (70%) and laboratory errors (30%) (132,133). True false-negative smears are free of abnormal cells, even on review of the slide, in the presence of histologically proven cervical disease. The main factors contributing to the false-negative rate are (a) specimen collection, (b) laboratory error, and (c) deficiencies in laboratory quality assurance mechanisms.

Specimen Collection The accuracy of cytologic diagnosis is highly sensitive to sample-to-sample variation in number of cells per smear. The quality of sample taking is the major factor contributing to this variability. Although most discussion concentrates on laboratory error as the major contributing factor to the false-negative rate of cytologic screening, quality of specimen collection is more important. The cervix may desquamate unpredictably. A large, four-quadrant HGL may fail to provide representative cells despite conscientious sampling, and this may occur on serial sampling. Although it is impossible to remove this source of false-negative screening, a number of steps, from patient education to improved sampling technique, can optimize sample collection.

The patient should be informed to refrain from douching or using tampons or intravaginal medications for at least 48 hours before the scheduled examination. She should also avoid intercourse for 48 hours before the visit and should reschedule if menstrual bleeding occurs. Best results are obtained by paired use of the Ayre's spatula and cytobrush or sampling devices that adequately sample both endocervix and ectocervix. Because virtually all preinvasive lesions arise within the transformation zone near the new squamocolumnar junction, sampling of the transformation zone should be performed first. The endocervical canal is then sampled by inserting the cytobrush no further than the length of the brush and rotating no more than 180 degrees to minimize bleeding. The samples should be smeared immediately onto separate slides, or together on a single slide and fixed promptly to avoid air drying. The single-slide technique, in which the material from the Ayre's spatula is first placed on one side of the slide and then the brush sample is rolled alongside, is preferable because it saves laboratory materials and time without diminishing detection rate.

Laboratory Error Much negative attention has focused on laboratory error as the major contributing factor to errors in cervical cytologic testing. One third of false-negative smear reporting is attributable to laboratory error (124,132,138). In response to medical and media pressure to address this problem, cytopathologists have tended to broaden the cytologic criteria that define abnormalities, particularly those related to the prediction of LGLs. This has resulted in a significant increase in the number of smears reported as showing minor abnormalities. The effect of this has been to decrease the specificity of cytologic methodology without significantly increasing the sensitivity of the test for HGLs and cancer, because many women with minor smear abnormalities have no disease present on the cervix (140,141), particularly in the perimenopausal age group (142,143).

Quality Assurance Since the early 1990s, cytology laboratories have been required to introduce comprehensive quality assurance mechanisms; and since 1990, laboratories in the United States have been required to rescreen 10% of randomly selected negative cases. This strategy has been of uncertain value because it provides limited assurance of quality given the relatively low prevalence of HGLs and cancer. It also has directly increased the cost and evaluation time for cervical smears. The Health Care Financing Agency has restricted the number of cervical smears that a cytopathologist can evaluate to 80 slides per day.

Specificity of Cervical Cytologic Screening

Historically, the primary aim of cervical screening was the detection of clinically occult cervical cancer. High specificity was required at the cost of reduced sensitivity. The recognition that cytologic screening prevents cervical cancer by detection of preinvasive disease has shifted this balance, favoring increased sensitivity (124). Cytologic criteria for HGLs and invasive cancer were formulated when specificity was demanded and competent laboratories operate with a very low false-positive rate, usually between 2% and 5%, for the diagnosis of high-grade disease (144). Clinicians must be extremely cautious in dismissing an unexplained high-grade cytologic report. The specificity of cytologic screening, which traditionally supported the claims of efficiency for the test, has been eroded by cytologic overcall of low-grade disease (140,141,142 and 143). Colposcopic assessment of women with low-grade cytologic abnormalities reveals no disease in as many as 30% of cases (141,145).

Modern Cytologic Terminology: The Bethesda System

In December, 1989, a multidisciplinary workshop was convened at the United States National Cancer Institutes (Bethesda, MD) to address the current “diagnostic chaos” in cervical cytology reporting through the development and introduction of a standardized reporting system (Table 8.1). Of paramount importance was the need to communicate to clinicians the cytologic findings in unambiguous terms that were clinically relevant. It was also intended to facilitate peer review and quality assurance in both laboratories and clinical practice. It was widely perceived that the historical Papanicolaou classification of cytologic abnormalities did not reliably communicate clinically relevant information, did not reflect current understanding of the etiology and natural history of cervical/vaginal neoplasia, and had no equivalence in histopathologic terminology. Since initial publication, the Bethesda system has undergone review and modification (27,28). It has been widely adopted in cytologic laboratories in the United States and abroad.

Table 8.1 The 1991 Bethesda System

A cervico-vaginal smear report using the Bethesda system has three components: (a) a description of smear adequacy; (b) a general classification (i.e.,“within normal limits” or “not within normal limits”); and (c) description of cytologic abnormality. Abnormal morphology that may represent preinvasive squamous disease falls into three descriptive categories: atypical squamous cells of undetermined significance (ASCUS), LSIL, and HSIL.

Atypical Squamous Cells of Undetermined Significance

In a deliberate attempt to reduce confusion and unnecessary colposcopic referrals associated with the previous Papanicolaou class II or “atypical” category, the Bethesda system introduced a purposely restricted ASCUS category (146). The previous class II smear included a wide range of cytologic changes from reactive, reparative, and inflammatory atypia to koilocytotic atypia. In the Bethesda system, reactive and reparative changes are classified as “within normal limits,” as are inflammatory changes associated with a specific pathogen other than HPV. Smears with cytologic changes consistent with HPV infection, koilocytotic atypia in particular, but without evidence of CIN are combined with CIN 1 (mild dysplasia) as LSIL. **The ASCUS category includes only smears that are possibly abnormal but cannot be definitely classified as reactive or neoplastic** (147). **This category represents the limitations of the light microscope in precisely defining uniform diagnostic criteria for premalignant disease and in predicting the association between certain cytologic appearances and HPV infection, CIN, and cervical cancer.** The ASCUS category represents abnormal cytologic findings that are truly of uncertain significance.

The frequency of ASCUS smear reporting is often viewed as a crude indicator of quality assurance within laboratories. **With recent attempts to standardize diagnostic criteria, the rate of ASCUS reporting should be 3% to 5%** (148). Reporting rates above this reflect overcall of benign reactive, inflammatory, and reparative changes, often in response to medicolegal pressure, resulting in unnecessary colposcopic referrals.

Even when rigorous cytologic criteria are used for the ASCUS report, proper clinical management remains controversial. As many as 70% of women with ASCUS smear reports have no cervical lesion identified on colposcopic examination (141,145), 20% to 40% have associated CIN, and high-grade preinvasive disease (CIN 2 or 3) is diagnosed in 5% to 15% of cases (140,141,149,150). This has led to both international criticism of the ASCUS category and attempts to refine the category further by the use of the descriptors “ASCUS: favor reactive” and “ASCUS: favor dysplasia.” The clinical reproducibility of this modification remains uncertain. Although a rare event, an ASCUS smear report conveys a greater risk of being associated with occult invasive cancer (0.1%) than does an LSIL smear report.

The recommended clinical response to the ASCUS smear report is to repeat the smear in 6 months. The safety of this response lies in the rarity of invasive cancer in the presence of an ASCUS smear report and the probability that an HGL, if present, will be detected by serial testing before invasion occurs. Evaluation of the accuracy of repeat cytologic testing in follow-up of atypical and low-grade smears reveals a wide range of false-negative reporting for existing high-grade disease, from 24% to 83% (140,150,151,152 and 153). The emotionally charged and complex interplay of false-negative follow-up cytologic testing, patient compliance difficulties, and delayed diagnosis of cervical cancer in women with a previously abnormal smear have conspired to produce a highly litigious issue. For this reason, many clinicians perform colposcopy on all women with an ASCUS diagnosis. This potentially results in the inclusion of three times as many women into colposcopic triage as would be referred for assessment of LSIL and HSIL smears combined, without a commensurate impact on cervical cancer prevention and diagnosis. This has resulted in significant overservicing and overtreatment. Compelling arguments can be made for the use of intermediate triage tests such as HPV testing or cervicography in this context. This is discussed later in this chapter.

Low-Grade Squamous Intraepithelial Lesion

The Bethesda system combines cytopathic effects of HPV infection in the absence of CIN with cytologic abnormalities suggestive of CIN 1 (mild dysplasia) into the category of LSIL (25,27,147). The inclusion of HPV infection alone with CIN 1 in the LSIL category has been the subject of significant criticism. A broadening of cytologic criteria for the diagnosis of HPV infection occurred coincidentally with the introduction of the Bethesda system. The overdiagnosis of cytopathic effects of HPV infection in an attempt to improve the sensitivity of cervical screening has resulted in a substantial increase in the referral of normal women for colposcopy. This has often led to unnecessary biopsy and, at times, treatment.

Some screening programs have persisted in attempting to differentiate cytologic abnormalities consistent with HPV infection alone from CIN 1 (mild dysplasia). **In studies assessing interobserver and intraobserver reproducibility within the CIN continuum, the greatest lack of reproducibility is between HPV infection (koilocytotic atypia) and CIN 1** (154,155). This distinction is further blurred by additional morphologic findings, molecular virologic studies, and natural history studies. The clinical management of LSIL smears and low-grade cervical lesions remains a dilemma, but this predates the introduction of the Bethesda system. In current practice guidelines, patients with LSIL smear reports should be referred for colposcopy.

New Cervical Screening Devices

The limitations of traditional cytologic screening remain a source of much attention and concern, in particular the rate of false-negative results. A meta-analysis of 28 studies in which conventional cytology was evaluated for accuracy as a screening test reported a mean sensitivity and specificity of 58% and 69%, respectively (139). In 1998, Gay et al. (156) documented a false-negative rate for conventional Pap smears at the Mayo Clinic of at least 20%, with 62% of errors due to sampling. Although such data have been available from the earliest years of cytologic screening, since the late 1980s, considerable effort has gone into developing and refining new cervical screening technologies to improve the accuracy of screening for cervical neoplasia. Several such technologies are approved for clinical use and have been demonstrated to afford significant advantages in both screening and triage of minor cytologic abnormalities.

Liquid-Based, Thin-Layer Cervical Cytology

Sampling and preparation errors are responsible for 70% to 90% of false-negative Pap smears (130,132,133). Only a small proportion of the cytologic sample taken from the cervix is transferred to the slide, with up to 80% of cervical cells discarded with collection devices used in taking conventional smears. When abnormal cells are present on the slide, they may be difficult to identify and interpret in conventional smears because of the obscuring effects of air-drying artifact, excess blood, mucus, and inflammatory debris, or areas of thick cellularity. When previous negative Pap smears of women diagnosed with cancer of the cervix are reviewed, many are shown to have been falsely reported as negative. To address these issues, a new slide preparation method applied to gynecologic specimens has been developed. The cervical sample is taken in the routine manner using conventional sampling devices. Instead of smearing the sample onto a glass slide, the collection device is rinsed in a vial containing 20 mL of a buffered alcohol liquid preservative. The vial is transferred at ambient temperature to the cytology laboratory, where a slide is prepared from the cells in suspension for Papanicolaou staining and cytologic screening. The slide is prepared with a thin, well distributed layer of cells in a defined area on the slide. The most widely researched of these technologies is the *ThinPrep* method [Cytyc Corporation, Boxborough, MA; approved by the Food and Drug Administration (FDA) in May, 1996]. The slide preparation technique is automated. Slide evaluation is usually performed by cytotechnicians/cytologists, but automated image analysis technology also may be used (Fig. 8.9).

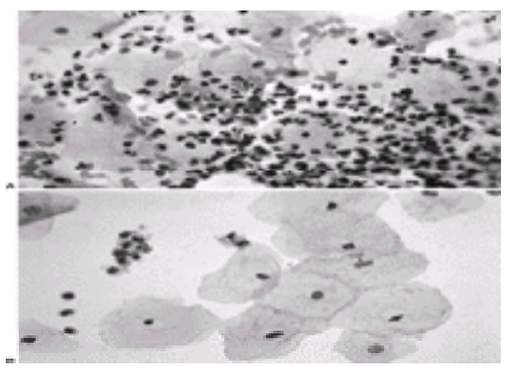

Figure 8.9 Comparison of (A) **standard Papanicolaou smear with** (B) **monolayer preparation.**

Studies assessing the *ThinPrep* method include both split-sample studies (157,158,159,160,161,162,163,164 and 165), where a conventional smear is first prepared and then the remainder of the specimen is rinsed into a vial for thin-layer preparation, and direct-to-vial studies (163,165,166,167,168 and 169), where the thin-layer sample is used as a replacement for routine cytology. These studies show a substantial increase in detection of biopsy-confirmed high-grade cervical abnormalities, ranging from 16% to over 100%. The same studies show significant decreases in “unsatisfactory” and “satisfactory but limited by” smear reports. Because “unsatisfactory” Pap smear reports are usually followed by repeat testing in 3 to 6 months, the cost of screening is doubled and unnecessary inconvenience and anxiety is incurred for patients, coupled with the risk of noncompliance. The *ThinPrep* Pap Test is FDA approved as a replacement for the conventional Pap smear on the basis that the test is significantly more effective than the conventional smear for the detection of low-grade and more severe cervical abnormalities in a variety of populations.

A study conducted for the U.S. Agency for Health Care Policy and Research by Duke University in partnership with the American College of Obstetricians and Gynecologists assessed the efficiency and cost effectiveness of new cervical cytologic screening technologies based on a meta-analysis of published research (170). This study reported that the *ThinPrep* Pap Test was the most cost-effective new cervical cytologic screening technology. It was calculated that the test would reduce cancer cases, deaths, and serious interventions such as hysterectomy by more than 50% with a lifetime incremental cost of 12% at 3-year screening intervals, and by 57% with a lifetime incremental cost of 14% at 2-year screening intervals. The report states “as expected, progressively better screening methods lead to fewer cervical cancer cases and deaths.”

Human Papillomavirus Testing

Improved HPV detection technology has corrected the major testing errors associated with archival *in-situ* hybridization and early polymerase chain reaction testing (171,172 and 173), which led to much skepticism in relation to the clinical applicability of HPV testing (174). **The relative risk association of HPV infection with invasive cervical cancer is 50 to 70.**

Case–control studies have established that women with CIN have detectable HPV DNA many times higher than control subjects (32,47). **HPV detection carries a minimum tenfold increase in risk of cervical neoplasia. The higher the grade of neoplasia, the greater the association with HPV** (43,44). **Over 90% of CIN lesions and 95% of invasive cervical cancers are attributable to HPV infection** (175). HPV detection in Pap smear–negative women predicts an increased risk of future detection of CIN (32,47). The risk of progression of low-grade HPV-related lesions may correlate with detection of specific HPV types (176). Such data argue a compelling case for augmenting cervical cancer screening programs by testing for cervical HPV infection. Potential clinical applications of HPV testing include primary screening, secondary triage of low-grade Pap smear abnormalities, particularly the ASCUS category, and selective use in certain clinical situations and in laboratory quality assurance (177).

Human Papillomavirus Testing in Primary Screening

Human papillomavirus testing may have an important role in primary cervical screening in developing countries where cytologic screening programs have been difficult to introduce and implement because of lack of trained cytotechnicians. The crude incidence rate of cervical cancer in some developing countries is as high as 100 cases per 100,000 women, compared with approximately 4 to 10 per 100,000 in developed countries. The simplicity of taking the sample, the stability of the transport medium, and the ability to automate the processing of the specimens suggest a possible role for HPV testing in primary screening in developing countries. For HPV testing to be implemented in developed countries for primary screening, it would be necessary to demonstrate that its use decreased the risk of interval cancers and allowed the screening interval to be increased. Several recent European studies assessing HPV testing in conjunction with cytologic testing have demonstrated significantly higher detection rates of high-grade CIN (178,179,180 and 181).

Human Papillomavirus Testing in the Triage of Minor Cytologic Abnormalities

An increasing volume of research demonstrates the potential value of HPV testing in the evaluation of equivocal and low-grade cytologic abnormalities (145,182,183,184 and 185). HPV testing has been demonstrated to be a cost-effective secondary triage test in the assessment of women with ASCUS smears. The modern HPV detection testing technology, such as Hybrid Capture II (Digene Diagnostics, Silver Spring, MD), has been demonstrated greatly to increase the detection of high-grade CIN in women with ASCUS smears compared with cytologic follow-up. The negative predictive value for the test is also high, which is of significance in decreasing costs associated with unnecessary colposcopic referrals.

Manos et al. (185) have reported the results of a large primary screening study conducted at Kaiser Permanente, Northern California. Of 46,009 women undergoing routine cervical screening, 995 women had an ASCUS Pap smear report, all of whom had repeat cytologic testing, HPV testing, and colposcopy performed. Of these women, 973 had both a definitive histologic diagnosis and HPV result. Sixty-five women (6.7%) had histologically proven CIN 2 or 3 or invasive cancer. HPV testing was positive in 89% of women with high-grade CIN, compared with 76% detection by cytologic testing alone. Referral for colposcopy after an ASCUS smear was not increased by HPV testing compared with repeat cytologic testing. An HPV-based algorithm, which included immediate colposcopy for HPV-positive women and repeat Pap testing for all others, provided an overall sensitivity of 96.9% for high-grade disease. The prevalence of high-risk HPV types associated with LGLs limits the applicability of HPV testing for the triage of women with LSIL smear reports.

Systematic Approach to Colposcopy

Colposcopy is the examination of the epithelia of the cervix, lower genital tract, and anogenital area using magnified illumination, after the application of specific solutions, to detect abnormal appearances consistent with neoplasia or to affirm normality. Integral to the procedure is targeting biopsies to areas of greatest abnormality. The characteristic colposcopic appearances that reflect normal tissues and disease states arise from magnification and illumination of the epithelium and capillaries in the underlying stroma. Correlation of the results of cervical smear cytologic testing, colposcopic appearances, and the histologic study of colposcopically directed biopsies represents the basis for appropriate patient management in the modern response to abnormal cervical screening.

Indications for Colposcopy

Colposcopy is most frequently performed in response to an abnormal cervical smear. Abnormal findings on adjunctive screening tests such as HPV testing and cervicography, particularly if performed in response to ASCUS smear reports, can also be the indication for colposcopy. If the cervix is clinically abnormal or suspicious on naked-eye examination, colposcopy is also indicated. Abnormal and unexplained intermenstrual or postcoital bleeding and unexplained, persistent vaginal discharge may also be assessed by colposcopy to exclude a neoplastic cause. Other indications include a personal history of *in utero* diethylstilbestrol (DES) exposure, vulvar or vaginal neoplasia, or condylomata acuminata, and possibly sexual partners of patients with genital tract neoplasia or condylomata acuminata.

There are no absolute contraindications to colposcopy. The examination may be deferred until after bleeding ceases for women who are menstruating. Acute cervicitis or vulvovaginitis should be evaluated and treated before colposcopy is performed unless poor patient compliance is anticipated. The colposcopic procedure is modified in pregnancy, with a less liberal use of biopsy in the absence of warning signs of high-grade disease or cancer and avoidance of endocervical curettage. Postmenopausal women who are not taking hormone replacement may benefit from a 3-week course of topical or oral estrogen before colposcopy. Patients should avoid use of all intravaginal products for 24 hours before the examination.

Initial Clinical Work-up

1. ***The patient should be prepared for the examination by a comprehensive explanation of the indication for colposcopy and a thorough verbal description of the procedure.***
2. ***A complete medical history and general examination should be obtained. A history of previous premalignant cervical disease or cervical treatment should be determined.*** History of endogenous or exogenous immune suppression is relevant. Social history of smoking or other “recreational” drug use should be obtained.
3. ***A clinical and speculum examination of the cervix, vagina, vulva, and perianal areas should be performed before the colposcopic examination.*** Squamous neoplasia may be multicentric (involving more than one genital tract site, i.e., cervix, vagina, or vulva) or multifocal (involving several areas at one site).
4. ***A bimanual pelvic and rectal examination should be performed, usually on completion of the colposcopy, to exclude clinically apparent coexistent gynecologic or pelvic disease.*** Uncommonly, abnormal cervical smears are caused by palpable malignancies of the endocervix, uterine body, adnexa, or bowel.

Locating the Source of Abnormal Cells

Colposcopy is performed in the dorsal lithotomy position with a drape covering the patient's legs. The cervix is visualized using a standard speculum. A repeat cervical smear, sampling ectocervix and endocervix, can be performed if required without compromising colposcopy. The colposcopic examination involves the application of three standard solutions to the cervix to determine the source of the abnormal cells in the cervical smear.

1. ***Normal saline is initially applied to remove obscuring mucus and debris, to moisten the cervix, and to examine the cervix unaltered by subsequent solutions.*** The two abnormal colposcopic findings detected after application of normal saline are *hyperkeratosis* (leukoplakia) and *atypical vessels.* Hyperkeratosis is a white, thickened epithelial area of the cervix (or lower genital tract) that is clinically apparent before application of acetic acid. Biopsy is indicated to exclude an underlying neoplastic process. Atypical vessels are the colposcopically apparent bizarre vascular abnormalities that occur in association with invasive cancer. Green-filter examination of the cervix enhances the angioarchitecture.
2. ***A 3% to 5% acetic acid solution is then liberally applied to the cervix using soaked swabs or a spray technique.*** A second application ensures an adequate time of at least 30 seconds for the acetic acid reaction to occur. The cervix should be viewed at low-power (2× to 5×) and at high power (10× to 15×). The abnormal colposcopic findings after application of acetic acid are acetowhite epithelium and abnormal vascular patterns. Abnormal vascular patterns, reflecting the underlying capillary distribution, are mosaicism and punctation. Tissue swelling associated with the initial application of acetic acid compresses subepithelial capillaries, rendering vascular patterns less distinct. As the acetic acid reaction fades, mosaicism and punctation become vivid against the whiter background.
3. ***Lugol's iodine (one-quarter strength) application to the cervix (if the patient is not allergic to iodine) is called Schiller's test.*** Normal ectocervical and vaginal squamous epithelium contains glycogen and stains mahogany-brown after application of iodine solution. Normal columnar epithelium and immature squamous metaplastic or neoplastic epithelium do not contain glycogen, are not stained by iodine solution, and appear mustard-yellow. Iodine solution application is considered an optional colposcopic procedure and is not uniformly performed. However, iodine staining is, at times, of great assistance in the detection of subtle high-grade cervical lesions. It is invaluable in the assessment of the vaginal mucosa.

Delineating the Margins of the Lesion

Once the source of abnormal cells in a cervical smear is located, the peripheral and distal margins of the lesion should be determined.

Distal Margin

The distal or peripheral margin of the lesion is usually readily identified. Occasionally, the lesion may extend onto the vaginal fornices, especially in the DES-exposed patient.

Proximal Margin

Delineation of the proximal or upper margin of the lesion requires the colposcopic visualization of the new squamocolumnar junction, which establishes the colposcopy as satisfactory or unsatisfactory. This determination has important implications for treatment. Failure accurately to delineate the position of the new squamocolumnar junction represents one of the most common colposcopic triage errors. An endocervical speculum may be helpful if the proximal margin is within the canal.

Endocervical Curettage

Endocervical curettage is performed to sample the nonvisualized portion of the endocervical canal. It is advocated to exclude an occult cancer in the canal and to exclude more high-grade CIN in the canal when colposcopy is unsatisfactory (186). With the increasing incidence of cervical adenocarcinoma *in situ* (AIS) and invasive adenocarcinoma, many of which are associated with squamous CIN lesions, endocervical curettage may provide a safeguard against missing such lesions (187).

The value of routine endocervical curettage, particularly when colposcopy is satisfactory, is controversial. When the entire new squamocolumnar junction can be visualized and 360 degrees of unequivocally normal columnar epithelium is seen on the ectocervix or in the distal endocervix, it seems reasonable to omit the routine endocervical curettage. A negative endocervical curettage from a patient with an abnormal smear and an unsatisfactory colposcopy does not exclude occult endocervical cancer, and excisional cone biopsy remains mandatory. When specifically indicated, collection of an endocervical sample using a cytobrush has been shown to be a more sensitive sampling device than endocervical curettage for endocervical squamous and glandular disease. Specificity, however, is decreased (188).

Colposcopically Directed Cervical Biopsy

Cervical biopsies should be directed to the most significant lesions. Multiquadrant lesions may require multiple biopsies. Any area suspicious for occult invasion must be carefully sampled. The most reliable method of ensuring the accuracy of targeted biopsies is to grade lesions by deriving a colposcopic score. Cervical biopsies should be taken through the colposcope. The colposcopic grading score of the lesions and the biopsy sites should be carefully recorded.

Documentation of Colposcopic Findings

The findings of the colposcopic examination should be carefully documented. The cervical diagram should accurately reflect the colposcopic findings, including colposcopic prediction of disease severity. Photodocumentation can be extremely valuable, assisting in accurate storage of clinical information, patient and clinician education, management decisions, and monitoring of prospective follow-up. A patient/laboratory results/management plan tracking log should be established and maintained to ensure appropriate patient care and follow-up. Modern computerized systems provide for many of these needs in a most effective manner.

The Abnormal Transformation Zone

If the transformation zone is deviated along a neoplastic pathway, epithelial and vascular alterations produce the characteristic morphologic appearances of the abnormal transformation zone. The colposcopic signs of the abnormal transformation zone are described in Table 8.2.

Appearance	Cause
Epithelial abnormalities	
Leukoplakia	Abnormal keratin production from an inflammatory, viral or neoplastic process Thickening of superficial epithelium in response to trauma
Acetowhite epithelium	Increased cellular and nuclear density Intracellular protein agglutination Abnormal intracellular keratins Intracellular dehydration
Vascular abnormalities	
Abnormal vessel patterns: mosaic and punctation	Alterations in the epithelial capillaries due to: 1. Normal metaplastic transformation 2. Capillary proliferative effect of human papillomavirus 3. Intraepithelial pressure created by expanding neoplastic tissue 4. Tumor angiogenesis factor
Atypical blood vessels	Tumor angiogenesis factor

Table 8.2 Colposcopic Signs of the Abnormal Transformation Zone

Squamous metaplasia, repair and regeneration, inflammation, and infection may all produce abnormal colposcopic transformation zone findings such as acetowhite epithelium and abnormal vessels. Significant changes in the hormonal milieu such as accompany pregnancy, oral contraceptive pill use, estrogen withdrawal, and estrogen replacement can produce abnormal colposcopic signs in the absence of cervical disease. Atypical vessels, considered one of the colposcopic hallmarks of invasive cancer, can also occur in association with benign conditions, including immature metaplasia, nabothian follicles, inflammation, radiation treatment, and granulation tissue.

No single colposcopic sign of the abnormal transformation zone permits differentiation of the normal transformation zone from the spectrum of cervical neoplasia. Greatest predictive accuracy is achieved when colposcopic assessment of the features of the abnormal transformation zone is performed using a modern colposcopic grading system.

Colposcopic Grading Systems

The basis of colposcopic management decision making is the process of cytologic–colposcopic–histologic correlation, with each component affording certain safeguards. **There are four basic colposcopic diagnoses: (a) normal, (b) low-grade disease (HPV infection/CIN 1), (c) high-grade disease (CIN 2 or 3), and (d) invasive cancer.**

Colposcopic grading systems have been developed to provide an objective, accurate, reproducible, and clinically meaningful prediction of the severity of CIN lesions based on discriminatory analysis of specific colposcopic signs (22,23,189,190,191 and 192). Significant subjectivity exists in both cytologic and histologic diagnoses. Formulation of a colposcopic diagnosis by use of a clinically robust and reproducible colposcopic grading system permits identification of discordance between laboratory diagnosis and clinical assessment. Historically, significant cervical neoplasia was managed by cold-knife conization and the clinical diagnosis was based on the histopathologic assessment of a large conization specimen. This traditional approach was associated with a significant rate of adverse fertility-related complications. Selective sampling of areas of most significant colposcopic abnormality and careful histologic review are pivotal to the modern management of cervical neoplasia.

Routine determination of a colposcopic diagnosis permits quality-control measures to be implemented in colposcopy (193). In the British Columbia colposcopy quality control program, the colposcopist is required to achieve an 80% accuracy rate in colposcopic–histologic correlation or receive remedial training in colposcopic assessment of cervical lesions. Colposcopic grading adds significantly to the safety of follow-up of LGLs, avoiding excessive biopsy and the attendant decrease in patient compliance, and permitting recognition of disease progression. In current colposcopic experience, the Reid Colposcopic Index represents the most reproducible and clinically valid means of standardizing the evaluation of cervical lesions (190,191 and 192) (Table 8.3).

Colposcopic Sign	Score		
	Zero Points	One Point	Two Points
Margin	Exophytic condylomas; areas showing a micropapillary contour Lesions with distinct edges Feathered, scalloped edges Lesions with an angular, jagged shape "Satellite" areas and acetowhitening distal to the original squamocolumnar junction	Lesions with a regular (circular or semicircular) shape, showing smooth, straight edges	Rolled, peeling edges Any internal demarcation between areas of differing colposcopic appearance
Color	Shiny, snow-white color Areas of faint (semitransparent) whitening	Intermediate shade (shiny, but gray-white)	Dull reflectance with oyster-white color
Vessels	Fine caliber vessels, poorly formed patterns	No surface vessels	Definite, coarse punctation or mosaic
Iodine	Any lesion staining mahogany brown; mustard-yellow staining by a minor lesion (in first three criteria)	Partial iodine staining; mottled patterns	Mustard-yellow staining of a significant lesion (an acetowhite area scoring 2 or more points for the first three criteria)

adapted from Reid R, Scalzi P. Genital warts and cervical cancer. VII. An improved colposcopic index for differentiating benign papillomaviral infections from high-grade cervical intraepithelial neoplasia. Am J Obstet Gynecol 1985;153:611–618.

Table 8.3 Scoring System for Deriving the Colposcopic Index

Reid Colposcopic Index The Reid Colposcopic Index uses four colposcopic features of premalignant cervical lesions to achieve predictive accuracy. The colposcopic index permits accurate differentiation of low-grade from high-grade disease. It is not designed to differentiate premalignant from malignant cervical neoplasia. The four colposcopic criteria used in the colposcopic index are (a) the margin of the lesion; (b) the color of the acetowhitening; (c) the type of vascular pattern, each assessed after application of 3% to 5% acetic acid solution; and (d) the iodine staining reaction, assessed after application of Lugol's iodine solution (one-quarter strength).

The four colposcopic signs are scored individually and sequentially. The value of these colposcopic signs is maximized by combining them into a weighted scoring system. Scores of 0, 1, or 2 are assigned for each criterion, as described in Table 8.3. A score of 0 points is indicative of HPV infection/CIN 1. CIN 1 to 2 lesions are assigned a score of 1 point, and a score of 2 points is suggestive of CIN 3. The total score is reported as a ratio, the denominator of which is constant at 8. The numerator is the score derived from adding the four scores derived from evaluation of the four colposcopic signs and fluctuates as the predictor of disease severity. Scores of 0 to 2 are predictive of LGLs (HPV infection/CIN 1; Fig. 8.10). Scores of 6 to 8 usually denote HGLs (CIN 2 to 3; Fig. 8.11). Scores of 3 to 5 represent an area of overlap between LGLs and HGLs. The overall predictive accuracy of the index exceeds 90% after a short training period. The colposcopic index permits a significantly more accurate colposcopic–histologic agreement than can be achieved by less systematic approaches to colposcopic diagnosis.

Figure 8.10 Colposcopy of low-grade cervical lesions showing acetowhite epithelium with fine abnormal vascular pattern.

Figure 8.10 Colposcopy of low-grade cervical lesions showing acetowhite epithelium with fine abnormal vascular pattern.

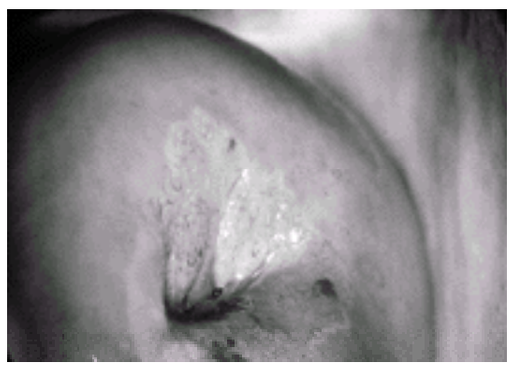

Figure 8.11 Colposcopy of high-grade cervical lesion showing dense acetowhite epithelium and coarse abnormal vascular pattern.

Colposcopic Warning Signs of Invasive Cancer

Although a rare event in many colposcopic settings, invasive cancer must not be missed and still remains the major challenge to the colposcopist. Clinicians working in oncology settings may over time acquire significant experience in the colposcopy of occult and overt cervical cancer. Although most invasive cancers are clinically apparent and do not require colposcopy for identification, early invasive lesions may be clinically occult. Exclusion of invasive cancer demands both a high index of suspicion and a knowledge of warning signs. Colposcopic warning signs are shown in Table 8.4.

1. Yellow, degenerate, friable epithelium particularly with contact bleeding
2. Irregular surface contour, particularly when occurring in a high-grade colposcopic abnormality (RCI score >6 points)
3. Surface ulceration or true "erosion," particularly when occurring in a high-grade colposcopic abnormality (RCI score >6 points)
4. Atypical blood vessels (coarse, varicose, bizarre subepithelial vessels with irregular caliber and nondichotomous branching or long, unbranched course)
5. Extremely coarse abnormal vascular patterns (i.e., mosaicism and punctation), especially with wide and irregular intercapillary distances and umbilication
6. Large, complex, high-grade lesions (RCI score >6 points) occupying three or four cervical quadrants
7. High-grade colposcopic lesions extending into cervical canal either >5 mm or beyond colposcopic view

RCI, Reid Colposcopic Index.

Table 8.4 Colposcopic Warning Signs of Invasive Cancer

Other warning signs for invasive cancer include:

1. Any cytologic evidence of possible squamous carcinoma, adenocarcinoma, or AIS or recurrent high-grade cytologic findings in a patient previously treated for CIN 3
2. Any histologic evidence of invasive cancer or CIN 2 or 3 in a tangentially sectioned punch biopsy in which the basement membrane cannot be adequately defined
3. High-grade cytologic abnormality in a postmenopausal or previously irradiated woman

Treatment of Cervical Intraepithelial Neoplasia

In 1965, Anderson (194) demonstrated that therapeutic conization afforded the same protection against eventual development of invasive cancer as did hysterectomy if close attention was paid to the margins of resection. In 1969, Kolstad and Klem (195) reported long-term follow-up data from Norway demonstrating that cone biopsy was as effective as hysterectomy in preventing progression of carcinoma *in situ* to invasive cancer. These landmark studies coincided with expanded use of colposcopy in the assessment of cytologic abnormalities and, in 1973, Stafl and Mattingly (23) demonstrated that colposcopically directed punch biopsies, taken by an experienced colposcopist, were as accurate as cone biopsy in obtaining a histologic diagnosis in women with abnormal cervical smears. This facilitated the use of physical modalities to destroy the abnormal transformation zone in selected patients. High primary cure rates with minimal morbidity have been reported for cryosurgery (196), electrocoagulation diathermy (197), and the carbon dioxide laser (198). Patient selection is based on a set of triage rules (Table 8.5). Diagnostic conization is performed for specific indications in which there remains a genuine risk of undisclosed invasive cancer.

1. Visualization of the entire new squamocolumnar junction, that is, 360 degrees of normal columnar epithelium seen with no significant disease extension within the endocervical canal
2. No colposcopic warning signs of invasive cancer
3. No cytologic or histologic evidence of invasive cancer
4. Concordance to within one degree of severity between the cytology and the histology of colposcopically directed biopsies
5. No evidence of high-grade disease on endocervical curettage
6. No cytologic or histologic suspicion of high-grade glandular neoplasia

Table 8.5 Triage Rules for Ablative Therapy for Cervical Intraepithelial Neoplasia

In the 1990s, loop electrosurgical excision procedures (LEEP) gained in popularity because of concerns regarding the occurrence of invasive cervical cancer in patients who have undergone ablative treatment (199). Invasive cancer has been reported after each of the ablative modalities (200). When cancer occurs after ablative therapy, it occurs within 12 months in 66% of cases and within 2 years in 90%. This suggests that a triage error was made in the initial assessment and invasive cancer was missed. Reports of a low incidence of misclassification of invasive cervical cancer or high-grade glandular neoplasia as squamous intraepithelial disease have raised concerns about the safety of ablation of high-grade squamous lesions (201,202 and 203).

LEEP allows for excision of the transformation zone with removal of a volume of tissue similar to that removed by ablative procedures, and with no greater morbidity. When the procedure is performed by an inexperienced operator, adequate histologic evaluation can be difficult because of diathermy artifact and orientation difficulties.

Treatment Modalities

The treatment modalities for preinvasive cervical disease are ablative procedures and include electrocoagulation diathermy, cryosurgery, and CO_2 laser, and excisional procedures, including cold-knife conization, CO_2 laser excision, LEEP, and hysterectomy.

Cryosurgery

Cryosurgery is a simple, effective, inexpensive, and relatively easy therapeutic option for treatment of selected patients with CIN. It was first introduced in 1968 and since then has been established as a cost-effective outpatient procedure that is well tolerated by patients. Cervical cryosurgery involves the destruction of the transformation zone and lesional tissue by cryonecrosis. Hypothermia is produced by the evaporation of liquid refrigerants. Compressed nitrous oxide (N_2O) is allowed to expand through a small jet, producing an iceball at the surface of a metal probe placed in contact with the surface of the tissues to be frozen. Crystallization of intracellular water results in cell death.

The machine must be checked before the procedure to ensure there is sufficient gas pressure in the N_2O tank. The most appropriate cryoprobe tip remains a matter of debate. Many surgeons prefer a larger flat tip, but the 19-and 25-mm minicone tips should be used. A water-soluble gel is used to coat the probe tip before the procedure. Temperatures achieved at the cryotip using N_2O are recorded at –65°C to –85°C. Cell death occurs in the range of –20°C to –30°C. The lethal zone during cryosurgery begins 2 mm proximal to the iceball margin, with the temperature at the margin of the iceball equal to 0°C. To ensure a 5-mm depth of freezing, a total lateral spread of freeze of 7 mm is required. For cervical cryosurgery, the probe must cover the lesion and the entire transformation zone.

If the transformation zone is large, successive overlap treatments are required, increasing the duration and discomfort of the procedure. Cryosurgery is therefore used mainly for smaller, ectocervical lesions. It is usually used for LGLs without extension to within the endocervical canal and without endocervical glandular involvement on colposcopically directed biopsies.

Technique The procedure is performed under colposcopic supervision without anesthesia. Prophylactic premedication with nonsteroidal antiinflammatory drugs 30 to 60 minutes before the procedure may reduce pain and cramping associated with prostaglandin release from dying cells. The procedure should not be performed in pregnancy or during the menstrual period. The procedure is performed as follows:

1. ***The cervix is exposed using a speculum and a careful colposcopy is performed to check the topography of the lesion and to ensure that the triage rules are fulfilled.***
2. ***A warm cryotip is chosen that best conforms to the topography of the cervix and a water-soluble gel is applied thinly to the tip.***
3. ***The cryotip is positioned at room temperature on the cervix with care taken to cover the entire lesion and the transformation zone.*** The probe must be clear of the vaginal walls. The procedure is initiated by activating a trigger on the cryogun. If the probe comes into contact with the vagina, the treatment is ceased and then reinitiated.
4. ***Crystallization begins on the back of the probe and proceeds until the iceball is seen to extend 7 mm laterally beyond the edge of the probe.*** This visual landmark is the indicator of the depth of the freeze (approximately 5 mm) and is the method for determining the duration of the procedure.
5. ***The probe is defrosted completely and then disengaged from the cervix.***
6. ***A freeze–thaw–freeze technique is then used.*** This technique was reported by Creasman et al. (204) to reduce the failure rate from 29% to 7%, although others claim similar results from a single freeze (205,206). The second freeze is not commenced until the tissues have visibly thawed from the initial treatment.

Patients experience a watery, malodorous, blood-tinged discharge for 2 to 3 weeks after the procedure. This can be decreased by debridement of the bullous, necrotic tissue using a ring forceps and gauze 48 hours after the procedure. The patient should abstain from vaginal intercourse and tampon use for 4 weeks after the procedure.

Primary cure rates in excess of 90% have been reported for cryosurgical management of CIN lesions (204,205,206,207,208,209,210,211,212 and 213). The larger the lesion, the lower the primary cure rate. Cryosurgery for large ectocervical lesions covering the ectocervix is associated with failure rates as high as 42%. Endocervical glandular involvement is reported to increase the failure rate from 9% to 27% (211,212 and 213). Decreasing cure rates with increasing severity of disease, specifically 94% for CIN 1, 93% for CIN 2, and 84% for CIN 3, have also been reported (213). This may in part reflect the increased size of HGLs, which more frequently occupy two or more quadrants of the cervix. Such lesions are best treated with other therapeutic modalities such as LEEP or CO_2 laser (Table 8.6).

Procedure Rates	*Technical Ease*	*Equipment Cost*	*Complication Rates*	*Primary Cure*
Cryosurgery	+++	+++	++	80%
Loop electrosurgical excision procedures	+++	++	+++	95%
Laser ablation	++	+	+++	95%
Laser excision	+	+	++	95%
Cold-knife conization	++	+++	+	98%

+, low; ++, medium; +++, high.

Table 8.6 Comparison of Therapeutic Modalities for Cervical Intraepithelial Neoplasia

Loop Electrosurgical Excision

Increasing numbers of women are being referred for colposcopy. Many of these examinations are now performed by providers who can dedicate only a limited amount of time and effort to colposcopy and who are less familiar with the colposcopic warning signs of occult invasive cancer. The potential for therapeutic mishaps with ablative procedures, particularly for HGLs, is perceived to have increased. Cold-knife conization is thought to be associated with increased morbidity, and CO_2 laser conization requires expensive equipment and advanced laser skills. To minimize the risk of failed detection of early invasive cancer and high-grade glandular neoplasia at the time of colposcopic triage, LEEP of the transformation zone has become a widely used and valuable therapeutic option. The equipment is relatively inexpensive and the surgical skills are readily acquired. The procedure combines the advantages of conservative ablative procedures in preserving cervical tissue with the safety of histologic assessment of the entire lesion.

Cartier originally developed an electrosurgical method for management of CIN using 5 × 5-mm rectangular, thin wire loops to sample and treat the cervix by removing the epithelium and underlying stroma in multiple 5-mm strips. The process was time consuming and thermal injury at the edge of the strips frequently compromised the specimen. Prendiville et al. (214,215) introduced larger loop electrodes, 1 to 2 cm in width and 0.7 to 1.5 cm in depth, for excision of the entire transformation zone, usually in a single pass. The combination of very thin wire loops and modern electrosurgical generators capable of delivering high powers (35 to 55 W) has allowed electrosurgical cutting with little associated thermal injury. The cutting is achieved by the generation of a steam envelope at the interface between the wire loop and the tissue that is laden with water. With correct technique, as the loop is moved slowly but purposefully through the tissue, the steam envelope is pushed through the tissue, separating it with minimal thermal conduction to surrounding tissue.

The technique for electrosurgical loop excision is as follows:

1. ***The cervix is visualized using a nonconductive nylon or plastic-coated speculum with suction attached.*** For parous patients, a nonconductive vaginal lateral wall retractor is advisable to improve access to the cervix and to minimize the risk of inadvertent injury to the vaginal side-wall.
2. ***The cervix is evaluated colposcopically to determine the distribution of the lesion and the transformation zone.*** The appropriate loop size is chosen. Lugol's iodine solution helps demarcate the outer margin of excision. The procedure is performed under colposcopic control.
3. ***The cervix is infiltrated with 4 to 6 mL of local anesthetic (1% to 2% lidocaine with epinephrine) using a dental syringe with a 27-gauge needle.*** The local anesthetic is injected as a slow subepithelial infiltrate at the 3, 6, 9, and 12 o'clock positions after a test dose of 1 mL is observed for side effects.
4. ***A grounding pad is attached to the patient's thigh with care taken to ensure proper adherence.***
5. ***The electrosurgical generator is set at an appropriate power setting for the size of loop chosen for the procedure, usually 35 to 55 W of either pure cutting or blended current.***
6. ***Suction is attached to the speculum.***
7. ***The specimen is excised by activating the generator with a foot pedal or hand switch with the loop 2 mm from the tissue.*** The loop is advanced perpendicularly into the cervix 2 to 3 mm lateral to the lesion and transformation zone to a depth of 5 to 7 mm and drawn across the cervix until 2 mm lateral to the opposite side of the transformation zone. The excised specimen is usually dome shaped, 5 to 6 mm deep at the lateral margins, and 7 to 10 mm deep in the center. This is almost identical to the volume of tissue ablated by the CO_2 laser. Larger lesions may require more than a single pass with the electrode. The central portion of the lesion should be excised first and remaining lesional tissue excised with additional passes. More peripheral CIN tissue can be destroyed with the ball electrode provided a directed biopsy is taken and the triage rules for ablation are fulfilled.
8. ***The base of the crater is lightly fulgurated using the 5-mm ball electrode with the electrosurgical generator at 40 to 60 W of coagulation current.*** This is intended to stop bleeding but not to char the tissue in the crater, which devitalizes a significant volume of tissue and increases the risk of postoperative bleeding and infection.
9. ***An endocervical curettage or sampling should be performed if one has not been previously performed.***
10. ***Monsel's solution is applied to the cervix to maintain hemostasis.***

Patients are advised to avoid intercourse, tampons, or douching for 3 weeks after the procedure. Strenuous activity is limited for 10 days to minimize the risk of secondary bleeding. A reddish-black discharge persists for 1 to 2 weeks posttreatment.

Complications are minimal, comparing favorably with those associated with CO_2 laser procedures. Postoperative bleeding occurs in 2% to 5% of patients. Postoperative infection is uncommon. Clinically significant cervical stenosis and cervical incompetence are rare complications, but the patient must be made aware of the possibility of such adverse reproductive sequelae. Cure rates are comparable with those achieved with CO_2 laser procedures, often in excess of 95% (214,215,216,217,218,219,220,221,222,223 and 224).

Electrosurgical loop excision offers several advantages over CO_2 laser ablation (225). The procedure is quicker and easier. However, ease of use carries an attendant risk of overuse. Patient acceptance is improved and intraoperative pain is decreased. The submission of the entire specimen for histologic study increases the probability that unsuspected cancer will be detected and not ablated. In many large studies of LEEP, the unsuspected invasive cancer and high-grade glandular disease rate has been as high as 1% to 2% (214,215,216,217,218,226,227,228 and 229).

Another potential advantage of LEEP is the ability to “see-and-treat” at one visit. This approach is justified for selected patients, particularly if compliance with follow-up visits is not certain. However, histologic study of loop-excised specimens removed at a single visit in a “see-and-treat“ approach, revealed no disease in 5% to 40% of specimens, particularly in young women referred with minor cytologic abnormalities (214,215,216,217,218,219 and 220).

CO_2 Laser Procedures

There are six physical and six surgical principles governing laser surgery for cervical and lower genital tract indications (230,231 and 232). The six physical principles are:

1. Choice of appropriate laser wavelength
2. Rapid delivery of the required energy dose
3. Choice of best temporal mode for the laser energy
4. Selection of appropriate power density
5. Selection of appropriate beam geometry
6. Use of intermittent pulsing to improve surgical control

The first three principles influence thermal conduction to surrounding tissue and hence the risk of thermal injury and scarring. The last three principles govern surgical control of the laser energy and thus the extent and pattern of tissue destruction or excision.

The six surgical strategies to control depth of destruction or excision and to delineate treatment margins are:

1. Choice of an appropriate beam delivery system
2. Minimization of thermal damage
3. Accurate delineation of treatment margins
4. Accurate depth control
5. Control of intraoperative pain and bleeding
6. Definition of appropriate therapeutic end points

CO_2 Laser Ablation of the Transformation Zone

The physical principles for laser ablation of the cervical transformation zone are:

1. ***Choice of an appropriate laser wavelength:*** The CO_2 laser is the ideal choice for vaporizing sharply defined tissue volumes to a precisely determined depth. Compared with other gynecologic laser wavelengths such as the argon and Nd:YAG (neodymium-yttrium aluminum garnet), the minimal forward conduction of the CO_2 laser energy ensures safety when used appropriately.
2. ***Optimal energy delivery rate:*** Lateral thermal conduction of CO_2 laser energy is primarily determined by the length of time the incident laser beam impinges on the tissue. To achieve optimal vaporization with minimal lateral thermal injury, the CO_2 laser should be used with the highest power output with which the surgeon is comfortable. This should be a minimum of 25 W but preferably above 60 W. The cautious use of low-power outputs is one of the most common CO_2 laser surgery errors causing thermal injury.
3. ***Choice of appropriate temporal mode:*** Most gynecologists treating cervical preinvasive lesions with the CO_2 laser have access to a laser providing 50 W maximum power or less. As such, the laser is best used in *continuous* mode for the ablation of cervical lesions. However, in addition to using the highest controllable power output, thermal conduction can be further minimized by the choice of *rapid superpulse* as the temporal mode. Rapid superpulse has the definite advantage of permitting tissue cooling and relaxation between pulses. However, when in the superpulse mode, the maximum average power from the laser falls by over 60%. This decrease in average power results in a much smaller spot size for the incident beam at the appropriate beam geometry for ablation. As such, the time required to destroy the required tissue volume increases. This time factor is the most important determinant of lateral heat conduction and thermal injury. With less powerful lasers (i.e., £50 W of maximum power), the advantage of the rapid superpulse in permitting tissue cooling between pulses is outweighed by the increased time required to destroy a given volume of tissue. The choice of continuous mode is therefore usually appropriate.

   The main advantage of higher-powered lasers is the higher average power achieved in rapid superpulse settings. This offers a distinct advantage in situations where control of thermal injury is critical, such as the DES-exposed, breastfeeding, postmenopausal, or postirradiation patient. Newer technology such as the *ultrapulse* temporal mode affords an even greater therapeutic advantage. Very high energy pulses can be delivered with a wide interpulse interval, permitting easier surgical control of high energy and the laser crater to cool to body temperature before successive pulses of energy are delivered. With the ultrapulse technology, instantaneous vaporization with minimal thermal conduction is attainable, creating char-free laser surgery. Although this degree of heat control is not imperative in most transformation zone ablation procedures, it is of great advantage in most lower genital tract procedures, particularly those involving the vulvar skin.
4. ***Choice of appropriate power density:*** For transformation zone ablative procedures, the average power density must be kept within the range of 750 to 2,000 W/cm^2 (233). The use of a power density below 750 W/cm^2 is contraindicated because this is below the threshold for vaporization and causes excessive carbonization with crater temperatures exceeding 600°C. Power densities above 2,000 W/cm^2 result in a series of deep craters and poor hemostasis.
5. ***Choice of appropriate beam geometry:*** Although power density is a very important physical principle governing surgical control of the CO_2 laser, it is a difficult clinical concept. Power density describes the average intensity within the focal impact spot of the laser. The incident laser beam produces a conical impact crater with marked variation in intensity of the beam from point to point in the focal spot. The average of these intensities does not have great clinical relevance.

   The clinical importance of the concept of beam geometry is that the crater shape mirrors the intensity profile of the incident energy (Fig. 8.12). A simple visual assessment of the surgical effect of the laser beam on the tissue is a reliable predictor of power density. When the incident laser beam is highly focused, the vaporization crater is a narrow, deep “drill-hole.” This reflects the high power density and is arbitrarily designated as the *X-beam geometry.* The X-beam geometry is for cutting and is therefore used for CO_2 laser excisional conization. The power density associated with the X-beam geometry is in excess of 10,000 W/cm^2. The X-beam geometry causes excessive ridging and guttering if used for ablation and carries a risk of bleeding and injury to deeper structures.

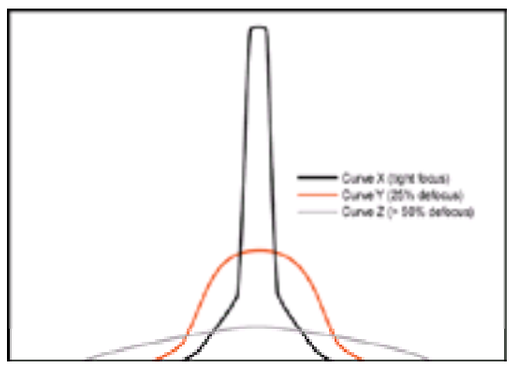

Figure 8.12 Diagrammatic representation of CO_2 laser beam geometry.

If the incident laser beam is flattened completely, the laser beam will simply heat a broad zone of tissue at the impact site to coagulation point but does not have sufficient power to vaporize tissue. The wide, flattened spot size produces the *Z-beam geometry.* Defocusing the CO_2 laser beam, at any power, to the Z-beam geometry causes carbonization and excessive tissue damage.

In contrast, defocusing the laser beam to an intermediate, round beam geometry produces a round, shallow vaporization crater at the impact site. This is designated the *Y-beam geometry* and permits controlled tissue vaporization to a relatively uniform and predictable depth. The CO_2 laser can be readily controlled by the surgeon at any power setting provided the appropriate Y-beam geometry is selected.

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For cervical transformation zone ablation, a high-power laser setting is selected. The spot diameter is progressively enlarged by defocusing the beam using the micromanipulator until a point is found where the impact crater (tested on a moistened wooden tongue blade) is hemispherical. This permits controlled tissue vaporization with minimal lateral heat conduction. The higher the average power setting on the laser, the larger the spot size or impact crater in a Y-beam geometry. For transformation zone ablation, this affords the advantage of minimizing thermal conduction with associated tissue damage.

6. ***Intermittent gated pulsing:*** Quality of outcome of CO_2 laser surgery is determined by the speed of energy delivery. To maintain surgical control, it is tempting to turn the laser power down. A more appropriate strategy to obtain accurate surgical control is to deliver the laser energy in short bursts either by use of the mechanical timer in the laser console or, preferably, by gating the laser pulses using the foot pedal. This permits precise, controlled tissue vaporization.

The surgical strategies governing laser ablation of the transformation zone are as follows:

1. ***Choice of appropriate beam delivery system:*** CO_2 laser ablation of the transformation zone should always be performed using a micromanipulator attached to a colposcope or operating microscope. This permits colposcopic reassessment of the abnormal transformation zone before ablation and allows for effective surgical control of the laser beam. The cervix is visualized using a speculum that has had the surface of the blades “roughened” at a microscopic level to minimize the risk of direct reflection of the laser beam. A plume evacuation channel is incorporated into the speculum for suction attachment.
2. ***Minimize thermal damage:*** Thermal injury is largely avoided by minimizing the time taken for the delivery of the laser energy to complete the procedure. A further strategy to decrease thermal injury is preoperative and intraoperative cooling of tissues if appropriate to the site and procedure. This strategy is of value for vulvar laser surgery but is of limited usefulness for cervical procedures.
3. ***Accurate delineation of treatment margins:*** Establishing accurate margins for destruction or excision of abnormal tissue is an essential ingredient for success. Careful colposcopy is required at the time of transformation zone ablation to determine the lateral extent of disease. The entire transformation zone must be treated. Selective ablation of areas of disease results in much lower primary cure rates than routine treatment of the entire transformation zone.
4. ***Accurate depth control:*** A major advantage of CO_2 laser ablation of the transformation zone is the ability to destroy tissue to a precisely controlled depth. In 1980, Anderson and Hartley (234) reported that the maximum depth of gland involvement with CIN was 5.2 mm, whereas the maximum depth of uninvolved glands was 7.9 mm. Frequency and depth of gland crypt involvement increase with the grade of CIN. The transformation zone is usually destroyed to a depth of 7 to 10 mm, achieving primary cure rates in appropriately selected patients in excess of 95%. Care should be taken to achieve a cylinder shape with perpendicular walls and a flat, slightly domed or “cowboy-hat” base to the laser crater (235) (Fig. 8.13, Fig. 8.14). A conical defect should be avoided.

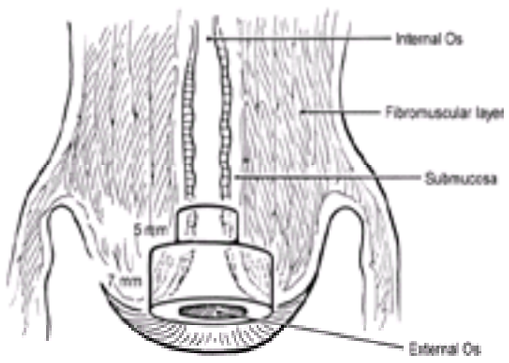

Figure 8.13 “Cowboy-hat” configuration for cervical transformation zone ablation.

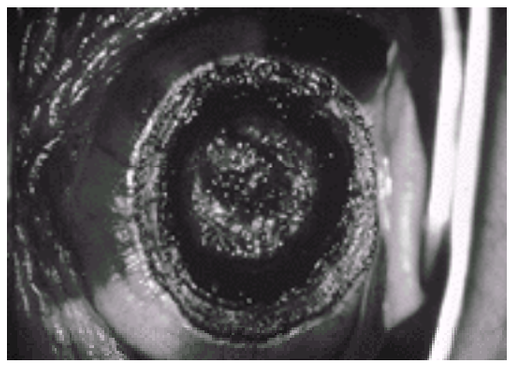

Figure 8.14 Cervical transformation zone ablation after using the CO_2 laser.

5. ***Control of intraoperative pain and bleeding:*** CO_2 laser ablation of the transformation zone is usually performed under local anesthesia. The cervix is infiltrated with 4 to 6 mL of local anesthetic such as 1% *lidocaine* with or without a vasospastic agent. The infiltration is best performed as a slow, subepithelial infiltrate using a dental syringe with a 27-gauge dental needle. A deeper, paracervical block does not always provide adequate anesthesia and its administration is associated with more discomfort and bleeding. Laser ablation is usually associated with minimal bleeding. Should a small vessel such as an arteriole be encountered, hemostasis is readily achieved by using direct pressure from a moistened cotton-tipped applicator and lasing immediately onto the applicator tip at the site of the vessel. Monsel's solution is applied to the cervix on completion of the procedure to minimize the risk of postoperative bleeding.
6. ***Definition of appropriate therapeutic end points:*** CO_2 laser ablation of the transformation zone is an excellent treatment for selected patients with CIN, achieving primary cure rates of up to 95%, with minimal morbidity (236,237,238,239,240 and 241).

Sequelae of Conservative Treatment Procedures A significant proportion of patients continue to show minor abnormalities on cervical smears in the first 12 months after treatment, reflecting reparative changes or continued expression of minimally developed HPV-induced changes. These patients rarely require further treatment. Patients can expect a vaginal discharge for up to 3 weeks after the procedure. Infection is rare, but persistence of an offensive discharge or development of postoperative pelvic pain warrants assessment. Minor spotting may occur in the first 2 postoperative weeks but usually settles promptly. If bleeding is heavier and does not settle quickly, the patient should be examined and hemostasis secured using Monsel's solution. The patient should refrain from tampon use, douching, and vaginal intercourse for 3 weeks after surgery. Repeat Pap smears and colposcopy should be performed at 4, 10, and 16 months posttreatment. If these assessments are normal, the patient may return to annual screening.

CO_2 Laser Excisional Conization

When excisional conization is indicated, the CO_2 laser can be effectively used (242,243,244,245 and 246). The width and the length of the cone biopsy can be tailored to the topography of the lesion and the transformation zone.

The physical principles governing CO_2 laser excisional conization are summarized as follows:

1. ***Choice of appropriate laser wavelength:*** The CO_2 laser wavelength affords precise excision with the potential for minimal thermal injury.
2. ***Optimal energy delivery rate:*** The laser should be set at the highest power with which the surgeon is comfortable. This is usually in the range of 25 to 60 W.
3. ***Choice of appropriate temporal mode:*** In excisional conization, the use of rapid superpulse or, preferably, ultrapulse temporal mode

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3. ***Choice of appropriate temporal mode:*** In excisional conization, the use of rapid superpulse or, preferably, ultrapulse temporal mode technologies affords a definite therapeutic advantage. Higher laser powers can be more readily controlled and the tissue cooling and relaxation associated with these temporal modes minimizes thermal damage and char. The delivery of high power through pulsed modes permits excision to continue through bleeding sites that may accompany the excisional procedure.
4. ***Choice of appropriate power density:*** Excisional conization requires high power density, usually in excess of 10,000 W/cm^2.
5. ***Choice of appropriate beam geometry:*** A tightly focused X-beam geometry is used for excisional procedures. This is produced by the high power density of the focused laser beam.
6. ***Intermittent gated pulsing:*** The delivery of laser energy is controlled by gating using the foot pedal. There is a very limited role for use of console timing for excisional procedures. The newer ultrapulse technology permits delivery of pulses of very high energy density while controlling the rate of delivery of pulses to assist surgical control of high power.

The geometry of the conization specimen may be individualized to three broad categories (Fig. 8.15).

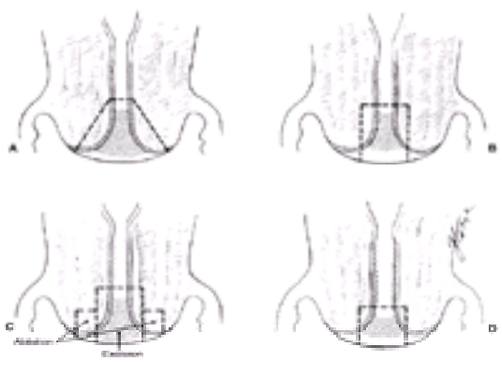

Figure 8.15 Geometry for cervical conization procedures.

Long Cylindrical Cone Most lesions requiring an excisional procedure do not have wide ectocervical extension. The CO_2 laser can be used to excise a conization specimen with a base of 1.5 to 2.0 cm and a vertical depth of up to 3.0 cm if required. This provides an excellent specimen for histologic assessment while usually causing minimal damage to the fibromuscular stroma of the cervix.

Broad, Deep Cone The traditional large-cone biopsy, removing a large surface area of the cervical epithelium and a significant volume of the underlying fibromuscular stroma of the cervix, is indicated when there is a strong clinical suspicion of occult invasive cancer. A specimen with diameter and depth of 2 to 3 cm can be readily excised with the CO_2 laser but carries an increased risk of adverse fertility- and pregnancy-related sequelae. Although the degree of cervical scarring and deformity associated with use of the CO_2 laser appears to be less than that with cold-knife excision of similar cervical volumes, the risk of complications remains relatively high.

"Mini-Cone" For some patients, particularly young women, the triage criteria for safe ablation of a lesion may not be met, but there is no suspicion of occult invasion or of significant, undisclosed disease within the endocervical canal. A small cylinder, 10 to 15 mm deep, can be easily excised in the office or outpatient setting using the CO_2 laser under local anesthesia and colposcopic control. The risk of complications is very small, similar to that associated with ablative procedures.

The cervix should be infiltrated with *lidocaine* with *epinephrine* or *Pitressin* solution before excisional conization to produce vasoconstriction of larger cervical arterioles. This often results in negligible blood loss. Relatively brisk bleeding may still be encountered. Firm traction on the cone specimen often stems the flow until the excision is complete, at which point the beam may be defocused to a Y-beam geometry and hemostasis secured as for an ablative procedure. Miniconization procedures are readily performed under local anesthesia, but larger cone biopsies are often best performed under general or regional anesthesia. Minimization of thermal eschar and postoperative, prophylactic application of Monsel's solution reduces the risk of secondary hemorrhage to less than 3%.

The primary cure rate for cervical preinvasive disease managed by CO_2 laser excisional conization should be in excess of 90% if the margins of excision are clear of disease (242,243,244 and 245). A positive endocervical excision margin decreases the primary cure rate to approximately 75% (243,244,245 and 246). This is not an automatic indication for repeat conization or hysterectomy. Selected patients, particularly if future fertility and childbearing remain an important consideration, may be followed closely by cytologic screening, colposcopy, and endocervical sampling, provided reliable compliance can be guaranteed. The risks of cervical stenosis and incompetence are very small after laser conization and are significantly less than for cold-knife conization (245,246).

Cold-Knife Conization

Excisional conization performed with a scalpel, referred to as a *cold-knife conization*, was traditionally the standard response to cytologic abnormalities (247) and remains an important therapeutic option in the management of CIN, particularly when an ablative procedure is contraindicated and the surgeon wants to avoid thermal injury to the excised specimen (248). Cold-knife conization is often both diagnostic and therapeutic, providing an excellent specimen for histologic assessment. The procedure is performed in the following manner:

1. ***Careful colposcopic examination is performed to delineate the lateral margins of the lesion and transformation zone.*** *Lugol's iodine solution aids in this determination.*
2. ***Lateral sutures are placed*** *at the 3 and 9 o'clock positions toward the lateral extent of the cervix to provide traction and hemostasis.*
3. ***The cervix is infiltrated with a vasospastic agent*** *to decrease intraoperative bleeding.*
4. ***The endocervical canal is sounded*** *to guide the direction and depth of the excision.*
5. ***The specimen is excised*** *using a no. 11 scalpel blade, preferably with a cylinder-shaped geometry.*
6. ***The excised specimen is tagged at the 12 o'clock position*** *using suture for proper orientation and is sent fresh to the pathology laboratory.*
7. ***A fractional curettage of the endocervical canal and endometrium is performed*** *to exclude residual squamous or glandular disease of the upper endocervical canal or disease of the endometrium.*
8. ***On completion of the procedure, the base of the surgical site can be cauterized*** *to secure or maintain hemostasis, or hemostatic sutures can be placed. The traditional Sturmdorf sutures are not advisable because of the risk of burying residual disease. Simple U-sutures placed anteriorly and posteriorly are usually adequate.*

Cold-knife conization achieves cure rates for high-grade CIN in excess of 95% (248). The risk of cervical stenosis and cervical incompetence is higher for cold-knife conization than for CO_2 laser and electrosurgical excisional conization. This in part reflects the fact that cold-knife conization has been traditionally used for the most severe lesions, where invasive cancer has not been excluded or where colposcopy is unsatisfactory, often with significant disease extension to within the endocervical canal (249).

Hysterectomy

Hysterectomy is rarely indicated in the primary management of CIN. The most common indication for hysterectomy in the management of preinvasive cervical disease is coexistent gynecologic conditions that warrant hysterectomy. These include dysfunctional uterine bleeding, fibroids, uterovaginal prolapse, or patient request for sterilization.

If hysterectomy is to be performed for a patient with CIN, an initial colposcopic examination must be performed. If the entire lesion and transformation zone is not seen, if there is any cytologic, colposcopic, or histologic suspicion of invasive cancer, if an endocervical specimen is positive for high-grade neoplasia, or if there is any evidence of high-grade glandular neoplasia, an excisional conization must be performed to exclude invasive cancer before hysterectomy is performed.

In 2% to 3% of patients with high-grade CIN, the disease extends to the vaginal vault (250). If the vaginal cuff is not carefully fashioned in these patients, preferably using a vaginal approach, neoplastic epithelium may be sutured into the vaginal vault. High-grade vaginal intraepithelial neoplasia (VAIN) occurs in the vaginal vault in 1% to 7% of patients who have undergone hysterectomy to treat CIN. Coppleson and Reid (251) reported 38 cases of invasive cancer occurring in the vaginal vault after hysterectomy among 8,998 women (0.4%).

If hysterectomy is performed for the management of CIN, the patient should have vault cytologic testing and colposcopy performed on two occasions in the 18 months after surgery, and she should be screened by vaginal vault cytologic testing on an annual basis thereafter.

Cervical Adenocarcinoma *In Situ*

The reported incidence of cervical glandular neoplasia has increased (252,253,254,255 and 256). Adenocarcinoma of the cervix represents up to 20% to 30% of primary cervical cancers, increased from the previously reported incidence of 5% to 10% (255,256). Adenocarcinoma is diagnosed with increased frequency in younger women, with up to 30% of cases occurring in women younger than 35 years of age (252,253 and 254). These changes in the clinical profile of cervical cancer have focused much attention toward AIS. There is convincing evidence that AIS is a precursor lesion. The mean age of diagnosis of AIS is 15 years younger than that for invasive adenocarcinoma. AIS frequently coexists with invasive adenocarcinoma in histologic specimens. Patients who have a cone biopsy performed in response to cytologic evidence of AIS already have invasive cancer in up to one third of cases. Women diagnosed with cervical adenocarcinoma frequently have had previous cytologic evidence of endocervical atypia on smears for intervals of 2 to 10 years.

The relationship between AIS and lesser degrees of cervical glandular neoplasia is more controversial. No prospective study of glandular dysplasia has been undertaken and the neoplastic potential of these lesions remains uncertain. Specific HPV types, in particular HPV 18, are strongly implicated in the etiology of high-grade glandular neoplasia. Glandular dysplasia is much less predictably associated with high-risk HPV types, further confusing understanding of the significance of such lesions. Prolonged oral contraceptive usage, beyond 5 years, may be a cofactor in the development of glandular neoplasia, particularly in young women (257).

Clinical Presentation

Adenocarcinoma *in situ* is usually diagnosed after abnormal cervical cytologic test results. The abnormal smear may predict the presence of high-grade glandular disease. Because AIS coexists with high-grade squamous CIN in 50% of cases, the abnormal smear will frequently predict only the squamous lesion. This represents a compelling argument for the routine excision of high-grade CIN.

The Bethesda system includes a category for *abnormal glandular cells of undetermined significance (AGUS)*. Patients with AGUS smear reports have a 30% to 50% risk of having high-grade cervical disease. The underlying lesion is most frequently high-grade CIN, which occurs in up to 25% of patients. AIS, cervical adenocarcinoma, and endometrial disease, including hyperplasia and carcinoma, occur in up to 20% of patients (258,259 and 260). Attempts to qualify AGUS smear reports to predict better the possibility of associated significant disease have been unreliable. These patients are at much higher risk of significant disease than those with ASCUS smear reports. An AGUS smear report is an indication for referral for colposcopy and careful endocervical assessment.

The colposcopic features of AIS and early adenocarcinoma are widely seen as nonspecific. Diagnosis relies on routine endocervical sampling in cytologic screening and careful clinical evaluation of squamous lesions to exclude coexistent glandular neoplasia. A minority view is that most high-grade glandular lesions do have specific colposcopic features. Discrete or extensive stark acetowhitening of individual or fused columnar villi may be seen surrounded by normal villiform structures (Fig. 8.16). Prominent atypical vessels may also be seen, particularly in association with early invasion. Although colposcopy should be performed in response to cytologic or clinical suspicion of glandular neoplasia, excisional conization is mandatory for definitive diagnosis.

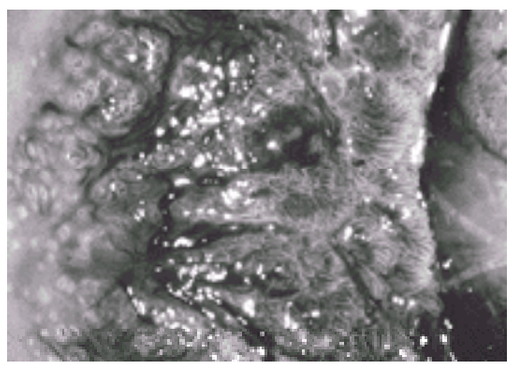

Figure 8.16 Colposcopy of adenocarcinoma *in situ* lesion showing prominent atypical vessels.

Management

The potential for AIS to involve the entire endocervical canal and the frequent association with invasive carcinoma demands formal excisional conization in the management of AIS. The cone biopsy should be fashioned as a cylinder of at least 3 cm in depth. Because histologic assessment of glandular architecture is critical to the diagnosis of AIS and early invasive adenocarcinoma, avoidance of thermal injury is crucial. Although thermal injury can be minimized with CO_2 laser technology, cold-knife conization is preferred. Care must be taken in particular with excision of the apex of the cone to avoid traumatic or thermal distortion. If the conization margins are clear of disease, over 80% of patients have negative cytologic and colposcopic follow-up beyond 12 months from treatment (261,262 and 263).

Younger women may be managed by excisional conization alone if margins of excision are clear. Invasive endocervical adenocarcinoma has been reported at hysterectomy performed as definitive treatment of AIS after excisional conization with negative conization margins. Residual squamous and glandular preinvasive disease is reported in as many as 33% of patients when the conization margins are free of disease (263,264 and 265). This emphasizes the importance of strict cytologic and colposcopic follow-up with careful endocervical assessment if the uterus is conserved. If the margins of excision are positive for disease, over 50% of patients have residual disease at hysterectomy (264). There is a high risk of undisclosed invasive cancer. Positive conization margins require repeat excisional conization to exclude invasive cancer. If the repeat cone biopsy is negative for invasive cancer, hysterectomy remains indicated in the older patient and is seriously considered in the younger patient, if fertility is not desired, because of the continued risk of residual and recurrent disease.

Vagina

Classification

Vaginal intraepithelial neoplasia is classified similarly to cervical lesions: VAIN 1 (mild dysplasia), VAIN 2 (moderate dysplasia), and VAIN 3 (severe dysplasia/carcinoma *in situ*). VAIN 3 is a premalignant lesion, but the natural history of the lesser degrees of VAIN has not been submitted to prospective study. VAIN 1 is an HPV-induced change without an established progressive potential. Management must be conservative, usually by observation. VAIN 2 to 3 are considered cancer precursor lesions although the true malignant potential has not been clearly defined. Conservative treatment and follow-up of high-grade VAIN is indicated.

Clinical Profile

Since the 1970s, the diagnosis of high-grade VAIN has been made with increasing frequency and the mean age at diagnosis has decreased to 30 years of age. The increased rate of diagnosis of high-grade VAIN is due to increased clinical awareness, improved screening, and an absolute increase in incidence. The rarity of primary vaginal squamous cancer, accounting for 1% to 2% of female genital tract cancers (266), suggests the malignant potential of VAIN is low, but progression to invasive cancer does occur (267).

High-grade VAIN lesions usually occur in association with high-grade CIN lesions, which extend into the vaginal fornices in approximately 3% of cases. Alternately, primary foci of high-grade VAIN do occur (268). VAIN involves the upper one third of the vagina in over 70% of cases and less commonly the lower one third, with the middle one third curiously spared. Occasionally, multifocal disease can extend throughout the vagina, particularly in the presence of extensive multicentric intraepithelial neoplasia. This reflects the field effect of squamous carcinogenesis in the lower genital tract related to specific oncogenic HPV types, and HPV 16 in particular (269).

High-grade VAIN lesions are asymptomatic and are usually detected after cytologic screening. Because VAIN often accompanies CIN, cervical cytologic testing is usually positive in the presence of VAIN. The vaginal vault, in particular, and the vaginal walls should be inspected at colposcopy for CIN. In addition, certain specific indications require careful vaginal colposcopy (Table 8.7).

1. Abnormal cytology after apparently successful treatment of CIN
2. Abnormal vaginal vault cytology posthysterectomy
3. Abnormal cytology in the presence of colposcopically normal cervix, particularly if colposcopy is satisfactory
4. Confirmed high-grade CIN in an immunosuppressed patient
5. Confirmed diagnosis of high-grade vulvar intraepithelial neoplasia
6. Abnormal gross vaginal examination
7. Confirmed or suspected intrauterine diethylstilbestrol exposure
8. Diagnosis and treatment of multicentric human papillomavirus infection, particularly if recalcitrant to conservative treatment

CIN, cervical intraepithelial neoplasia.

Table 8.7 Indications for Vaginal Colposcopy

Diagnosis

High-grade VAIN is largely diagnosed by colposcopy and histologic study of directed biopsies. VAIN 2 to 3 has a colposcopic appearance similar to that of high-grade CIN (Fig. 8.17, Fig. 8.18). Lesions are usually flat and inconspicuous before application of acetic acid, although occasionally raised pink, red, or white lesions may be seen. Clinically apparent hyperkeratosis or leukoplakia may represent an underlying VAIN lesion. Peeling or ulceration of the vaginal epithelium, particularly in the perimenopausal and postmenopausal patient, may be an indicator of underlying high-grade VAIN.

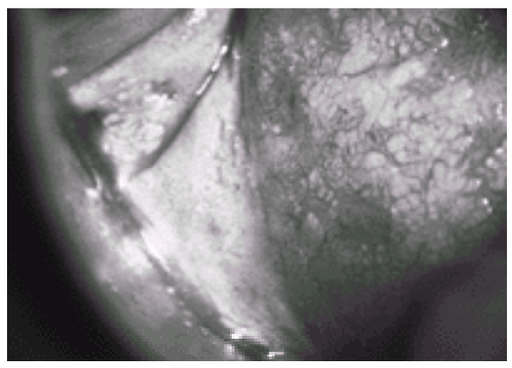

Figure 8.17 Colposcopy of high-grade vaginal intraepithelial neoplasia with acetic acid.

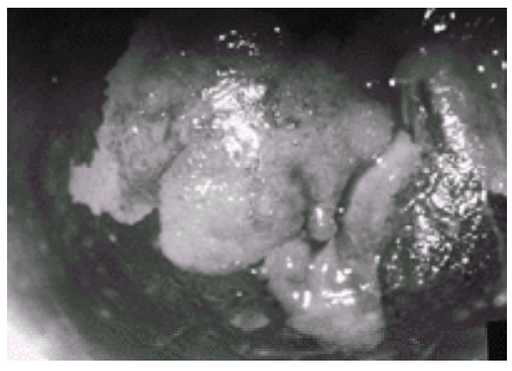

Figure 8.18 Colposcopy of high-grade vaginal intraepithelial neoplasia with iodine.

High-grade VAIN lesions blanch acetowhite after application of 5% acetic acid. The reaction takes longer to develop than for CIN and the rugosity of the vagina further impairs detection. Vascular patterns are usually indistinct or absent. A fine capillary punctation is often seen with high-grade VAIN as the acetic acid reaction fades. Prominent abnormal vascular patterns develop late in the neoplastic process. Widely spaced, varicose punctation and, less frequently, mosaicism occurring in an area of high-grade VAIN are highly suspicious for invasive cancer.

High-grade VAIN lesions can be unifocal or multifocal in the vagina. Lesions can be coalescent or discrete. Occasionally, recalcitrant condylomatous lesions of the vagina reveal a high-grade dysplastic morphology. The ability reliably to predict the probable histologic status of vaginal colposcopic lesions is a challenge for the most experienced colposcopist. A lesion may appear very inconspicuous and trivial but reveal high-grade dysplasia on biopsy. Examination under general or regional anesthesia may be required, particularly in the presence of extensive disease, to permit accurate diagnosis before destructive therapy.

The difficulty in colposcopic assessment of the vagina renders examination after application of aqueous iodine solution invaluable. Poorly differentiated vaginal epithelium is unglycogenated and rejects iodine staining. High-grade VAIN lesions appear mustard-yellow against the mahogany-brown staining of normal surrounding mucosa. This assists in the mapping of significant lesions and in obtaining accurate biopsies. The application of aqueous iodine is mandatory for delineation of treatment margins.

Treatment of High-Grade Vaginal Intraepithelial Neoplasia

Vaginal intraepithelial neoplasia can be very difficult to treat, particularly in the presence of extensive, multifocal disease or when the vaginal vault is involved posthysterectomy. Surgical excision, often requiring partial vaginectomy, or vaginal irradiation were historically used as the main treatment modalities. Significant morbidity is associated with both approaches. The CO_2 laser is now regarded as the treatment of choice for most VAIN cases (270,271). The vaginal wall is relatively thin compared with other genital tract sites, with vital organs in close proximity. Surgical access is, at times, difficult. The CO_2 laser provides the surgeon with the ability to treat to a precisely controlled depth and achieve very high cure rates for selected patients. Topical 5-*fluorouracil (5-FU)* cream can also be used with good effect for carefully selected patients (272,273). *5-FU* cream produces chemoinflammation and chemoulceration that often adequately treats VAIN lesions. Conservative ablative therapy requires expert colposcopy, liberal use of directed biopsies, and no cytologic, colposcopic, or histologic evidence of invasive cancer.

Carbon dioxide laser treatment for high-grade VAIN is best performed using a high-powered superpulse or ultrapulse laser. The beam is defocused to a Y-beam geometry and controlled by a micromanipulator attached to a colposcope or operating microscope. The vulvar mucosa is destroyed to the depth of the lamina propria, which is at most 2 to 3 mm deep. Because the vaginal mucosa contains no gland crypts or skin appendages, superficial treatment is required. Conservatism is of extreme importance because delayed healing and scarring of the vagina occurs after unskilled or overenthusiastic destruction of vaginal mucosa. Treatment complications, including scarring or delayed healing, create difficulties in postoperative follow-up and with sexual function.

Treatment of high-grade VAIN in the vaginal vault represents a particular surgical challenge. Woodman et al. (274) reported results of vaginal vault laser surgery for VAIN 2 to 3 posthysterectomy in 23 patients followed for a mean period of 30 months. Only six patients remained disease free, and invasive cancer developed in two patients. Hoffman et al. (275) reported 32 patients who underwent upper vaginectomy for VAIN 3. Occult invasive cancer was found in 9 patients (28%). CO_2 laser ablation may have a role for treatment of high-grade VAIN in the vaginal vault posthysterectomy if the patient is young and reliable for close follow-up. However, this very difficult problem is increasingly viewed as an indication for excision.

Vulva and Perianal Area

Since approximately 1970, there have been significant changes in the clinical profile of vulvar neoplasia. Chief among these have been a marked increase in the incidence of high-grade preinvasive disease and a decrease in the modal age of diagnosis. There has not been an associated increase in the incidence of invasive vulvar cancer, however, presumably because the preinvasive disease is actively treated.

Classification

Preinvasive neoplasia of the vulva has been recognized for over 75 years, but the descriptive terminology has been confusing. Vulvar carcinoma *in situ* has been described as *Bowen's disease, erythroplasia of Queyrat, carcinoma in situ simplex, bowenoid papulosis, kraurosis vulvae*, and *leukoplakia* (276). This confusion was compounded by the use of similar terms to describe a group of nonneoplastic vulvar diseases to which Jeffcoate (277) in 1966 assigned the term *chronic vulvar dystrophy.* In 1989, the International Society for the Study of Vulvo-vaginal Diseases (278) agreed on a new classification of vulvar epithelial disorders (Table 8.8).

Nonneoplastic epithelial disorders of skin and mucosa
Lichen sclerosis (formerly lichen sclerosis et atrophicus)
Squamous hyperplasia (formerly hyperplastic dystrophy)
Other dermatoses (e.g., psoriasis)
Intraepithelial neoplasia
Squamous intraepithelial neoplasia
VIN 1 (mild dysplasia)
VIN 2 (moderate dysplasia)
VIN 3 (severe dysplasia/carcinoma *in situ*)
Nonsquamous intraepithelial neoplasia
Paget's disease
Tumors of the melanocytes, noninvasive (melanoma *in situ*)
Mixed nonneoplastic and neoplastic epithelial disorders
Invasive tumors

VIN, vulvar intraepithelial neoplasia.
From Committee on Terminology, International Society for the Study of Vulvar Disease. New nomenclature for vulvar disease. Int J Gynecol Pathol 1987;6:83.

Table 8.8 Classification of Epithelial Vulvar Disorders

Although this classification represented a significant advance in rationalizing previously confusing terminology, significant shortcomings exist. The vulvar intraepithelial neoplasia (VIN) terminology was introduced for uniformity and consistency with the grade classification for CIN. Although this seems logical, there exists an established biologic continuum from CIN 1 to CIN 3. **The neoplastic biologic continuum from VIN 1 through VIN 3 to invasive cancer has not been established. Although the progression rate of VIN 3 to invasive cancer remains controversial, the malignant potential is undisputed. By contrast, there is no evidence that VIN 1 has any malignant potential.** The inclusion of such lesions in the neoplastic continuum creates pressure for a more aggressive therapeutic approach to low-grade vulvar lesions than can be justified. **VIN is best classified into two clinically meaningful categories: low-grade VIN (subclinical HPV infection and VIN 1/mild dysplasia) and high-grade VIN (VIN 2 to 3/moderate to severe dysplasia/carcinoma *in situ).* There also exists a compelling argument for excluding low-grade VIN from the "intraepithelial neoplasia" category until biologic data justifying its inclusion have evolved.**

The current classification of neoplastic vulvar diseases was developed at a time of considerable excitement in relation to the epidemiologic, molecular biologic, and clinical data that implicated specific oncogenic types of HPV in cervical and lower genital tract neoplasia. Although more than 95% of cervical malignancies are HPV-associated cancers, HPV DNA is detected only in approximately 50% of vulvar cancers (279). Many of the HPV-negative cancers, particularly in older women, are associated with lichen sclerosus (280,281,282,283,284,285 and 286).

Careful histologic and molecular review in the 1990s, particularly by Kurman and associates, has led to a reclassification of VIN 3 into three histologic subtypes, namely, basaloid, warty (or bowenoid), and differentiated (or carcinoma simplex) (287,288,289,290 and 291). Differentiated VIN is frequently found adjacent to invasive squamous cell carcinoma in older patients and is often associated with chronic vulvar dystrophy, particularly lichen sclerosus, but including lichen simplex chronicus and erosive lichen planus. Clinically, these lesions are difficult to distinguish against a dystrophic background. A keratotic nodule or shallow ulcer may be the only clinical indicator.

Paget's Disease Paget's disease of the vulva is an uncommon intraepithelial lesion. It is sometimes associated with underlying invasive carcinoma. These conditions are discussed in Chapter 13.

Clinical Profile of High-Grade Vulvar Intraepithelial Neoplasia

The increased incidence of VIN 3 in recent decades reflects increased clinical awareness, improved diagnostic accuracy, and an absolute increase in disease incidence. **Specific genital HPV types, in particular HPV 16, are strongly implicated in the causation of high-grade VIN** (292,293,294,295,296 and 297). Other vulvar HPV-induced lesions, including condylomata acuminata and subclinical HPV infection, frequently either coexist with or predate the diagnosis of VIN 3. Cigarette smoking, nutritional deficiency, poor personal hygiene, granulomatous vulvar diseases, endogenous and exogenous systemic immune suppression, and pregnancy have been implicated as cofactors in the pathogenesis of VIN 3 (296,297,298,299,300 and 301). There is a strong association between VIN 3 and sexually transmitted disease, with rates varying from 20% to 60% (291,299).

Distribution

High-grade VIN lesions tend to be localized and unifocal in the older patient. A higher malignant potential is presumed for such lesions because invasive vulvar cancer occurs predominantly in the older age groups. However, many of the invasive cancers in elderly women occur against a background of chronic vulvar dystrophy and without a prior history of VIN 3 or coexisting histologic evidence of VIN 3 (280,281,282,283,284,285 and 286).

In younger patients, high-grade VIN lesions are frequently multifocal and extensive. Lesions may remain discrete or coalesce to develop a large field of disease. Lesions may extend laterally from the inner aspect of the mucous membranes of the labia minora to the hair-bearing skin of the labia majora and from the clitoris, periclitoral area, and mons pubis anteriorly to the perineum and perianal area posteriorly. Difficult-to-access sanctuary sites such as the urethra, clitoris, vagina, and anal canal need to be carefully inspected.

Symptoms

Over 30% of women with VIN 3 experience vulvar symptomatology. The most common symptoms are pruritus, burning, pain, and dysuria (291,292). Vulvar symptoms are often exacerbated by voiding. Patients may present complaining of a localized lump or thickening in the vulvar skin or they may notice an area of increased or decreased pigmentation. The patient may present with a history of recalcitrant vulvar condylomata acuminata. Delay in diagnosis of high-grade VIN, even in symptomatic patients, is common. Most women diagnosed with VIN 3 are asymptomatic and are diagnosed coincidentally during clinical examination or procedures.

Clinical Appearance

The clinical appearance of VIN 3 lesions varies according to patient age and skin color, as well as the location of the lesions in the vulva and perianal region (Fig. 8.19, Fig. 8.20). In both the hair-bearing and non–hair-bearing keratinized vulvar skin, lesions tend to be raised or papular. They may be white, red, or brown in color. White lesions are due to hyperkeratosis or dehydration of the outer keratinized layer. Red lesions result from increased vascularity, reflecting either an inflammatory response or increased blood vessel formation secondary to angiogenic factors of neoplasia. Brown or pigmented lesions, which occur in over 10% of patients, result from melanin incontinence, usually in the keratinized squamous epithelium. On the mucosal surfaces and less frequently on the keratinized surfaces, VIN 3 lesions may be flat or macular. Occasionally, such macular lesions are evident through associated erythema or pigmentation. Usually, macular lesions are subclinical and are detected on colposcopic examination after application of 5% acetic acid solution (291,292).

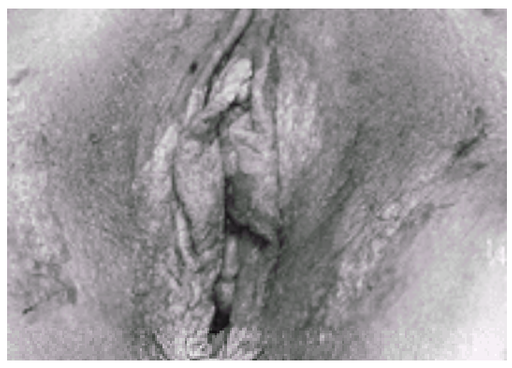

Figure 8.19 Clinical appearance of vulvar intraepithelial neoplasia showing hyperkeratotic papular lesions.

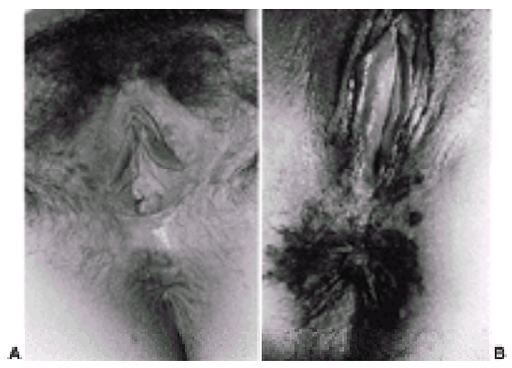

Figure 8.20 A: **A multifocal VIN 3 lesion with multiple small hyperpigmented lesions on the labia major. B:** VIN 3 with more confluent hyperpigmented areas on the posterior fourchette with extensive perianal involvement.

The clinical appearance of VIN 3 in dark-skinned women is similar when detected on mucosal surfaces but may differ in keratinized and hair-bearing areas. Lesions may be white because of hyperkeratosis or hyperpigmented because of melanin incontinence. Relative hypopigmentation may occur, producing pink or erythematous plaques. Such lesions may blanch densely acetowhite after application of acetic acid solution. Unifocal, localized lesions in older women less frequently involve the mucous membranes. Care must be taken in the assessment of suspicious vulvar lesions in older women because of the increased risk of undisclosed invasive cancer. Warning signs of an occult invasive lesion include yellow discoloration, nodularity, ulceration, thick scale, and abnormal vascularity.

Vulvar intraepithelial neoplasia grade 3 is often found on biopsy of recalcitrant and abnormal appearing condylomata acuminata. VIN 3 is reported in biopsies from 30% of patients with large, persistent condylomatous lesions, particularly if the lesions are pigmented or coalescent and sessile with a micropapilliferous surface (292,293 and 294). Condylomatous lesions exhibiting a severely dysplastic morphology on biopsy frequently harbor high-risk HPV types, with HPV 16 and 18 detected in over 70% of such lesions (271).

Diagnosis

Colposcopy has replaced the application of 1% toluidine blue solution in the diagnosis and evaluation of VIN. Toluidine blue is a nuclear stain promulgated by Collins in the 1950s for the early detection of vulvar malignancy. The efficiency of the test is very poor. Sensitivity is diminished by the hyperkeratosis associated with many high-grade VIN lesions. False-positive staining by nonneoplastic, inflammatory lesions, particularly in the presence of ulceration, is also common, decreasing specificity.

Colposcopy is now an accepted standard in the diagnostic assessment of preinvasive vulvar disease. After application of 5% acetic acid solution and colposcopic assessment using a magnification of at least 7×, lesions appear as clearly demarcated, dense acetowhite areas. The multifocal distribution is usually evident. The acetic acid reaction is best seen in lesions that are nonpigmented or red. Pigmented lesions often develop an acetowhite hue or a rim of acetowhitening. Initial clinical examination may identify clinically apparent lesions. Colposcopy may permit identification of previously unidentified, subclinical lesions and better define the distribution of clinically evident disease.

In high-grade vulvar preinvasive lesions, vascular patterns are often inconspicuous or absent, particularly in the presence of hyperkeratosis. Macular lesions on the mucous membranes may reveal a capillary punctation pattern, and a fine punctation is sometimes observed in papular lesions. Marked vascular abnormalities characterized by a varicose, widely spaced punctation and, rarely, mosaicism occur late in the neoplastic process. Such vascular abnormalities represent a strong warning sign of possible invasive cancer, and the lesion must be excised.

Diagnosis ultimately depends on liberal use of directed biopsy. These are best taken with a Keyes biopsy instrument under local anesthetic in the office setting.

Natural History of High-Grade Vulvar Intraepithelial Neoplasia

Vulvar intraepithelial neoplasia grade 3 coexists with invasive cancer in 30% to 50% of cases. Vulvar dystrophy occurs in up to 50% of specimens, with lichen sclerosus and squamous hyperplasia equally represented. There is no coexistent disease in 10% to 15% of specimens (280,281 and 282,289,291,302).

Few studies have examined the natural history of untreated VIN. Jones and Rowan (303) reported in 1994 on the prospective follow-up of 113 women with VIN 3 diagnosed between 1961 and 1993. Of 105 women whose disease was treated, 4 (3.8%) developed invasive cancer 7 to 18 years after treatment. Of eight untreated cases of VIN 3, progression to invasive cancer was reported in seven patients (87.5%) within 8 years, and the disease regressed spontaneously in the remaining patient. This very high incidence of progression within a reasonably short time is troubling and frequently quoted. However, the progression rate of untreated VIN 3 reported in this study may not be truly representative. Most of the untreated patients had a previous diagnosis of invasive cervical cancer and had undergone appropriate radical treatment, including radiation therapy. The median age of this small subgroup was significantly older than the current median age of diagnosis of VIN 3. In addition, the study was a retrospective audit as opposed to a true prospective study.

The natural history of high-grade VIN has not been systematically studied. Spontaneous regression and long-term persistence of VIN 3, particularly in younger women, are well recognized. There remains a substantial risk that untreated VIN 3 will progress to invasive cancer, and it would be unethical to conduct a prospective study of natural history. These facts argue for conservative but effective therapy for VIN 3 with conscientious follow-up.

The occurrence, usually in younger women, of multifocal, pigmented, papular vulvar lesions reported histologically as VIN 3 is well recognized and has been described as “bowenoid papulosis” (293,294,304). Reports of spontaneous regression, especially associated with pregnancy, suggested distinctive epidemiologic features for bowenoid papulosis, but the term has been abandoned by the International Society for the Study of Vulvar Disease and the International Society for Gynecologic Pathologists. High-grade VIN is a disease with a varied and individual clinical profile and histologic appearance. This range encompasses the entity previously described as “bowenoid papulosis.”

Treatment of High-Grade Vulvar Intraepithelial Neoplasia

Treatment is aimed at control of symptoms and prevention of progression to invasive cancer (305). Many treatment modalities have been used and, historically, vulvar carcinoma *in situ* was managed by simple vulvectomy (306). Such a radical approach is unjustified and is associated with significant morbidity, particularly for young women, including scarring, dyspareunia, urinary stream difficulties, loss of elasticity for vaginal delivery, and a “castration-like” self-image. Since the 1970s, there has been a trend toward more conservative therapy, initially using excisional approaches and more recently, ablative modalities (307).

The risk of occult malignancy occurring in association with VIN 3 is too low to mandate complete excision of disease in all patients but too high to allow routine ablation. The clinical profile of VIN, including a broad age range and marked variability in extent, distribution, and symptomatology, demands individualization of the therapeutic approach for each patient. A period of close prospective follow-up without treatment may be appropriate for young, immunocompetent women with multifocal disease, particularly if they are pregnant. The patient must comply with close follow-up and understand and accept the risks of treatment delay.

Wide Local Excision and Superficial (Skinning) Vulvectomy

Localized high-grade VIN lesions are best managed by local, superficial excision. The lesion should be excised with a disease-free margin of at least 5 mm. Wide, local excision is ideal for unifocal and lateral lesions or for hemorrhoids involved with high-grade intraepithelial neoplasia. It is mandatory if a lesion has warning signs of possible invasive cancer. Primary closure of the defect usually achieves uncomplicated healing and a very satisfactory cosmetic and functional outcome. The elasticity of the vulvar skin permits preservation of sexual and reproductive functions, of particular importance in the young patient. The surgical specimen should be submitted to careful histologic evaluation to exclude invasive disease and to ensure clear margins of excision. Wide local excision with disease-free surgical margins achieves a 90% cure rate for localized disease. If the margins of excision are involved with disease, the cure rate falls to 50%, demanding very close follow-up (305,307). As long as all macroscopic disease has been removed, reexcision is not justified.

Large, confluent lesions or extensive multifocal disease, particularly in the presence of colposcopic warning signs of early invasion, require more extensive excisional procedures with rotational flaps to fill the defect or skinning vulvectomy with a split-thickness skin graft. “Skinning” vulvectomy was introduced by Rutledge and Sinclair (308) for extensive VIN lesions, particularly in the hair-bearing skin where the skin appendages may be involved. Lesions are carefully mapped and a shallow layer of vulvar skin is excised, preserving the subcutaneous tissues. The vulvar skin at risk is replaced with epidermis from a donor site on the inner aspect of the thigh or buttock. The clitoris is preserved, with lesions on the prepuce or glans being superficially excised. The epithelium regenerates without loss of sensation.

DiSaia (309) reported a 39% recurrence rate in patients with VIN 3 treated by skinning vulvectomy with split-thickness skin grafting. There were no recurrences in grafted areas, although such recurrence has been reported. Although this procedure has been largely outmoded by CO_2 laser treatment for many patients with extensive disease, it remains an important therapeutic option when there is an increased risk of occult invasive cancer.

CO_2 Laser Surgery

Vulvar intraepithelial neoplasia is occurring more frequently in young women and the disease may be very extensive, involving the hair-bearing area of the labia majora in over 30% of cases. Excision of such wide areas, even with skin grafting, can cause significant scarring and anatomic distortion. With careful, expert colposcopy and liberal use of directed biopsy, the undisclosed cancer risk in selected patients is low. An ablative procedure in these patients using the CO_2 laser is the treatment of choice (310,311,312,313 and 314).

Physical Principles Governing Vulvar Laser Surgery

1. ***Choice of appropriate laser wavelength:*** The CO_2 laser is the only laser proven to be safe and effective for the management of high-grade VIN.
2. ***Rapid delivery of the required energy dose:*** Vulvar laser surgery demands minimization of lateral thermal injury to prevent scarring and morbidity. The surgeon must be able to control higher powers to permit precise, rapid ablation. For ablative procedures, powers of less than 50 W in continuous mode are associated with an increased risk of thermal injury and should be avoided.
3. ***Choice of appropriate temporal mode:*** The option of choosing rapid superpulse or the newer ultrapulse technology affords a definite therapeutic advantage in CO_2 laser ablation of vulvar lesions. The ability precisely to vaporize diseased tissue under visual control with minimal heat propagation to adjacent tissue is the key to nonmorbid laser surgery.
4. ***Choice of appropriate power density:*** CO_2 laser ablation requires power densities in the range of 800 to 1,400 W/cm^2.
5. ***Choice of appropriate beam geometry:*** The precise setting of a Y-beam geometry before using the laser on the vulvar skin is of great importance. The laser should be first tested on a moistened tongue blade to defocus the beam to the hemispherical Y-beam geometry before use on the skin.
6. ***Intermittent gated pulsing:*** CO_2 laser surgery to the vulvar skin requires training and skill in the use of the foot pedal to deliver the laser energy in short bursts to control the depth of ablation.

Surgical Strategies Governing Vulvar CO_2 Laser Surgery

1. ***Choice of appropriate beam delivery system:*** Although excisional procedures can be performed using the CO_2 laser, there is no therapeutic advantage over other excisional modalities. For ablative procedures, the laser must be controlled using a micromanipulator through a colposcope or operating microscope with a 300-mm objective to produce a relatively large spot size with excellent depth of field. The hand-held probe is very difficult to control and tends to produce a series of nonuniform, poorly localized cuts. The angle of impact of the laser is controlled by traction on the skin. A hand-held mirror may occasionally be required to direct the beam to difficult-to-access sites.
2. ***Minimization of thermal injury:*** In addition to the use of precise bursts of high-powered, pulsed laser energy in an appropriate Y-beam geometry, thermal injury can be further minimized by chilling the vulvar skin, before and during surgery, with laparotomy packs soaked in iced saline solution. This simple strategy diminishes postoperative pain and swelling and promotes healing.
3. ***Accurate delineation of treatment margins:*** The laser can be used initially to circumscribe the distribution of the lesions before the acetic acid reaction fades or the appearance of the skin is altered by treatment of surrounding areas. Exposure of internal surfaces such as the distal urethra and anal canal requires appropriate instruments.
4. ***Accurate depth control:*** The depth of destruction required is too shallow to control by measurement. Determination of depth of ablation is best achieved by a precise understanding of the visual landmarks of the surgical planes of the vulva as described by Reid et al. (311,312).

   First surgical plane: Destruction to the first surgical plane removes the surface epithelium to the level of the basement membrane. The laser beam, set according to the physical principles outlined previously, is rapidly oscillated across the target tissue with the spot describing a series of roughly parallel lines. When the impact debris is wiped away with a moistened swab, the moist “sand-grain” appearance of the papillary dermis will be evident.

   Second surgical plane: Ablation to the second plane removes the epidermis and the superficial papillary dermis. This plane is achieved by a slightly slower oscillation of the laser beam across the first surgical plane, scorching but not penetrating the papillary dermis. The visual effect is a shrinking of the target tissue due to dehydration, and a finely roughened, yellowish surface similar in appearance to chamois cloth is produced. Ablation extends to the deep papillary dermis with minimal thermal injury to the underlying reticular dermis. The second surgical plane is the preferred depth of ablation for condylomata acuminata treated with the CO_2 laser.

   Third surgical plane: Destruction to the third surgical plane removes the epidermis, papillary dermis, and superficial reticular dermis containing the upper portions of the skin appendages, specifically the pilosebaceous ducts and hair follicles. This is achieved by a slower, purposeful movement of the laser beam across the second surgical plane. The tissue is seen to relax and separate as the mid-reticular dermis is exposed as moistened gray-white fibers representing coarse collagen bundles. Healing occurs from the base of the skin appendages and scarring is absent or minimal. Ablative procedures for VIN 3 should be carried to the depth of the third surgical plane (Fig. 8.21).

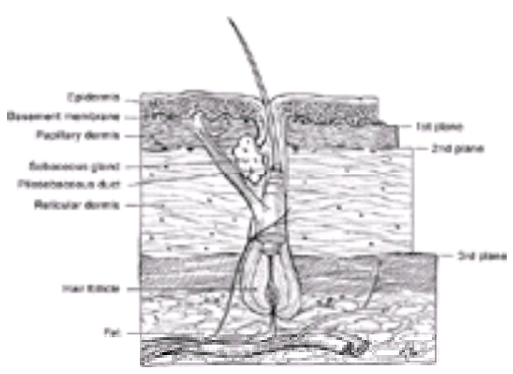

Figure 8.21 Diagrammatic representation of third surgical plane with conservation of skin appendages.

   The skin appendages are involved with the VIN process in over 50% of cases (312). Depth of hair follicle involvement is usually less than 1 mm but may extend to 2 mm. Measured sweat gland involvement has been more than 3 mm in depth. Based on experience with ablative procedures for CIN, where depth of gland crypt involvement extends to 4.6 mm and failure to destroy beyond this depth results in increased failure rates, it has been suggested that ablative procedures for VIN involving skin appendages must be beyond 3 mm. At this depth, the equivalent of a third-degree thermal defect is created, resulting in delayed healing, scarring, and alopecia. The implications of residual disease after treatment of VIN are different from those of residual CIN, which may be buried and escape detection. Although the surgeon should be aware of vulvar skin appendage involvement, this is not an indication to destroy beyond the mid-reticular dermis.

   Fourth surgical plane: Destruction of the reticular dermis creates a thermal injury extending to the subcutaneous tissues. If it is necessary to treat to this depth, an excisional procedure with skin grafting is indicated.
5. ***Control of intraoperative and postoperative pain and bleeding:*** CO_2 laser procedures for high-grade VIN are performed under general or regional anesthesia unless the disease is localized. Subcutaneous injection of a long-acting local anesthetic under the laser crater on completion of the procedure diminishes pain in the immediate postoperative period. Intraoperative bleeding is usually minimal but may result from puncture of a small vessel. Hemostasis is usually readily obtained by lasing directly onto a moistened cotton-tipped applicator, which is used to tamponade the vessel. If this is unsuccessful, a suture is preferable to continued application of the laser and increased thermal injury.

   Postoperative pain management is a very significant component of vulvar CO_2 laser surgery. Narcotic analgesics frequently are

but may result from puncture of a small vessel. Hemostasis is usually readily obtained by lasing directly onto a moistened cotton-tipped applicator, which is used to tamponade the vessel. If this is unsuccessful, a suture is preferable to continued application of the laser and increased thermal injury.

Postoperative pain management is a very significant component of vulvar CO_2 laser surgery. Narcotic analgesics frequently are required in the immediate postoperative period, preferably administered using a patient-controlled analgesia pump. Alternatively, prolonged epidural or caudal analgesia can be used. Regular sitz baths followed by topical application of a mixture of equal parts 1% *lidocaine* and 2% *silver sulfadiazine* creams to the surgical site aid in pain relief. The postoperative discomfort is often most severe on the third to the sixth postoperative days. Patients should be aware of this frequent exacerbation of burning and discomfort occurring after discharge from inpatient care and have available appropriate oral narcotic analgesics to provide relief.

6. ***Definition of appropriate therapeutic end points:*** Regardless of treatment modality, recurrence of VIN is common. Consideration should be given to the use of a postoperative adjuvant interferon regimen to diminish recurrence rates (315,316 and 317). Development of disease at other lower genital tract sites is also frequent. The future risk of lower genital tract invasive cancer is increased. Life-long vigilance is an important component of the management of high-grade VIN.

Multicentric Lower Genital Tract Neoplasia

The concept of multicentricity of lower genital tract neoplasia, encompassing the large epithelial region represented by the cervix, vagina, vulva, and perianal area, is well established (318). The cervix and lower genital tract have a similar squamous epithelium of closely related embryologic derivation. Multiple primary preinvasive or invasive lesions can occur synchronously or metachronously in this region. The detection of high-grade squamous disease at one lower genital tract site defines an increased risk of disease at other sites.

High-grade *perianal intraepithelial neoplasia (PAIN)* occurs in over 30% of patients with VIN 3 or multicentric squamous neoplasia (318). High-grade PAIN may occur in recalcitrant perianal condylomata acuminata or as thickened, hyperkeratotic, often pigmented papular lesions usually visible to the naked eye. Proctoscopic examination using the colposcope after application of acetic acid may reveal high-grade squamous preinvasive disease extending to above the dentate line. Squamous cancer of the anus remains an uncommon disease (319), although its incidence has increased significantly in homosexual men (320,321). Viral analysis confirms a strong association with HPV 16 (322,323).

High-grade PAIN is managed similarly to VIN 3. Conservation of normal tissues by careful colposcopic delineation of diseased areas is important. The CO_2 laser may afford some therapeutic advantage in this area because disruption of nerve fibers with full-thickness excision can lead to diminished ability to differentiate feces and flatus, leading to a degree of anal incontinence. Disease may also extend posterior to the anus to the natal cleft. Although considerable postoperative care is required for pain control and wound care, modern CO_2 laser surgery is usually the treatment of choice in this difficult situation.

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9 Cervical Cancer

Neville F. Hacker

Invasive cancer of the cervix is the major cause of death from gynecologic cancer worldwide, with almost half a million cases diagnosed each year. **Reported incidence rates in developing countries are much higher than those in developed countries,** and both incidence and mortality rates are likely to be underestimated in these countries. Reported age-standardized incidence rates per 100,000 for cervical cancer range from 83.2 in Recife, Brazil, to 3 for non-Jews in Israel (1). In the United States, 12,800 new cases were anticipated in 2000, with 4,600 deaths (2).

The mean age for cervical cancer is 51.4 years, with the number of patients fairly evenly divided between the age groups 30 to 39 and 60 to 69 years (1). There is a trend toward increasing stage with increasing age, suggesting that older patients are not being screened as often as younger patients (1).

Cervical cancer progresses slowly from preinvasive cervical intraepithelial neoplasia (CIN) to invasive cancer, and screening asymptomatic women with regular Papanicolaou (Pap) smears allows diagnosis of the readily treatable preinvasive phase. **In developed countries, most cases of cervical cancer occur in women who have not had regular Pap smear screening.**

In developing countries, facilities for screening asymptomatic women are not readily available, whereas cultural attitudes and lack of public education also discourage early diagnosis. Hence, **most patients in developing countries present with advanced disease that may have already eroded into the bladder, rectum, pelvic nerves, or bone.** Because radiation therapy and palliative care facilities are also usually inadequate in these countries, many of these women die as social outcasts, with severe pain and a foul-smelling vaginal discharge. Most of these women have dependent children, so the social devastation caused by this disease can be readily appreciated.

Diagnosis

Early diagnosis of cervical cancer can be extremely challenging because of three factors:

1. **The frequently asymptomatic nature of early stage disease**
2. **The origin of some tumors from within the endocervical canal or beneath the epithelium of the ectocervix,** making visualization on speculum examination impossible
3. **The significant false-negative rate for Pap smears,** even in women having regular screening

Symptoms

Abnormal vaginal bleeding is the most common presenting symptom of invasive cancer of the cervix. In sexually active women, this usually includes postcoital bleeding, but there may also be intermenstrual or postmenopausal bleeding. Unlike endometrial cancer, which usually bleeds early, **cervical cancer often is asymptomatic until quite advanced in women who are not sexually active.** Large tumors commonly become infected, and a vaginal discharge, sometimes malodorous, may occur before the onset of bleeding. In very advanced cases, pelvic pain, pressure symptoms pertaining to the bowel or bladder, and occasionally vaginal passage of urine or feces may be presenting symptoms.

In a review of 81 patients diagnosed with cervical cancer in southern California, Pretorius et al. (3) reported that 56% presented with abnormal vaginal bleeding, 28% with an abnormal Pap smear, 9% with pain, 4% with vaginal discharge, and 4% with other symptoms. Patients presenting with an abnormal Pap smear had smaller tumors and earlier-stage disease.

Cytology

The presence of malignant cells in a background of necrotic debris, blood, and inflammatory cells is typical of invasive carcinoma (Fig. 9.1). Differentiation between squamous and glandular cells is usually possible except for poorly differentiated lesions. **The false-negative rate for Pap smears in the presence of invasive cancer is up to 50%, so a negative Pap smear should never be relied on in a symptomatic patient** (4).

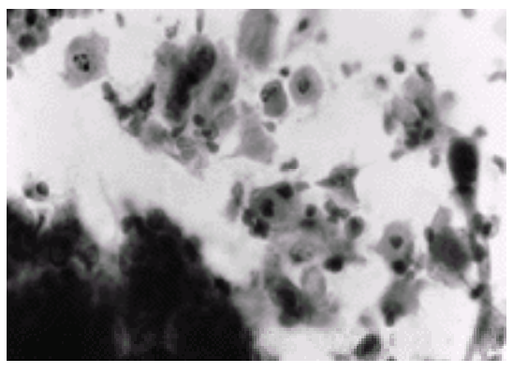

Figure 9.1 Pap smear of cervical squamous cell carcinoma. Malignant squamous cells, singly and in groups, show nuclear pleomorphism. A "tadpole" cell is present on the right. (Original magnification 165×.)

Signs

Physical examination should include palpation of the liver, supraclavicular, and groin nodes to exclude metastatic disease. On speculum examination, the primary lesion may be exophytic, endophytic, ulcerative, or polypoid. If the tumor arises beneath the epithelium or in the endocervical canal, the ectocervix may appear macroscopically normal. Direct extension to the vagina is usually grossly apparent, but the infiltration may be subepithelial and suspected only on the basis of obliteration of the vaginal fornices or the presence of apical stenosis. In the latter situation, it may be difficult to visualize the cervix. On palpation, the cervix is firm (except during pregnancy) and usually expanded. **The size of the cervix is best determined by rectal examination, which is also necessary for the detection of any extension of disease into the parametrium.**

Biopsy

Any obvious tumor growth or ulceration should undergo office punch biopsy or diathermy loop excision for histologic confirmation. Any cervix that is unusually firm or expanded should also undergo biopsy and endocervical curettage (ECC).

If the patient has a normal-appearing cervix but is symptomatic, or has an abnormal Pap smear, colposcopy should be performed. If a definitive diagnosis of invasive cancer cannot be made on the basis of an office biopsy, diagnostic conization may be necessary.

Colposcopy for Invasive Cancer

Colposcopic detection of a microinvasive carcinoma depends on its size and location. Very small lesions may be missed, although the likelihood of having early stromal invasion increases with the surface extent of the preinvasive lesion (5). If the microinvasive carcinoma is entirely within the endocervical canal, the ectocervix may be colposcopically normal.

Ectocervical microcarcinomas are classically associated with atypical vessels, which are prone to bleed. **Atypical vessels show a completely irregular and haphazard disposition, great variation in caliber, and abrupt changes in direction, often forming acute angles** (Fig. 9.2). The intercapillary distance is increased and tends to be variable (5).

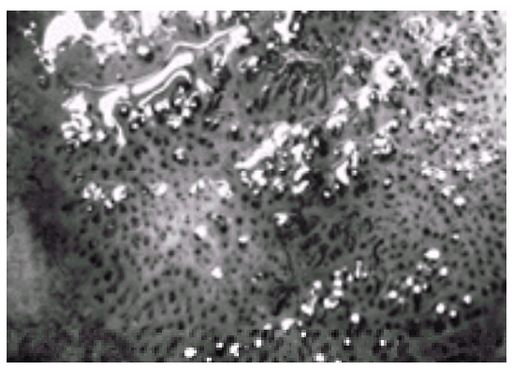

Figure 9.2 Colposcopic appearance of microinvasive cervical cancer.

Frankly invasive cancers can usually be seen with the naked eye, but the colposcope highlights their surface irregularity and highly atypical blood vessels (Fig. 9.3). Endophytic tumors may present as an "erosion," the true nature of which can be recognized only by their papillary surface and atypical vessels. A keratotic surface may mask the colposcopic features of an endophytic lesion, so biopsy of areas of keratosis is mandatory.

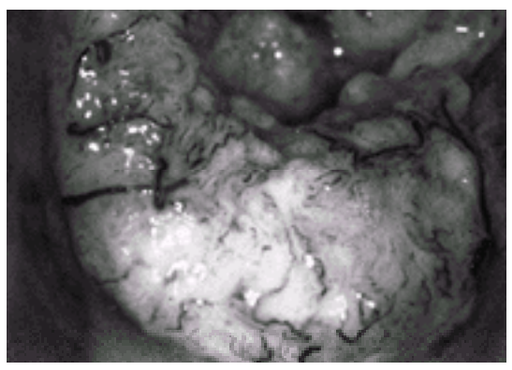

Figure 9.3 Colposcopic appearance of invasive cervical cancer.

Adenocarcinomas present no specific features. They often occur in association with squamous CIN and all of the vascular changes described previously may be seen with these lesions.

Staging

Cervical cancer is staged clinically because most patients worldwide are treated only with radiation therapy.

The 1994 staging system of the International Federation of Gynecology and Obstetrics (FIGO) is shown in Table 9.1. A comparison of the FIGO staging and the TNM classification is shown in Table 9.2.

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Table 9.1 Carcinoma of the Cervix Uteri: FIGO Nomenclature (Montreal, 1994)

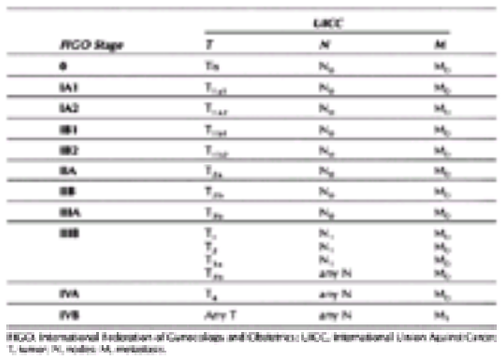

Table 9.2 Carcinoma of the Cervix Uteri: Stage Grouping

Clinical Staging

Clinical staging is often inaccurate in defining the extent of disease. The Gynecologic Oncology Group (GOG) (7), in a study of 290 patients with surgically staged cervical cancer, reported errors in FIGO clinical staging ranging from 24% in stage IB to 67% for stage IVA disease. A report from the University of Southern California indicated only a 52% correlation between clinical stage and subsequent surgical findings (8).

Most patients are upstaged on the basis of surgical exploration, with the most likely sites of occult metastases being the pelvic and paraaortic lymph nodes. Other sites of occult disease are the parametrium, peritoneum, and omentum. Up to 14% of patients may also be downstaged (8), usually because a benign pathologic process is discovered, such as pelvic inflammatory disease, endometriosis, or fibroids.

Noninvasive Diagnostic Studies

Because information about the extent of disease is critical for treatment planning, various radiologic studies have been used to define more accurately the extent of disease.

Bipedal Lymphangiogram Lymphangiography gained popularity in the United States in the 1960s, but the initial enthusiasm has been tempered as increasing experience has revealed that very small metastatic deposits cannot be discerned, and benign conditions such as fatty degeneration, fibrosis, or periadenitis may simulate a malignant process (9,10). In a review of the literature, Hacker and Berek (11) reported an overall accuracy for lymphangiograms of 84.8%, with a false-positive rate of approximately 32% (19 of 60 positive studies) and a false-negative rate of approximately 10% (21 of 204 negative studies).

Computed Tomography Computed tomography (CT) has been used to help stage pelvic cancers since approximately 1975. In addition to the lymph nodes, a pelvic and abdominal CT scan allows an evaluation of the liver, urinary tract, and bony structures. **Unlike lymphangiograms, which can define changes in nodal architecture, CT can detect only changes in the size of the nodes, those greater than 1 cm in diameter usually being considered positive.** Normal-sized nodes containing microscopic deposits give false-negative results, whereas nodal enlargement from inflammatory or hyperplastic changes gives false-positive results. If nodes greater than 1.5 cm in diameter are considered positive, the sensitivity of the test is improved at the expense of the specificity.

In a review of the literature, Hacker and Berek (11) reported that the sensitivity and specificity of CT for the detection of paraaortic lymph node metastases were comparable with those of lymphangiography. The overall accuracy was 84.4%, with a false-positive rate of approximately 21% (9 of 41 positive readings) and a false-negative rate of approximately 13% (13 of 99 negative readings). Compared with lymphangiography, CT is less time consuming, less technically difficult, and provides more information (12,13).

Ultrasonography As with CT, ultrasonography is unable to differentiate between benign and malignant enlargement of lymph nodes, but it has the advantage of being less costly, less time consuming, and avoiding exposure to radiation (14).

Magnetic Resonance Imaging Because CT cannot discriminate between cancer and normal soft tissue of the cervix and uterus, it is limited in the evaluation of early cervical cancer. Magnetic resonance imaging (MRI), which has been used since the early 1980s, has high-contrast resolution and multiplanar imaging capability, and is **a valuable modality for determining tumor size, degree of stromal penetration, vaginal extension, parametrial extension, and lymph node status** (15,16).

Subak et al. (17) evaluated CT and/or MRI before surgical exploration in 79 patients with FIGO stage IB, IIA, or IIB cervical carcinoma. They reported that MRI estimated tumor size to within 0.5 cm of the surgical specimen in 64 of 69 patients (93%) and had an accuracy of 78% for measuring depth of stromal invasion. By contrast, CT was unable to evaluate tumor size or depth of invasion. For the evaluation of stage of disease, MRI had an accuracy of 90% compared with 65% for CT ($p < 0.005$) and it was also more accurate in assessing parametrial invasion (94 vs. 76%, $p < 0.005$). Both modalities were comparable for the evaluation of lymph node metastases (each 86% accurate). These results confirmed an earlier study by Kim et al. (16), and it would seem that **MRI may have a role in the identification of parametrial infiltration in patients with bulky cervical tumors, and therefore in the identification of candidates suitable for primary surgery. MRI is also appropriate for the evaluation of pregnant patients because it poses no risk to the fetus.**

Positron Emission Tomography This is a newer imaging technique that relies on the use of radionuclides, which decay with the emission of positrons (positively charged particles). Because cancer cells are avid users of glucose, a radionuclide-labeled analogue of glucose, 2-[18F] fluoro-2-deoxy-D-glucose, can be used to detect sites of malignancy. The PET scan has the potential more accurately to delineate the extent of disease at the primary site and in lymph nodes. Rose et al. (18) performed PET scanning on 32 patients with stage IIB to IVA cervical cancer before surgical staging lymphadenectomy. For the paraaortic lymph nodes, PET scanning had a sensitivity of 75%, a specificity of 92%, a positive predictive value of 75%, and negative predictive value of 92% (18).

Fine-Needle Aspiration Cytology If pelvic or abdominal masses or enlarged lymph nodes are detected during physical examination or imaging studies, fine-needle aspiration may be performed under CT or ultrasonic guidance. The procedure is performed under local anesthesia and is free of major complications, even in the presence of clotting problems or perforation of a hollow viscus. The reported accuracy for abdominopelvic nodes ranges from 74% to 95% (19,20). **Only a positive cytologic diagnosis should be used as a basis for therapeutic decision making.**

Surgical Staging

The inability of available noninvasive diagnostic tests to detect small lymph node metastases led many investigators in the 1970s to undertake pretreatment staging laparotomies to identify patients with positive paraaortic nodes. These patients were then treated with extended-field radiation to encompass the involved nodes.

The initial approach used was transperitoneal, but this was associated with a significant risk of postoperative adherent, fixed loops of bowel and increased postradiation morbidity (21,22). Of the first 33 patients staged with this approach at the University of California, Los Angeles (UCLA), 10 (30.3%) subsequently had small bowel complications requiring surgical correction (23). The complications included enterovaginal fistulas in five patients, small bowel obstruction in nine, and radiation enteritis in six.

After this experience, the UCLA group introduced the extraperitoneal approach (23). Although originally described through a left lateral J-shaped incision, it is most readily performed through a midline incision, which facilitates easy access to both sides of the pelvis. The midline incision does not delay the onset of radiation therapy. Before the node dissection, the peritoneum is opened and a thorough exploration of the peritoneal cavity carried out. The peritoneum is then stripped off the anterior and lateral abdominal wall to expose the pelvic sidewall on each side. Each round ligament must be transected extraperitoneally to facilitate exposure. The dissection may be extended cephalad as far as necessary by extending the lower midline incision around the umbilicus to the epigastrium.

Surgical complications of staging laparotomies include damage to the great vessels, particularly the inferior vena cava, and ureteric injury, but are infrequent in the hands of an experienced surgeon. In the GOG report of almost 300 patients (7), the operative mortality was 0.3% (1 case), intraoperative injuries to the vein or ureter occurred in 4 cases (1.6%), and a postoperative urinary fistula or bowel obstruction occurred in 7 patients (2.9%).

Laparoscopic Staging

In the 1990s, some investigators have proposed laparoscopic staging (24). This is discussed in Chapter 20.

Patterns of Spread

Cervical cancer spreads by the following means:

1. **Direct invasion** into the cervical stroma, corpus, vagina, and parametrium
2. **Lymphatic permeation and metastasis**
3. **Hematogenous dissemination**

Direct Infiltration

Invasive cervical cancer, whether squamous or glandular, arises from intraepithelial neoplasia. Malignant cells penetrate the basement membrane, then progressively infiltrate the underlying stroma. They may progressively infiltrate laterally to involve the cardinal and uterosacral ligaments, superiorly to involve the endometrium, inferiorly to involve the vagina, anteriorly to involve the bladder, and posteriorly to involve the peritoneum of the pouch of Douglas and the rectum.

Lymphatic Spread

Cervical cancer can spread to all pelvic node groups, although the obturator nodes are most frequently involved. The parametrial nodes are not necessarily involved before the nodes on the pelvic sidewall. Although tumor cells can reach the common iliac and paraaortic nodes directly by the posterior cervical trunk (25), this is very uncommon, and **lymph node spread in cervical cancer almost invariably occurs in an orderly fashion from the nodes on the pelvic sidewall to the common iliac, and then the paraaortic group.** From the paraaortic nodes, spread can occasionally occur through the thoracic duct to the left scalene nodes (26,27). The incidence of pelvic lymph node metastases in stage IB cervical cancer is shown in Table 9.3. The incidence of paraaortic nodal metastases in stages II and III cervical cancer is shown in Table 9.4.

Author	Patients	Positive Nodes	%
Zander et al., 1981 (28)	860	163	18.9
Fuller et al., 1982 (29)	280	42	15.0
Tiemann et al., 1984 (30)	119	18	15.1
Inoue and Okamura, 1984 (31)	362	47	13.0
Creasman et al., 1986 (32)	258	36	14.0
Finan et al., 1986 (33)	229	49	21.4
Artman et al., 1987 (34)	153	13	8.5
Monaghan et al., 1990 (35)	494	102	20.6
Samlal et al., 1997 (36)	271	53	19.6
Total	3026	523	17.3

Table 9.3 Incidence of Pelvic Lymph Node Metastases in Stage IB Cervical Cancer

	Stage II			Stage III		
Author	Explored	Positive	%	Explored	Positive	%
Nelson et al., 1977 (22)	63	9	14.3	39	15	38.5
Delgado et al., 1977 (37)	18	8	44.4	13	5	38.5
Piver and Barlow, 1977 (38)	46	6	13.0	49	18	36.7
Subramanian et al., 1978 (39)	43	7	16.3	19	3	15.8
Buchsbaum, 1979 (26)	19	1	5.3	104	34	32.7
Hughes et al., 1980 (40)	80	14	17.5	96	23	24.0
Ballon et al., 1981 (41)	48	9	18.8	24	4	16.7
Welander et al., 1982 (42)	63	13	20.6	38	10	26.3
Berman et al., 1984 (43)	265	43	16.2	180	40	22.0
Polish et al., 1985 (44)	47	5	10.6	11	4	36.4
La Polla et al., 1986 (8)	47	6	12.8	28	14	50.0
Total	739	121	16.4	611	170	28.6

Table 9.4 Incidence of Paraaortic Lymph Node Metastases in Stages II and III Cervical Cancer

Lymphatic invasion by tumor cells is commonly seen in the primary tumor, and tumor cells are also seen occasionally in lymphatic channels in the parametrium. Burghardt and Girardi (45) believe that tumor emboli are sometimes held up in a lymphatic vessel, and grow to become foci of discontinuous parametrial involvement.

Ovarian involvement by cervical cancer is rare, but most likely occurs through the lymphatic connection between the uterus and the adnexal structures (46). In a study of patients with clinical stage IB cervical cancer, the GOG reported ovarian spread in 4 of 770 patients (0.5%) with squamous carcinoma, and in 2 of 121 patients (1.7%) with adenocarcinoma. All six patients with ovarian metastases had other evidence of extracervical spread (47).

Hematogenous Spread

Although spread to virtually all parts of the body has been reported, the most common organs for hematogenous spread are the lungs, liver, and bone. Less common sites are the bowel, adrenal glands, spleen, and brain (48).

Treatment

Treatment of invasive cancer involves appropriate management for both the primary lesion and potential sites of metastatic disease. Both surgery and radiation therapy may be used for primary treatment, although definitive surgery is usually limited to patients with stages I or early IIA disease. Some European and Japanese centers also treat patients with stage IIB disease with primary surgery.

Microinvasive Carcinoma

The term *microcarcinoma of the uterine cervix* was first introduced by Mestwerdt (49) in the German literature in 1947. He suggested that 5 mm was the deepest penetration acceptable. Since then, both terminology and treatment have been the subject of much debate.

In 1961, the Cancer Committee of FIGO recommended that clinical stage I cervical cancer should be subdivided into stage IA and stage IB, and stage IA was vaguely defined as a preclinical cancer with early stromal invasion. This did little to clarify even the definition.

In 1974, the Committee on Nomenclature of **the Society of Gynecologic Oncologists (SGO) in the United States proposed that microinvasive carcinoma should be defined as a lesion that invaded below the basement membrane to a depth of 3 mm or less, and in which there was no evidence of lymph vascular space invasion.** Although this definition provided no horizontal dimension, patients whose disease fulfilled these criteria were shown to have virtually no risk of lymph node metastases and to be adequately treated by either hysterectomy or cone biopsy (50,51 and 52).

In 1985, FIGO included measurements in the definition of stage IA disease for the first time (53). The new definition stated that stage IA was a preclinical carcinoma (i.e., diagnosed only by microscopy) and should be divided into two groups: stage IA1, minimal microscopically evident stromal invasion, and stage IA2, in which the depth of stromal invasion should not exceed 5 mm and the horizontal spread should not exceed 7 mm. Vascular space invasion did not influence the staging. This definition was a compromise of the volume concept proposed by Burghardt and Holzer (54) and Lohe (55), but still failed to define the border between stage IA1 and IA2 lesions.

A more precise definition of microinvasive carcinoma was adopted by FIGO in 1994. Stage IA1 was defined as a tumor that invaded to a depth of 3 mm or less, whereas stage IA2 referred to a tumor that invaded to a depth greater than 3 mm, up to 5 mm. In both stages, the horizontal spread should not exceed 7 mm. Lymph vascular space invasion was not included as part of the definition.

Stage IA1 Cervical Carcinoma

In an extensive review of the literature, Ostor (56) reported that among 2,274 squamous lesions with invasion of less than 1 mm, there were only 3 cases of lymph node metastases (0.1%) and 8 cases in which invasive recurrence developed (0.4%). Among 1,324 squamous lesions invading between 1 and 3 mm, there were 7 cases with lymph node metastases (0.5%) and 26 cases in which invasive recurrence developed (2%). Most of these cases were treated without lymph node dissection.

Although stromal invasion can be seen in small punch biopsies, a definitive diagnosis of microinvasion can be made only in conization (or hysterectomy) specimens (57). The conization specimen must be thoroughly sampled, not only to make the correct diagnosis, but to be certain about the margins.

Roman et al. (58) reported 87 cases of microinvasive carcinoma diagnosed on cone biopsy and followed by either repeat cone biopsy or hysterectomy. Significant predictors of residual invasion included status of the internal margin (residual invasion present in 22% of women with dysplasia at the margin vs. 3% with a negative margin; $p < 0.03$) and the combined status of the internal margin and the postconization ECC (residual invasion 4% if both negative, 13% if one positive, and 33% if both positive; $p < 0.015$). Depth of invasion and the number of invasive foci were not significant. They concluded that **if either the internal margin or the postconization ECC contained dysplasia or carcinoma, the risk of residual invasion was high and warranted repeat conization before definitive treatment planning.**

In view of these considerations, a cone biopsy with clear surgical margins and a negative ECC should be considered adequate treatment for a patient with stage IA1 squamous carcinoma of the cervix. If future childbearing is not required, extrafascial hysterectomy may be considered. If the cone margins or postconization ECC reveal dysplasia or microinvasive carcinoma, a repeat conization should be performed before proceeding to simple hysterectomy because more extensively invasive disease may be present.

Lymph vascular space invasion is uncommon in stage IA1 lesions, with Ostor (56) reporting an incidence of 15% from a literature review. Its significance is controversial, and it is not mentioned in the FIGO definition. It probably should be disregarded when planning treatment, unless it is extensive. A proposed algorithm for the management of microinvasive cervical cancer is shown in Fig. 9.4.

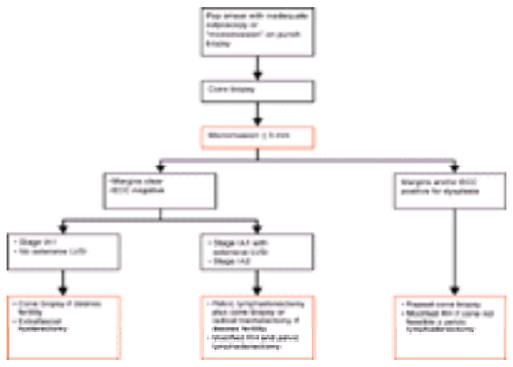

Figure 9.4 Algorithm for the management of patients with an abnormal Pap smear and inadequate colposcopy or with microinvasive squamous cervical carcinoma on punch biopsy. ECC, Endocervical curettage; LVSI, lymph vascular space invasion; RH, radical hysterectomy.

Stage IA2 Cervical Carcinoma

In spite of the extensive literature on microinvasive cervical carcinoma, there is limited information available on lesions 3 to 5 mm deep with up to 7 mm of horizontal spread (i.e., 1994 FIGO stage IA2 lesions). The 1985 FIGO definition of stage IA2 included all cases other than those with early stromal invasion, which usually meant approximately 1 mm of invasion. Hence, some large European studies of this group of patients would have underestimated the risk of lymph node metastases and invasive recurrence for patients whose tumors invaded 3 to 5 mm. For example, Kolstad (59), in a review of 411 patients with 1985 FIGO stage IA2 squamous carcinoma of the cervix, reported only 4 cancer-related deaths (1%) and 12 local recurrences (2.9%). Similarly, Burghardt et al. (60) reported 2 pelvic sidewall recurrences after abdominal hysterectomy among 89 patients (2.2%). A local recurrence developed in three other patients (3.4%). Four of the five recurrences had vascular space invasion.

Investigators in the United States have tended to separate lesions with invasion of 3 mm or less and no vascular space involvement from stage IA2 lesions because such cases met the SGO criteria for conservative management. Therefore, a few publications, mainly from the United States, have reported cases with stromal invasion of 3 to 5 mm, although most have not included the horizontal dimension currently required in the FIGO definition. The overall incidence of lymph node metastases in such cases was 7.3%, although it varied from 0% to 13.8% (Table 9.5). The incidence of invasive recurrence was 3%, whereas 2.3% of patients died of their disease. Most patients were treated by radical hysterectomy and pelvic lymph node dissection.

Author	No.	Nodal Metastases	Invasive Recurrences	Dead of Disease
Van Nagell et al., 1983 (61)	32	3 (9.4%)	3	2
Hasumi et al., 1980 (62)	29	4 (13.8%)	NS	NS
Simon et al., 1986 (52)	26	1 (3.8%)	0	0
Maiman et al., 1988 (63)	30	4 (13.3%)	0	0
Buckley et al., 1996 (64)	94	7 (7.4%)	5	4
Crossman et al., 1988 (65)	51	0 (0.0%)	0	0
Total	262	19 (7.3%)	8 (3.1%)	6 (2.3%)

NS, not stated.

Table 9.5 Incidence of Lymph Node Metastases with Stromal Invasion of 3 to 5 mm—Horizontal Dimension Not Stated

It is apparent that more data are needed for this group of patients, and it is hoped that the Cancer Committee of FIGO will not change the current definition, so that more information can be obtained about the risk of lymph node metastases and the risk of recurrence with various treatment approaches.

Our **recommended treatment for stage IA2 squamous carcinoma of the cervix is modified radical hysterectomy and pelvic lymph node dissection.** If childbearing is desired, cone biopsy with extraperitoneal or laparoscopic pelvic lymphadenectomy may be considered, although if there is vascular space invasion, a safer option may be to perform radical trachelectomy and pelvic lymphadenectomy (66). **In a medically unfit patient, intracavitary radiation may be used.**

Microinvasive Adenocarcinoma

Although the concept of microinvasive squamous carcinoma is well accepted, the concept for the glandular counterpart is more controversial, partly because of the lack of available data, but also because of the difficulty in accurately determining the true extent of glandular lesions. Microinvasion has usually been reported as depth of invasion or tumor thickness of 5 mm or less, the measurement being taken from the mucosal surface (67,68) or from the base of the surface epithelium (69). Width and volume of tumor involvement have varied considerably, and most reports have not looked specifically at microinvasion as now defined by the FIGO staging.

Most cases arise adjacent to the transformation zone, although Teshima et al. (70) reported that 3 of 30 cases (10%) were separate from it. They also reported that normal endocervical glands can vary in depth from 2 to 9 mm and that 10 of 22 cases (45.5%) of microinvasive adenocarcinomas had invasion beyond the level of the deepest endocervical gland.

Whereas squamous lesions are usually unifocal, glandular lesions are often multifocal. Ostor et al. (68) reported that 21 of 77 cases (27.3%) were multicentric, meaning that both cervical lips were affected, without continuity around the “edges” at 3 and 9 o'clock. They reported no “skip” lesions, which they arbitrarily defined as separation between discrete microinvasive adenocarcinomas in the same lip of greater than 3 mm.

Positive lymph nodes have not been reported in FIGO stage IA1 lesions. Berek et al. (67), in a report of 102 patients with primary adenocarcinoma of the cervix, reported no lymph node metastases in patients whose tumor was less than 2 cm in diameter, although 2 of 18 patients (11.1%) with 2 to 5 mm of invasion had positive nodes. Kaku et al. (69) reported recurrences at the vaginal vault in 2 of 30 patients (6.7%) with less than 5 mm of invasion. One patient had a tumor volume of 1,222 mm^3, but the other had a tumor with a depth of 3.9 mm and a width of 4.9 mm (i.e., FIGO stage IA2). The only adenocarcinoma recurrence in the 77 patients reported by Ostor et al. (68) involved a patient whose tumor invaded to a depth of 3.2 mm, but was 21 mm in length.

In view of these observations, **it seems reasonable to treat the disease in a similar manner to its squamous counterpart, with the proviso that cone biopsy for stage IA1 disease is likely to carry a somewhat increased risk because of the difficulty with follow-up.** Pap smears and colposcopy are less reliable, and Poynor et al. (71) reported that ECC was positive before cervical conization in only 43% of patients with glandular lesions.

Stage IB1 and Early Stage IIA Cancer

In 1994, FIGO recognized the prognostic significance of tumor size by subdividing stage IB disease into stage IB1 (primary lesion £4 cm diameter) and stage IB2 (primary lesion >4 cm diameter).

Patients with stage IB1 are universally regarded as being ideal candidates for radical hysterectomy and pelvic lymphadenectomy, although equal cure rates may be obtained with primary radiation therapy (72). The choice of modality should depend mainly on the availability of the appropriate expertise. Since the introduction of Fellowship training in gynecologic oncology, expertise in radical pelvic surgery is widely available in the United States and most developed countries. The recent “Patterns of Care” study in the United States suggests that the same may not be true for radiation oncology, particularly outside of tertiary referral units (73). If both surgical and radiotherapeutic expertise are available, radiation is usually reserved for the surgically unfit patient. **Chronologic age should not be considered a contraindication to radical surgery because elderly patients experience morbidity similar to that of younger patients** (74).

Primary surgery has the advantage of removing the primary disease and allowing accurate surgical staging, thereby allowing any adjuvant therapy to be more accurately targeted. In addition, it avoids the possible chronic radiation damage to the bladder, small and large bowel, and vagina, which is difficult to manage. Surgical injuries to the same organs are more readily repaired because the blood supply is not compromised. Sexual dysfunction is in general underreported, but is a real problem for many patients who have had both external-beam therapy and brachytherapy because of vaginal atrophy, fibrosis, and stenosis. Although the vagina is shortened by approximately 1.5 cm after radical hysterectomy, it is more elastic, and in premenopausal patients ovarian function can be preserved. In postmenopausal patients, the nonirradiated vagina responds much better to estrogen therapy.

Influence of Diagnostic Conization

The influence of previous cone biopsy on the morbidity of radical hysterectomy is controversial. Mikuta et al. (75) reported an increased risk of postoperative complications, including febrile morbidity and urinary fistulas, although the interval between conization and radical hysterectomy was less than 3 weeks. Samlal et al. (76) reported no significant difference in morbidity, but the conization–radical hysterectomy interval in their study was 6 weeks. They believed that delaying the definitive surgery may allow the tissue reaction to subside, thereby decreasing morbidity. Others have found the interval between the conization and radical hysterectomy to have no influence on morbidity, and recommend proceeding without delay (77,78). Our policy is to proceed immediately with radical hysterectomy if the surgical margins of the cone biopsy are involved, but to postpone surgery for 6 weeks if the cone margins are clear.

Types of Radical Hysterectomy

In 1974, Piver et al. (79) described the following five types of hysterectomy.

Extrafascial Hysterectomy (Type I) This is a simple hysterectomy and is suitable for stage IA1 cervical carcinoma.

Modified Radical Hysterectomy (Type II) This is basically the hysterectomy described by Ernst Wertheim (80). The uterine artery is ligated where it crosses the ureter, and the medial half of the cardinal ligaments and proximal uterosacral ligaments are resected. Piver et al. (79) described removal of the upper one third of the vagina, but this is rarely necessary unless vaginal intraepithelial neoplasia (VAIN) 3 extends well down the upper vagina. The operation described by Wertheim involved selective removal of enlarged nodes, rather than systematic pelvic lymphadenectomy. **The modified radical hysterectomy is appropriate for stage IA2 cervical cancer.**

Radical Hysterectomy (Type III) The most commonly performed operation for stage IB cervical cancer is that originally described by Meigs in 1944 (81). The uterine artery is ligated at its origin from the superior vesicle or internal iliac artery, allowing removal of the entire width of the cardinal ligaments. Piver et al. (79) originally described excision of the uterosacral ligaments at their sacral attachments, and resection of the upper half of the vagina. Such extensive dissection of the uterosacral ligaments and vagina is seldom required for stage IB cervical cancer.

Extended Radical Hysterectomy (Type IV) This differs from the type III operation in three aspects: (a) the ureter is completely dissected from the vesicouterine ligament, (b) the superior vesicle artery is sacrificed, and (c) three fourths of the vagina is excised. The risk of fistula is increased with this procedure, which Piver et al. (79) used for selected small central recurrences after radiation therapy.

Partial Exenteration (Type V) The indication for this procedure was removal of a central recurrence involving a portion of the distal ureter or bladder. The relevant organ was partially excised and the ureter reimplanted into the bladder. This procedure is occasionally performed if cancer is found to be unexpectedly encasing the distal ureter at the time of radical hysterectomy. Alternatively, the operation may be aborted and the patient treated with primary radiation.

Technique for Radical Hysterectomy

The patient is given prophylactic antibiotics for 24 hours and pneumatic calf compressors are used during and after surgery until the patient is fully mobilized. In addition, prophylactic subcutaneous *heparin* is given for 5 days after surgery.

Incision The abdomen may be opened either through a lower midline incision extending to the left of the umbilicus or through a low transverse **Maylard or Cherney** incision. The low transverse incision, which is described in Chapter 19, requires division of the rectus abdominis muscle but provides excellent exposure of the primary tumor and pelvic sidewalls. The midline incision, which can be readily extended, provides better exposure of the paraaortic region, but this is seldom necessary for early-stage cervical cancer.

Exploration After entering the peritoneal cavity, all organs are systematically palpated and any evidence of metastatic spread is documented by frozen section. The vesicouterine fold and pouch of Douglas peritoneum are examined for evidence of tumor infiltration and the tubes and ovaries are examined for any abnormalities. Any bulky pelvic or paraaortic nodes are noted and frozen sections obtained to differentiate between inflammatory and malignant changes.

Radical Hysterectomy With the uterus under traction, the retroperitoneum is entered through the round ligaments bilaterally. The ureter is identified as it crosses the pelvic rim, and the pelvic sidewall spaces are developed by a combination of sharp and blunt dissection (Fig. 9.5).

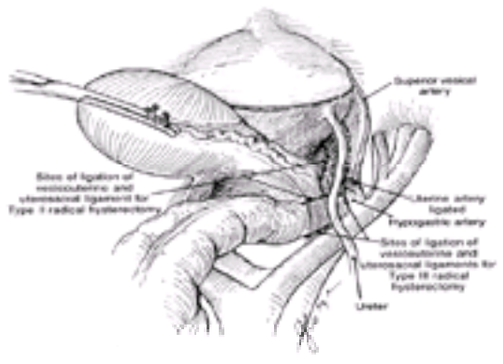

Figure 9.5 Radical hysterectomy. Uterine artery is ligated, ureter is dissected, and sites for division of the vesicouterine and uterosacral ligaments are shown.

The **paravesicle space** is bordered by:

1. The obliterated umbilical artery (a continuation of the superior vesicle artery) running along the bladder medially
2. The obturator internus muscle laterally
3. The cardinal ligament posteriorly
4. The pubic symphysis anteriorly

The **pararectal space** is bordered by:

1. The rectum medially
2. The hypogastric artery laterally
3. The cardinal ligament anteriorly
4. The sacrum posteriorly

The floor of the spaces is formed by the levator ani muscle.

Bladder Takedown The vesicouterine fold of peritoneum is opened and the bladder dissected off the anterior cervix and upper vagina. This should be done before any blood supply is ligated, because occasionally tumor may infiltrate into the bladder base, making hysterectomy impossible. Rather than resecting the relevant section of the bladder in this situation, the abdomen is usually closed and the patient treated with primary radiation.

Ligation of the Uterine Artery The uterine artery usually arises from the superior vesicle artery, close to its origin from the hypogastric artery. The artery is ligated at its origin, then mobilized over the ureter by gentle traction and dissection. The uterine veins must be identified and clipped or troublesome bleeding will occur.

Dissection of the Ureter The roof of the ureteric tunnel is the anterior vesicouterine ligament. This can be taken down in a piecemeal fashion bilaterally, thereby avoiding the troublesome venous bleeding that can occur by blindly advancing a right-angled forceps into the tunnel. Each ureter is mobilized off its peritoneal attachment fairly low in the pelvis to avoid unnecessary stripping from its peritoneal blood supply. It is also mobilized off the side of the uterus. This exposes the posterior vesicouterine ligament, which is also divided in a type III hysterectomy, but not in a type II procedure. The anterolateral surface of the distal ureter is left attached to the bladder in a further effort to preserve the blood supply.

Posterior Dissection The peritoneum across the pouch of Douglas is incised and the rectovaginal space identified by posterior traction on the rectum. The rectum is taken off the posterior vagina and the uterosacral ligaments using sharp and blunt dissection, and the latter are divided midway to the sacrum (Fig. 9.6).

supply.

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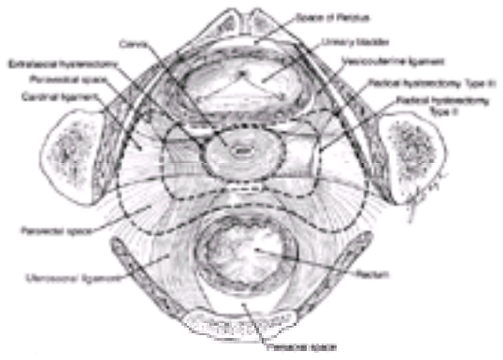

Figure 9.6 The pelvic ligaments and spaces.

Lateral Dissection After division of the uterosacral ligaments, the cardinal ligaments are clamped at the level of the pelvic sidewall, after which a further two clamps are usually required across the paravaginal tissues to reach the vagina. If the ovaries are to be removed, the infundibulopelvic ligaments are divided at this stage. If they are to be retained, they are freed from the fundus by transecting the ovarian ligament and fallopian tube.

Vaginal Resection The length of vagina to be removed depends on the nature of the primary lesion and the colposcopic findings in the vagina. If the primary lesion is confined to the cervix and there is no evidence of VAIN, it is necessary to resect only 1.5 to 2 cm of upper vagina. This is achieved by entering the vagina anteriorly and transecting it with a knife or scissors. The vault is closed, making sure to avoid “dog ears.” The vaginal angles are sutured to the paravaginal tissues.

Pelvic Lymphadenectomy Once the uterus has been removed, the pelvic sidewall exposure is excellent. If there are any bulky positive pelvic or paraaortic lymph nodes confirmed by frozen section, our policy is to remove only the enlarged nodes and rely on external-beam radiation to sterilize any micrometastases. If there are no suspicious nodes, full pelvic lymphadenectomy is performed (Fig. 9.7). Using sharp dissection with Metzenbaum scissors, all fatty tissue is stripped off the vessels from the middle common iliac region to the circumflex iliac vein distally, preserving the genitofemoral nerve on the psoas muscle. The obturator fossa is entered by retracting the external iliac artery and vein medially, then stripping the fatty tissue off the pelvic sidewall. All fatty tissue is then sharply dissected out of the obturator fossa, taking care particularly to avoid the obturator nerve, which enters the fossa at the bifurcation of the common iliac vein. An accessory obturator vein is seen in approximately 20% of patients and is easily torn if not identified. It enters the distal external iliac vein inferiorly.

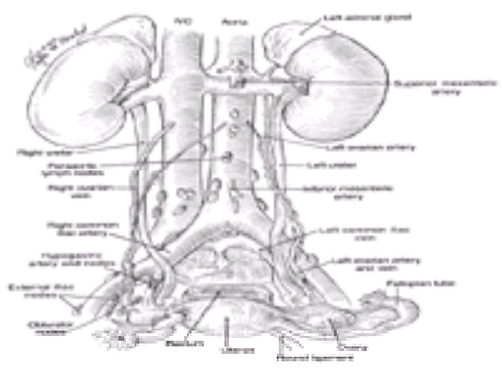

Figure 9.7 The pelvic and paraaortic lymph nodes and their relationship to the major retroperitoneal vessels. (From Hacker NF, Moore JG, eds. *Essentials of obstetrics and gynecology.* Philadelphia: WB Saunders, 1986:8, with permission.)

Postextirpation The peritoneal cavity is irrigated with warm water or saline. The pelvic peritoneum is not closed, and no drains are used unless there is concern about hemostasis. When the retroperitoneal space is left open and prophylactic antibiotics are used, drains may actually increase febrile morbidity, pelvic cellulitis, and length of postoperative ileus (82). A suprapubic catheter is placed in the bladder, and the abdomen closed with a continuous mass closure technique.

Complications of Radical Hysterectomy

Intraoperative The average blood loss reported is usually between 800 (83) and 1,500 mL (84). Intraoperative injuries occasionally occur to the pelvic blood vessels, ureter, bladder, rectum, or obturator nerve. These injuries should be recognized immediately and repaired. Even complete severance of the obturator nerve does not usually cause problems with walking.

Postoperative Complications Detailed information about postoperative morbidity is infrequently supplied. Table 9.6 gives data from three series from which detailed information is available. It can be seen that urinary tract infection is the most common complication, related to the need for prolonged catheter drainage. Other febrile morbidity from such causes as atelectasis or wound infection is also relatively common. Venous thrombosis is undoubtedly underdiagnosed, but with proper prophylactic measures, pulmonary embolism is infrequent. Vesicovaginal or ureterovaginal fistulas occur in approximately 1% of cases.

Complication	Powell et al. (1988) (83) N = 135 (%)	Samlal et al. (1998) (84) N = 271 (%)	Sivanesaratnam et al. (1990) (86) N = 397 (%)
Early			
Urinary tract infection	10 (7.4)	NS	36 (9.1)
Venous thrombosis	6 (4.4)	6 (2.2)	9 (2.3)
Pulmonary embolism	4 (3.0)	1 (0.4)	2 (0.5)
Ureterovaginal fistula	0 (0.0)	5 (1.8)	1 (0.3)
Vesicovaginal fistula	2 (1.5)	2 (0.7)	2 (0.5)
*Fever**	16 (11.9)	10 (3.7)	2 (0.5)
Lymphocyst	2 (1.5)	8 (3.0)	3 (0.8)
Ileus	3 (2.2)	9 (3.3)	NS
Burst abdomen	0 (0.0)	1 (0.4)	1 (0.2)
Ureteral obstruction	2 (1.5)	1 (0.4)	0 (0.0)
Late			
Prolonged bladder dysfunction	4 (3.0)	14 (5.2)	3 (0.8)
Lymphedema	NS	20 (7.4)	4 (1.0)
Sexual dysfunction	NS	6 (2.2)	NS

*Pelvic abscess, pelvic cellulitis, atelectasis, wound infection, ileus, abscess not specified.

Table 9.6 Postoperative Complications of Radical Hysterectomy

Late Complications The most distressing late complication is prolonged bladder dysfunction, necessitating voiding by the clock with the aid of the abdominal muscles, and, in some cases, self-catheterization. Although not all investigators have been able to correlate bladder dysfunction with surgical radicality (87), Covens et al. (88) reported a significant difference in the incidence of bladder dysfunction at 3 months among different surgeons at the University of Toronto. Twenty-one percent of patients reported objective or subjective bladder dysfunction, but the range among the 8 surgeons concerned varied from 0% to 44%. Samlal et al. (84) from Amsterdam, using a more radical dissection of the cardinal ligaments than is usually done in the United States (Okabayashi technique), reported a 5.1% incidence of this complication.

Voiding difficulties are inevitable in the immediate postoperative period and suprapubic or urethral catheter drainage is desirable for the first week. If cystometry is performed, two abnormal patterns are found (89). The hypertonic bladder with elevated urethral pressure is most common. The hypotonic bladder occurs much less frequently. Patients with a hypertonic pattern have the normal bladder filling sensation and the usual discomfort of a full bladder. The condition is self-limiting, usually within 3 weeks of surgery. The prognosis is much worse for patients with a hypotonic bladder, and some of these patients eventually require lifelong self-catheterization.

Lymphedema is a late complication that may not appear for several months or years. Because of its delayed onset, its true incidence is almost certainly underreported. Fortunately, in the absence of pelvic radiation or groin node dissection, the lymphedema associated with pelvic lymphadenectomy is seldom severe.

Sexual Dysfunction The reported incidence of sexual dysfunction after radical hysterectomy is tolerably low, except for patients receiving postoperative radiation therapy (90). However, this aspect of surgical mortality has been inadequately studied.

Stage IB2 Cervical Carcinoma

Optimal management of patients with primary tumors greater than 4 cm in diameter is controversial. Local, regional, and distant failure are more likely than for stage IB1 lesions whatever primary modality of treatment is chosen. Most patients are cured, so quality of life is an important issue, and properly randomized trials are necessary to determine the best approach.

Primary Radiation Therapy This has usually been recommended, but high doses of brachytherapy must be given, and complication rates are high. Perez et al. (91), in a study of 56 patients with stage IB to IIA cervical cancer treated with radiation alone, reported serious morbidity in 28% of cases, including one rectovaginal fistula, two vesicovaginal fistulas, one rectal stricture, one ureteral stricture, one severe pelvic infection, two vault necroses, and five vaginal stenoses. In this study, patients with endocervical tumors greater than 5 cm in diameter were excluded, yet pelvic failure still occurred in five patients (9%). Montana et al. (92) reported grade II and III morbidity in 8% of cases of stage IB squamous carcinoma treated with radiation alone, and noted a relationship between the dose to point A and the dose to the bladder and rectum, and the incidence of complications.

Radiation and Extrafascial Hysterectomy To decrease the central failure rate, several authors have advocated a completion simple hysterectomy after pelvic radiation. In 1969, Durrance et al. (93) initially reported that central failure could be reduced from 15% (14 of 94 patients) to 2.6% (1 of 39 patients) by the addition of extrafascial hysterectomy. Gallion et al. (94), in a study of 75 patients with bulky, barrel-shaped stage IB cervical cancers, reported recurrence in 47% of patients treated with radiation alone, compared with 16% of those treated with adjuvant hysterectomy ($p < 0.01$). Pelvic recurrence was reduced from 19% to 2% and extrapelvic recurrence from 16% to 7%. They did not note an increased risk of complications, but other investigators have noted higher morbidity with this approach, without significant survival advantage (95).

Radiation, Extrafascial Hysterectomy, and Chemotherapy A 1999 GOG study (96) of bulky (≥4 cm) cervical cancers randomly assigned patients to be treated with radiation therapy (external beam and intracavitary cesium) and adjuvant extrafascial hysterectomy 3 to 6 weeks later, with or without weekly *cisplatin* during the external radiation. *Cisplatin* was to be delivered at a dose of 40 mg/m^2 (maximum dose, 70 mg/week) weekly for 6 weeks. There were 374 patients entered into the study. Residual cancer in the hysterectomy specimen was significantly reduced in the group receiving *cisplatin* (47% vs. 57%). Survival at 24 months was significantly improved by the addition of *cisplatin* (89% vs. 79%), as was recurrence-free survival (81% versus 69%). Grade 3 and 4 hematologic and gastrointestinal toxicities were more frequent in the group receiving *cisplatin*, whereas other toxicities were equivalent in both treatment arms.

Preoperative Brachytherapy This approach has been used for many years in Great Britain and Australia for early cervical cancer, and a contemporary series of patients treated in this manner from Groningen, The Netherlands was reported in 1984 (97). Between 1970 and 1978, 119 patients with stage IB and 58 patients with stage IIA disease were treated with preoperative radium followed by Wertheim hysterectomy and pelvic lymphadenectomy. A potential problem with this approach is that if positive nodes are found at surgery, and postoperative external-beam therapy is added, complication rates are increased. For example, in the Groningen study, ureteric obstruction was reported in 12 patients (7%), 8 of whom had received postoperative pelvic radiation.

Neoadjuvant Chemotherapy In 1993, Sardi et al. (98) reported the results of a randomized trial of neoadjuvant chemotherapy for patients with bulky stage IB cervical cancer. In the control arm (75 patients), a Wertheim-Meigs operation followed by adjuvant whole-pelvic radiation was carried out, whereas in the neoadjuvant group (76 patients), the same procedures were preceded by three cycles of chemotherapy with the "quick" VBP regimen *(vincristine, bleomycin, cisplatin)*. The chemotherapy protocol consisted of *cisplatin* 50 mg/m^2 on day 1, *vincristine* 1 mg/m^2 on day 1, and *bleomycin* 25 mg/m^2 on days 1, 2, and 3 (the latter given as a 6-hour infusion). Three cycles were given at 10-day intervals. Survival and progression-free interval were significantly improved for patients with an echographic volume greater than 60 mL, mainly because of a decrease in the incidence of locoregional failures. In the control group, pelvic recurrences were observed in 24.3% of patients, compared with 7.6% of patients in the neoadjuvant group.

Although these results are provocative, these patients received radical surgery, pelvic radiation, and neoadjuvant chemotherapy, and the role of neoadjuvant therapy must await further randomized trials.

Primary Radical Hysterectomy and Tailored Postoperative Radiation Our preferred option for the management of stage IB2 carcinoma of the cervix is primary radical hysterectomy and postoperative adjuvant radiation, with or without chemotherapy, depending on the operative

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Primary Radical Hysterectomy and Tailored Postoperative Radiation Our preferred option for the management of stage IB2 carcinoma of the cervix is primary radical hysterectomy and postoperative adjuvant radiation, with or without chemotherapy, depending on the operative findings (Fig. 9.8). This philosophy is also applied to patients with stage IIA disease, provided the tumor does not come down the anterior vaginal wall. Our approach to stage IB or IIA cervical cancer is shown in Fig. 9.9. **Older patients tolerate radical surgery remarkably well, although approximately 10% of patients older than 70 years of age have a medical contraindication to surgery** (74). These patients require primary radiation therapy, but comorbid conditions in the elderly necessitate more frequent treatment breaks and less ability to deliver intracavitary therapy, thereby impairing overall prognosis (99).

Figure 9.8 Radical hysterectomy specimen from a patient with an exophytic stage IB2 cervical cancer.

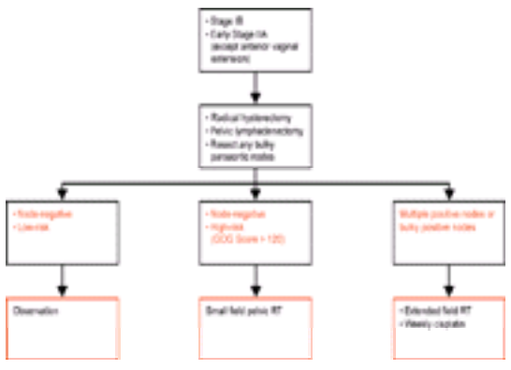

Figure 9.9 Algorithm for the management of stages IB and early IIA carcinoma of the cervix. RT, radiation therapy; GOG, Gynecologic Oncology Group.

There are several advantages to a primary surgical approach. First, it allows for accurate staging of the disease, thereby allowing adjuvant therapy to be modified according to needs (100). **Second, it allows resection of bulky positive lymph nodes,** thereby improving the prognosis significantly (101,102). **Third, it allows removal of the primary cancer,** thereby avoiding the difficulty of determining whether there is viable residual disease after the cervix has responded to radiation. **Finally, for most premenopausal patients, it allows preservation of ovarian function.** A primary surgical approach is mandatory in patients with acute or chronic pelvic inflammatory disease, anatomic problems making optimal radiation therapy difficult, or an undiagnosed coexistent pelvic mass (103).

In a retrospective study comparing radical hysterectomy for stage IB1 versus IB2 disease, Finan et al. (33) reported no significant increase in morbidity for patients with stage IB2 disease. They noted positive nodes in 15.5% of patients (28 of 181) with stage IB1 disease versus 43.8% (21 of 48) with stage IB2. Positive paraaortic nodes were present in 1.8% of patients having paraaortic dissection for stage IB1 disease (2 of 111) versus 6.3% of patients with stage IB2 (2 of 32). These patients cannot be salvaged without extended-field radiation (40).

In addition, **approximately half of patients with positive nodes have bulky nodal metastases. These patients are also unlikely to be salvaged without resection of the bulky nodes, but if the bulky nodes are resected and the patient is given adjuvant radiation, the prognosis is converted to that of a patient with nodal micrometastases** (101,102,104).

In the report by Finan et al. (33), positive surgical margins were noted in 5.0% of patients (9 of 181) with stage IB1 disease versus 12.5% of patients (6 of 48) with stage IB2. In addition, 77% of patients (27 of 35) with stage IB2 disease had more than 15 mm of stromal invasion, compared with 27.3% of patients (30 of 110) with stage IB1. Patients with positive margins and deep stromal invasion are likely to benefit from external radiation. The group at the University of California, Irvine reported delayed complications, including fistulas and bowel obstructions, in 4.8% of patients (2 of 42) with stage IB2 disease treated with surgery alone, compared with 14.3% of women (6 of 42) treated with combined therapy (105). **At the Royal Hospital for Women in Sydney, we have devised a small field of pelvic radiation to decrease the delayed complication rate in patients requiring adjuvant pelvic radiation but with negative lymph nodes. Pilot data suggest that this approach can decrease the local recurrence rate, as well as decrease serious morbidity** (106).

In the only randomized, prospective study looking at radical surgery versus primary radiation for stage IB to IIA cervical cancer, Landoni et al. (72) reported that for patients with a cervical diameter larger than 4 cm, the rate of pelvic relapse in the group treated with radiation therapy was more than twice the rate of distant relapse (30% vs. 13%). In addition, there was a significantly higher rate of pelvic relapse among those who had radiation alone (16 of 54; 30%) compared with those who had surgery plus adjuvant radiation (9 of 46; 20%).

Prognostic Factors for Stage IB to IIA

The major prognostic factors for patients having radical hysterectomy and pelvic lymphadenectomy for stage IB to IIA are:

1. Status of the lymph nodes
2. Size of the primary tumor
3. Depth of stromal invasion
4. Presence or absence of lymph-vascular space invasion
5. Presence or absence of parametrial extension
6. Histologic cell type
7. Close vaginal margins

Lymph Node Status The most important prognostic factor is the status of the lymph nodes. Survival data for patients with positive nodes are shown in Table 9.7. The influence of the number of positive nodes is shown in Table 9.8. Patients with positive paraaortic nodes treated with extended-field radiation have a 5-year survival rate of approximately 50% (102,116).

		5-Year Survival Rate (%)		
Author	No.	Negative Nodes	Positive Nodes	Overall
Langley et al., 1980 (107)	204	94	65	87
Benedet et al., 1980 (108)	202	81	66	73
Kenter et al., 1989 (109)	213	94	65	87
Lee et al., 1989 (110)	954	88	73	86
Monaghan et al., 1990 (111)	498	91	51	83
Aghan et al., 1991 (112)	278	91	63	84
Averette et al., 1993 (113)	978	96	64	90
Samlal et al., 1996 (36)	271	95	76	90

Table 9.7 Survival after Radical Hysterectomy for Stages IB and IIA Cervical Cancer

		No. of Positive Nodes		
Author	Patients	1	1-3	>4
Noguchi et al., 1987 (114)	177	–	54	43
Lee et al., 1989 (110)	954	62	–	44
Inoue and Morita, 1990 (115)	464	91	–	50

Table 9.8 Five-Year Survival Rate (%) versus Number of Positive Pelvic Nodes in Stage IB Cervical Carcinoma

Tumor Size, Depth of Stromal Invasion, Lymph-Vascular Space Invasion In 1989, the GOG (117) published the results of a prospective clinicopathologic study of 732 patients with stage IB cervical carcinoma treated by radical hysterectomy and bilateral pelvic lymphadenectomy. Of these, 645 patients had no gross disease beyond the cervix/uterus and negative paraaortic nodes. One hundred patients had micrometastases in pelvic nodes, but their survival was not significantly different from patients with negative nodes.

There were three independent prognostic factors:

1. Clinical tumor size
2. Lymph-vascular space invasion
3. Depth of tumor invasion

A relative risk (RR) was calculated for each prognostic variable, and an overall estimate of risk determined by multiplying the appropriate RR for the three independent variables. For example, a tumor 4 cm in diameter was estimated to have a RR of 2.9. If it invaded 12 mm into the outer third of the cervix, the RR was estimated to be 37. Lymph-vascular space invasion conferred a RR of 1.7. The overall estimate of risk was therefore 2.9 × 37 × 1.7 = 182.4. The latter figure may be termed the GOG score. Disease-free survival curves were constructed for several RR groups (Fig. 9.10). It can be seen that the likelihood of recurrence for a patient with a GOG score greater than 120 is 40% at 3 years.

Figure 9.10 Disease-free survival for patients with cervical cancer after radical hysterectomy and bilateral pelvic lymphadenectomy. (From Delgado G, Bundy B, Zaino R, Sevin B-U, Creasman WT, Major F. Prospective surgical-pathological study of disease-free interval in patients with stage IB squamous cell carcinoma of the cervix: a Gynecologic Oncology Group study. *Gynecol Oncol* 1990;38:352–357, with permission.)

The extent of lymph-vascular space invasion varies markedly between tumors, and Roman et al. (118) have shown that **the quantity of lymph-vascular space invasion correlates significantly with the risk of nodal metastases in women with early-stage cervical cancer**.

Parametrial Invasion Burghardt et al. (119) analyzed 1,004 cases of stage IB, IIA, or IIB cervical carcinoma treated by radical hysterectomy at Graz, Munich, and Erlangen, with all surgical specimens processed as giant sections. This processing technique allows accurate assessment of tumor volume and parametrial extension. The 5-year survival rate for 734 patients with no parametrial extension was 85.8%, compared with 62.4% for 270 patients with parametrial extension. The group at Yale (120) reported that patients with parametrial extension, regardless of lymph node status, had a significantly shorter disease-free interval than patients with positive nodes alone, with 12 of 19 such patients (63%) recurring in the pelvis.

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Histologic Cell Type **Small cell carcinoma of the cervix is uncommon but has an unequivocally poor prognosis** (121).

The prognostic significance of adenocarcinoma histologic type is more controversial. These tumors usually arise in the endocervical canal and diagnosis is often delayed, so it is difficult to be certain that lesions of comparable size are being compared. **An increasing number of centers are reporting adenocarcinoma histologic type as a poor prognostic factor in multivariate analysis** (120,121,122,123 and 124), but Shingleton et al. (125) were unable to confirm this. In a Patient Care Evaluation Study of the American College of Surgeons, they evaluated 11,157 patients from 703 hospitals with cervical cancer treated in 1984 and 1990. There were 9,351 cases of squamous carcinoma (83.8%), 1,405 cases of adenocarcinoma (12.6%), and 401 cases of adenosquamous carcinoma (3.6%). In a multivariate analysis of patients with clinical stage IB disease, histologic type had no significant effect on survival.

The prognostic significance of adenosquamous carcinoma of the cervix is also controversial, with some authors reporting a significantly worse prognosis for patients with these tumors (126,127), whereas others report no difference from squamous lesions with respect to metastatic potential or outcome (128).

Close Vaginal Margins Investigators at the Jackson Memorial Hospital in Miami, Florida reviewed the charts of 1,223 patients with stage IA2, IB, or IIA cervical cancer who had undergone radical hysterectomy (113). Fifty-one patients (4.2%) had positive or close vaginal margins, the latter being defined as tumor no more than 0.5 cm from the vaginal margin of resection. Twenty-three of these cases had negative nodes and no parametrial involvement, and 16 of the 23 (69.6%) received postoperative radiation. The 5-year survival rate was significantly improved by the addition of adjuvant radiation (81.3% vs. 28.6%; $p < 0.05$). They recommended that close vaginal margins without other high-risk factors should be considered a poor prognostic variable.

Newer Markers

Several newer markers have been reported to have prognostic value in early stage cervical cancer.

Serum Squamous Cell Carcinoma Antigen Level The group at Groningen, The Netherlands, have demonstrated that increased pretreatment serum squamous cell carcinoma antigen (SCC-Ag) levels correlate strongly with FIGO stage, tumor size, deep stromal invasion, and lymph node metastases (129). Even in node-negative patients, the risk of recurrence was three times higher if the SCC-Ag level was elevated before surgery.

Human Papillomavirus Genotype Cervical tumors associated with human papillomavirus (HPV) type 18 have been associated with an increased risk of recurrence and death in patients with surgically treated cervical cancer (130,131). It has also been suggested that HPV-18–containing tumors may progress to invasion without a prolonged preinvasive phase (132).

Microvessel Density Because angiogenesis is considered essential for tumor growth and the development of metastases, it is not surprising that high microvessel density has been reported adversely to influence survival in clinical stage IB cervical cancer, and to identify patients with negative nodes at risk for relapse (133).

Postoperative Radiation

Traditionally, adjuvant pelvic radiation has been given for positive pelvic nodes and positive or close surgical margins. For the latter indication, pelvic radiation effectively reduces the risk of relapse (134). For the former indication, pelvic radiation reduces the risk of pelvic recurrence, but does not improve survival (135,136). These findings are not surprising because patients with close surgical margins are mainly at risk for pelvic recurrence, whereas patients with positive pelvic nodes are mainly at risk for paraaortic and systemic recurrence.

The Southwest Oncology Group (137) reported that the addition of chemotherapy to pelvic radiation did improve survival for high-risk patients. They **conducted a randomized study of women with FIGO stage IA2, IB, and IIA carcinoma of the cervix found to have metastatic disease in pelvic lymph nodes, positive parametrial involvement, or positive surgical margins at the time of primary radical hysterectomy and pelvic lymphadenectomy.** Patients had to have confirmed negative paraaortic nodes. The regimens were as follows:

Regimen I: external pelvic radiation with *cisplatin* and *5-fluorouracil (5-FU)* infusion

Regimen II: external pelvic radiation

Patients on regimen I received intravenous *cisplatin* 70 mg/m^2 followed by a 96-hour continuous intravenous infusion of *5-FU* (4,000 mg/m^2) every 3 weeks for 4 courses. Radiation therapy in both arms delivered 4,930 cGy to the pelvis using a four-field box technique. Patients with metastatic disease in high common iliac nodes also received 4,500 cGy to a paraaortic field.

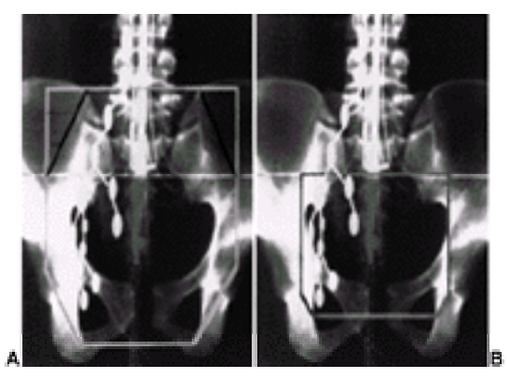
The 3-year survival rate for women on the adjuvant chemotherapy plus radiation arm was 87%, compared with 77% for women receiving adjuvant radiation alone. This difference was statistically significant.

The situation with respect to patients with negative nodes is different. Although these patients have an 85% to 90% survival rate after radical hysterectomy and pelvic lymphadenectomy, they contribute approximately 50% of the treatment failures, with most of the failures (about 70%) occurring in the pelvis (138,139). Therefore, **if a group of high-risk, node-negative patients could be identified, and treated with adjuvant pelvic irradiation, it might be expected that both pelvic recurrence and overall survival would be increased.**

The problem with combining pelvic radiation with radical hysterectomy is the increased morbidity to bowel and bladder in particular (140,141). Radiation morbidity is highly correlated with the target volume, and a clinical review of our experience in patients with stage IB, node-negative, cervical cancer at the Royal Hospital for Women in Sydney revealed that 87% of recurrences occurred in the central pelvis (vaginal vault or paravaginal soft tissues). We therefore decided to pilot a study involving a radiation field focused on the central pelvis to see if the central failure rate could be decreased without causing significant morbidity. The portals for the standard and small pelvic radiation fields used on patients treated at the Royal Hospital for Women are shown in Table 9.9 (Fig. 9.11). The small field decreases the amount of small and large bowel that is irradiated (106).

	Standard Field	Small Field
Anteroposterior		
Superior	L4-5 junction	S1-2 junction
Inferior	Inferior obturator foramen	Mid-obturator foramen
Lateral	1.5 cm lateral to pelvic brim	Bony pelvic brim
Lateral		
Anterior	Outer edge of pubic symphysis	1 cm posterior to pubic tubercle
Posterior	Ischial tuberosities	Anterior sacral plane

Table 9.9 Anteroposterior and Lateral Portals for Standard- and Small-Field Pelvic Radiation Used for Patients from the Royal Hospital for Women, Sydney



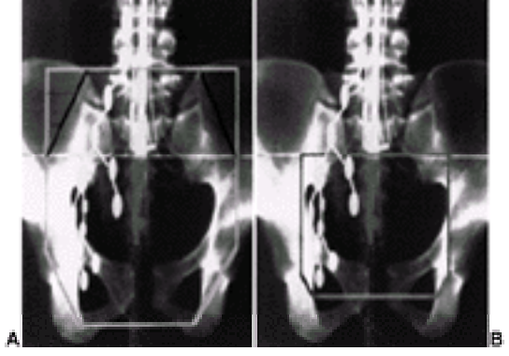


Figure 9.11 Comparison between (A) **standard field and** (B) **small field for pelvic radiation.**

High-risk, node-negative patients were selected on the basis of a GOG score of at least 120 (Fig. 9.11). Twenty-five consecutive patients were selected, with a mean GOG score of 166 (range, 120 to 263). With a mean follow-up of 32 months (range, 12 to 64 months), there was only one recurrence (4%), at 16 months. A log-rank analysis demonstrated a significant improvement in the 5-year disease-free survival rate when this group was compared with the high-risk patients in the GOG study (GOG score >120) who were observed without postoperative radiation (p = 0.005) (106). No major morbidity occurred, but minor morbidity was recorded in four patients: lymphedema in three, and mild rectal incontinence in one.

If this pilot data can be verified in other centers, a randomized, prospective study would be justified to determine whether small-field adjuvant pelvic radiation should become the standard approach for patients with high-risk, node-negative cervical cancer after radical hysterectomy and pelvic lymphadenectomy.

The GOG has presented preliminary results of a randomized study of adjuvant whole-pelvic radiation at a dose of 50.4 Gy versus no further treatment after radical hysterectomy for patients with high-risk, node-negative stage IB cervical cancer (142). To be eligible for the study, patients had to have at least two of the following risk factors: greater than one-third stromal invasion, lymph vascular space invasion, and large tumor size (usually ³4 cm). There were 277 patients entered into the study. **The addition of radiation significantly reduced the risk of recurrence, with a recurrence-free rate of 88% for radiation and 79% for no further treatment at 2 years.** Survival analysis awaits longer follow-up. Severe (GOG grade 3/4) gastrointestinal or urologic toxicity occurred in 5.8% of cases.

Stage IIB to IVA Disease

Primary Radiation Therapy

Radiation therapy can be used to treat all stages of cervical cancer, but for early-stage disease, it is usually reserved for medically unfit patients. Radical external-beam radiation therapy plus brachytherapy is the gold standard for advanced cervical cancer, but as the volume of the primary lesion increases, the likelihood of sterilizing it with radiation decreases. Increasing the dose of radiation increases the late morbidity to the bowel, bladder, and vaginal vault, so **various strategies have been investigated to try to improve local control, without compromising survival.**

Strategies that have been investigated include:

1. **Hyperfractionation** of the radiation
2. **Use of hypoxic cell radiation sensitizers**
3. **Concurrent use of radiation and chemotherapy** (chemoradiation)
4. **Neoadjuvant chemotherapy before radiation**

Six randomized trials of neoadjuvant chemotherapy followed by radiation have failed to show any advantage in terms of local control or survival (143). Hyperfractionated radiation has not been adequately tested, so the two most promising approaches appear to be the use of hypoxic cell radiation sensitizers and the use of concurrent chemotherapy and radiation.

Radiation Sensitizers

Hydroxyurea is the best-studied radiation sensitizer. It inhibits ribonucleotide diphosphate reductase, an enzyme necessary for DNA synthesis and repair, thereby killing cells during the S phase, a time of relative radioresistance. In addition, *hydroxyurea* blocks cells at the G_1–S interphase, rendering those cells remaining in G_1 more radiosensitive and thereby increasing the number of vulnerable cells (144).

The GOG conducted a randomized, prospective study of standard pelvic radiation with *hydroxyurea* or placebo for patients with stage IIIB and IVA disease (145). Complete tumor regression, progression-free interval, and survival probability were all increased in patients in the *hydroxyurea* arm.

Subsequently, the GOG compared *hydroxyurea* with *misonidazole* in a randomized study of 294 patients with stage IIB to IVA disease (146). *Hydroxyurea* proved to be superior to *misonidazole* in terms of progression-free interval and survival.

Concurrent Chemotherapy and Radiation

The main agents that have been used are *5-FU* and *cisplatin*, and both are also radiation sensitizers. Concurrent chemotherapy offers several theoretical advantages over the neoadjuvant strategy. These include no delay in the start of definitive radiation and no prolongation of overall treatment time (thus minimizing the theoretical risk of accelerated clonogenic proliferation during the antineoplastic course). In addition, there is a possible interaction of the concurrently administered chemotherapy with radiation through such mechanisms as inhibition of repair of radiation damage, cell synchronization, recruitment of nonproliferating cells into cell cycle, and reduction of the hypoxic fraction (147).

Thomas et al. (143) conducted a randomized, four-arm study for patients with FIGO stage IB/IIA (³5 cm) to IVA disease. The four arms were:

1. Standard pelvic radiation, 5,000 cGy in 25 fractions followed by a linear source of intracavitary radiation to deliver 40 Gy
2. Standard pelvic radiation plus intravenous *5-FU* 1,000 mg/m^2 daily for the first and last 4 days of radiation treatment
3. Partially hyperfractionated radiation, 5,280 cGy in 33 fractions, two fractions per day on the first and last 4 days of radiation
4. The same as 3, plus *5-FU* given as in 2

There were 221 evaluable patients, and the median duration of follow-up was 59 months. Possibly because of the suboptimal patient accrual to this trial, there were no significant differences in pelvic control or survival, except for a subset of patients with stage IB/IIA or medial parametrial IIB disease. A multivariate analysis identified only the use of *5-FU* to account for the observed difference.

The GOG has reported the preliminary results of a phase III randomized study of external-beam pelvic radiation and intracavitary radiation combined with concomitant *hydroxyurea* versus weekly *cisplatin* versus *5 FU-cisplatin* and *hydroxyurea (HFC)* in patients with stage IIB, III, and IVA cervical cancer who had undergone extraperitoneal surgical sampling of the paraaortic lymph nodes. Women with intraperitoneal disease or disease metastatic to the paraaortic lymph nodes were ineligible (148). Chemotherapy regimes were as follows:

Regimen I: weekly *cisplatin* 40 mg/m^2/week for 6 weeks

Regimen II: *hydroxyurea* orally 2 mg/m^2 twice weekly for 6 weeks, *5-FU* 1,000 mg/m^2/day as a 96-hour infusion on days 1 and 29, *cisplatin* 50 mg/m^2 days 1 and 29

Regimen III: *hydroxyurea* orally 3g twice weekly

Both platinum-containing regimens improved the progression-free survival compared with *hydroxyurea* alone (p < 0.005). The percentage of patients recurrence free at 24 months was 70% for weekly cisplatin, 67% for *HFC*, and 50% for *hydroxyurea*. Grade 3 or 4

cisplatin 50 mg/m² days 1 and 29

Regimen III: *hydroxyurea* orally 3g twice weekly

Both platinum-containing regimens improved the progression-free survival compared with *hydroxyurea* alone ($p < 0.005$). The percentage of patients recurrence free at 24 months was 70% for weekly cisplatin, 67% for *HFC*, and 50% for *hydroxyurea*. Grade 3 or 4 leukopenia and grade 4 gastrointestinal toxicity were increased with *HFC* compared with weekly *cisplatin* or *hydroxyurea* ($p = 0.0001$ and $p = 0.02$, respectively). Although further follow-up is needed for long-term survival analysis, the investigators concluded that weekly *cisplatin* was more effective than *hydroxyurea*, and more tolerable than *HFC* as a concomitant chemoradiation regimen for locally advanced cervical cancer.

Similarly, preliminary results from Radiation Therapy Oncology Group (RTOG) 9001 demonstrated an improved survival for patients receiving chemoradiation (149). The 3-year survival rate for patients with advanced disease having concurrent radiation and chemotherapy with *cisplatin* and *5-FU* was 75%, compared with 63% for those having pelvic and paraaortic external-beam radiation plus brachytherapy. This difference was statistically significant.

These data suggest that strong consideration should be given to the incorporation of concurrent chemotherapy into the radiation treatment of patients with advanced cervical cancer. The optimal regime is yet to be defined.

Extended-Field Radiation

Clinical staging fails to detect extension of disease to the paraaortic lymph nodes in approximately 7% of patients with stage IB disease, 17% with stage IIB, and 29% with stage III (Table 9.4). Such patients have “geographic” treatment failure if standard radiation therapy ports are used (100).

As a routine procedure, operative staging has failed to realize its intended goal of substantially increasing survival. There are three principal reasons for this. First, **patients with positive paraaortic nodes often have occult distant metastases** and therefore require an effective systemic chemotherapy. Second, **failure to control the pelvic disease has contributed significantly to the poor overall survival for this group of patients** (Table 9.10). Finally, if it is assumed that approximately 25% of patients will have positive paraaortic nodes and about 25% of these will benefit from extended-field radiation (Table 9.11), it is evident that **only approximately 6% of patients undergoing a staging laparotomy will have a survival benefit as a consequence of the altered therapy.**

Author	*Patients*	*Distant Metastases*	*Pelvic Recurrence*
Nelson et al., 1977 (22)	23	12 (52%)	NS
Piver et al., 1981 (150)	31	14 (43%)	NS
Wolander et al., 1982 (42)	31	17 (53%)	12 (38%)
Tewfik et al., 1982 (151)	23	10 (44%)	5 (22%)
Berman et al., 1984 (43)	90	32 (36%)	25 (28%)
Rubin et al., 1984 (116)	14	5 (36%)	2 (14%)
La Polla et al., 1986 (8)	13	8 (62%)	7 (54%)
Vigliotti et al., 1992 (152)	43	23 (53%)	20 (46%)
Total	**268**	**121 (45.1%)**	**71/214 (33.1%)**

NS, Not stated.
Modified from Hacker NF. Clinical and operative staging of cervical cancer. Baillieres Clin Obstet Gynaecol 1988;2:747–759, with permission.

Table 9.10 Sites of Recurrence in Patients with Cervical Cancer Having Extended-Field Radiation for Positive Paraaortic Nodes

Author	*Patients*	*Five-Year Survival Rate (%)*
Buchsbaum, 1979 (26)	21	23.0
Hughes et al., 1980 (40)	22	29.0
Ballon et al., 1981 (41)	18	23.0
Piver et al., 1981 (150)	31	9.6
Wolander et al., 1982 (42)	31	25.8
Rubin et al., 1984 (116)	14*	57.1
Potish et al., 1985 (44)	17	40.0
La Polla et al., 1986 (8)	16	30.0
Vigliotti et al., 1992 (152)	43	28.0
Total	**213**	**27.2**

*All patients had stage III or IV disease.
Modified from Hacker NF. Clinical and operative staging of cervical cancer. Baillieres Clin Obstet Gynaecol 1988;2:747–759, with permission.

Table 9.11 Survival after Extended-Field Radiation

Because of the demonstrated high incidence of positive paraaortic lymph nodes in patients with advanced cervical cancer, prophylactic extended-field radiation may be justified, in view of the acceptable incidence of complications in the absence of prior laparotomy (153).

The European Oncology Radiation Therapy Council's (EORTC) prospective study of 441 patients with stage I, II, and III disease was unable to detect a survival benefit for prophylactic paraaortic radiation, although the incidence of paraaortic metastases and distant metastases without tumor at pelvic sites was significantly higher in patients receiving pelvic radiation only (154). In this study, patients with evidence of paraaortic nodal disease on lymphangiography or surgical staging were excluded, so the numbers of patients with positive paraaortic nodes would have been small. In addition, approximately 25% of failures had an isolated central pelvic recurrence, reflecting the inclusion of stage III patients in the study. The authors believed that patients with a high probability of local control would benefit from extended-field radiation.

The RTOG in the United States conducted a randomized trial of prophylactic paraaortic radiation (4,500 cGy) in 330 patients with stage IB/IIA (>4 cm) or IIB cervical cancer (155). Again, patients with lymphangiographic or surgical evidence of paraaortic nodal involvement were excluded, but with a greater likelihood of pelvic control without any stage III patients, **the RTOG was able to demonstrate significantly better 5-year survival rates (66% vs. 55%) for the patients receiving extended-field radiation therapy.** In addition, patients treated with pelvic radiation alone had a higher risk of distant failure (32% vs. 25%). Severe gastrointestinal morbidity was more common in the group receiving extended-field therapy, but was mainly seen in patients having prior abdominal surgery.

In view of the most recent RTOG study showing that pelvic radiation plus concurrent chemotherapy was superior to extended-field radiation, the question remains whether extended-field radiation with concurrent chemotherapy would be even better. Doses of chemotherapy often need to be modified because of bone marrow toxicity when given in conjunction with extended-field radiation.

Plan of Management for Advanced Cervical Cancer

In view of the aforementioned results, our current approach to patients with advanced cervical cancer at the Royal Hospital for Women in Sydney is summarized in Fig. 9.12. All patients are subjected to a pelvic and abdominal CT scan, and if this is positive, a chest CT scan. **Pretreatment laparotomy is undertaken if there is (a) adnexal pathology, and (b) pelvic or paraaortic lymph nodes at least 1.5 cm diameter,** as long as the chest CT scan is clear. **Enlarged nodes are resected by an extraperitoneal approach because of the evidence strongly suggesting that such an approach converts the prognosis to that of patients with micrometastases** (101,102). Patients with bulky positive nodes that have been resected from the pelvic or paraaortic area are given extended-field radiation with weekly *cisplatin* 40mg/m^2, and all other medically fit patients are given prophylactic extended field-radiation with weekly *cisplatin.*

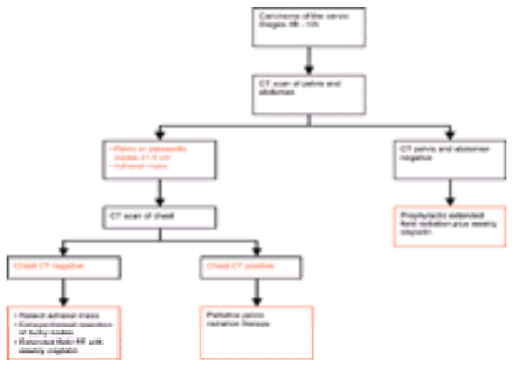


Figure 9.12 Algorithm for the management of patients with advanced cervical cancer. RT, radiation therapy.

We do not perform fine-needle aspiration cytologic testing on enlarged nodes because of the 10% false-negative rate, which necessitates removal and histologic evaluation for definitive diagnosis. Similarly, we do not routinely sample scalene nodes if they are not palpable. If nodes subsequently become palpable in the left supraclavicular region, which is uncommon in our experience, we treat them with radiation therapy and *cisplatin*, with or without resection.

Stage IVA Disease with Vesicovaginal or Rectovaginal Fistula An occasional patient in Western countries has a vesicovaginal or rectovaginal fistula at presentation. If a CT scan of the chest, pelvis, and abdomen demonstrates no evidence of systemic disease, these patients are suitable for primary pelvic exenteration.

Prognosis

The survival of patients with cervical cancer according to the *Annual Report on the Results of Treatment in Gynaecological Cancer* is shown in Table 9.12. Older patients have a lower survival for any given stage. The *Annual Report* states “Centers should be careful in comparing their data to these results as differences due to case mix, age group, type of tumor and other factors may be responsible for variations or differences between centers.”

		Overall Survival Rates (%)				
Stage	*Patients*	*1 yr*	*2 yr*	*3 yr*	*4 yr*	*5 yr*
Stage IA1	518	99.2	97.4	96.3	95.4	95.1
Stage IA2	384	98.9	97.9	96.2	95.3	94.9
Stage IB	4,657	95.5	89.3	85.1	82.3	80.1
Stage IIA	813	91.8	80.8	74.6	70.3	66.3
Stage IIB	2,551	92.1	78.9	70.8	66.9	63.5
Stage IIIA	180	79.4	57.4	46.5	39.7	33.3
Stage IIIB	2,330	76.7	55.3	47.2	41.9	38.7
Stage IVA	294	52.2	30.9	23.5	19.8	17.1
Stage IVB	198	35.1	23.4	16.7	10.6	9.4

From Benedet J, Odicino F, Maisonneuve P, et al. Carcinoma of the cervix uteri. Annual report on the results of treatment in gynecological cancer. J Epidemiol Biostat 1998;3:5–34, with permission.

Table 9.12 Carcinoma of the Cervix Uteri in Patients Treated 1990 to 1992: Survival by FIGO Stage (N = 11,945)

Posttreatment Surveillance

After radiation therapy, the patient should be monitored monthly for the first 3 months. Regression may continue throughout the period, but if any progression of disease occurs, histologic confirmation should be obtained and consideration given to surgery. Small lesions (£2 cm in diameter) may be amenable to radical hysterectomy, but larger lesions usually necessitate pelvic exenteration (see Chapter 21).

After the immediate postradiation surveillance or postoperative check-up, patients should be seen every 3 months until 2 years, every 6 months until 5 years, and annually thereafter. Larson et al. (156) reported that 89% of recurrences after radical hysterectomy occurred in the first 2 years.

At each visit, patients should be questioned about symptoms, and physical examination should include assessment of the supraclavicular and inguinal nodes, as well as abdominal and rectovaginal examination. A Pap smear should be obtained at each visit. Chen et al. (157) reported that 72% of vaginal recurrences were asymptomatic, and most had an abnormal cytologic smear. The others were detected by noting ulceration on visual inspection or by palpation of a nodule or cuff induration.

Because the only realistic chance of cure is in patients with a central pelvic recurrence, it is not necessary routinely to obtain a chest radiograph or CT scan of the pelvis or abdomen. Any symptoms (e.g., cough) should be promptly investigated because occasionally an isolated metastasis may be amenable to surgical resection (158).

Nonsquamous Histologic Types

Adenocarcinoma

The incidence of adenocarcinoma is increasing relative to squamous carcinoma. Older reports indicated that adenocarcinomas represented approximately 5% of all cervical cancer (159), whereas a more recent report revealed an incidence of 21% (160). Most of this relative increase is related to a decreasing incidence of squamous carcinomas secondary to screening programs. However, there have been reports of a true increase in incidence in women younger than 35 years of age, and oral contraceptive use has been implicated (161,162).

Etiologically, adenocarcinomas appear to be less related to sexual, reproductive, or socioeconomic factors (163), **although HPV is frequently implicated and adenocarcinoma is commonly associated with squamous CIN.** A Canadian study reported HPV in 70% of cases (53 of 77), with HPV 16 the predominant type (164). There was no correlation between HPV status and outcome.

Adenocarcinomas, particularly adenosquamous carcinomas, have in general been regarded as having a worse prognosis than squamous lesions, and some have regarded them as relatively more radioresistant. **In the Italian randomized study of radical surgery versus radiation therapy for stage IB to IIA cervical cancer,** 46 of 343 patients (13.4%) had adenocarcinomas (72). Surgery and radiation therapy were found to be identical in terms of 5-year survival and disease-free survival rates for the entire group, but **for patients with adenocarcinomas, surgery was significantly better in terms of both overall survival (79% vs. 59%, $p = 0.05$) and disease-free survival rates (66% vs. 47%, $p = 0.02$).**

Workers in The Netherlands have shown that pretreatment serum CA125 titers are of prognostic significance for adenocarcinomas (165). The 5-year survival rate for stage IB adenocarcinomas was 52.4% when CA125 titers were elevated, versus 95.6% when normal titers were present ($p < 0.01$). Similarly, 42% of patients with elevated serum CA125 titers had lymph node metastases, versus 4% when normal titers were found ($p = 0.012$).

Adenosquamous Carcinoma

Adenosquamous carcinomas represent approximately 20% to 30% of all adenocarcinomas of the cervix. **Most studies report a poorer outcome, although interpretation of the literature is confounded by a failure of investigators to adopt uniform criteria for diagnosis.** The main issue is whether to include poorly differentiated squamous cell carcinomas in which the glandular elements are identified only by the use of mucin stains. In the largest reported series, Kottmeier (166) did include such cases, and reported a worse prognosis compared with adenocarcinomas or squamous carcinomas.

In the largest series of surgically staged IB cases, Helm et al. (167) matched 38 patients with adenosquamous carcinomas with patients with other histologic subtypes of adenocarcinoma with respect to stage, lesion size, nodal status, grade of adenocarcinoma, and age at diagnosis. Diagnosis was based on hematoxylin and eosin staining, without use of mucin staining. Glassy cell carcinomas were included. **Overall 5-year survival and disease-free survival rates for the matched adenosquamous and adenocarcinomas were not significantly different (83 vs. 90%, and 78 vs. 81%, respectively), but the mean time to recurrence was significantly shorter in the adenosquamous group: 11 versus 32 months ($p = 0.003$).** In addition, six patients with adenosquamous carcinomas could not be matched. Five of these had positive nodes in association with lesions measuring between 2 and 4 cm in diameter, and one had an 8-cm lesion with negative nodes.

Adenoma Malignum

The term *adenoma malignum* of the cervix was first used in 1870 by Gusserow to describe a very highly differentiated adenocarcinoma. McKelvey and Goodlin (168) reported five cases in 1963, four of which were fatal within 4 years of presentation. They pointed out the deceptively benign histologic appearance of the tumor and stated that **"if a lesion can be recognized as malignant by the usual criteria for adenocarcinoma of the cervix, it should be excluded from the adenoma malignum group."** McKelvey and Goodlin suggested that these tumors were radioresistant.

In 1975, Silverberg and Hart (169) reported five additional cases. All patients were treated by modern radiotherapeutic techniques, and four of the five were long-term survivors. The authors believed that with proper therapy, the tumor was no more malignant than might be expected for a highly differentiated adenocarcinoma, and they suggested the name *minimal deviation adenocarcinoma.*

An association has been noted with Peutz-Jeghers syndrome, as well as with sex cord tumors with annular tubules, a distinctive ovarian neoplasm with features intermediate between those of the granulosa and Sertoli cell type (170).

These tumors represent approximately 1% of adenocarcinomas of the cervix and occur mainly in the fifth and sixth decades. **Diagnosis is often delayed because Pap smears may be normal or show very minor abnormalities.**

Clinically, patients usually present with a watery or mucous discharge or with abnormal uterine bleeding. On physical examination, the cervix is usually firm and indurated (171). **Punch biopsy is not helpful and deep wedge or cone biopsy is necessary to demonstrate the depth of glandular penetration.**

Radical hysterectomy, bilateral salpingo-oophorectomy, and pelvic lymphadenectomy is the treatment of choice for operable cases, and the prognosis for such cases appears to be very good (169). For more advanced cases, lymph node metastases are common, and the overall prognosis is poor, with only 3 of 22 patients (14%) alive and disease free at 2 years in one large series (172).

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma is sometimes also referred to as a *cylindroma*, a term first used by Billroth (173) in 1859. It is a rare tumor that occurs most frequently in the salivary glands, but also in the respiratory tract, skin, mucous membranes of the head and neck, and in the breast. **In the female genital tract, it is a rare tumor, but occurs in Bartholin's gland, the endometrium, and most commonly in the cervix** (174). Ultrastructural features of both squamous and glandular epithelium are seen, leaving the issue of the etiology of these tumors unresolved. Approximately half the tumors have associated squamous carcinoma or dysplasia (175). Adenocarcinoma is a less frequent association.

These tumors usually occur in postmenopausal black women of high parity (174,176). Most present with postmenopausal bleeding, but some may be suspected by the presence of small "undifferentiated" cells on a routine Pap smear (174). Approximately half the cases are stage I at presentation, but **overall survival is poor.** Prempree et al. (176), in a review of the literature, reported a 3- to 5-year survival rate of only 56.3% (9 of 16) for patients with stage I disease, regardless of the type of treatment. The survival rate for stage II disease was 27.3% (3 of 11), and no patient with stage III or IV disease survived. **Lung metastases are common, whereas the tumors spread locally by direct tissue invasion and perineural infiltration.** A single case report has demonstrated chemosensitivity to *cyclophosphamide, doxorubicin*, and *cisplatin* (177).

Clear Cell Adenocarcinoma

Clear cell adenocarcinoma of the cervix was rare until 1970, when the incidence rose because of its association with *in utero* exposure before the 18th week of pregnancy to *diethylstilbestrol* and related nonsteroidal estrogens (178). The tumor occurs in two distinct age groups, those younger than 24 years and those older than 45 years (179). The latter are unrelated to *in utero diethylstilbestrol* exposure, but **even in young women, there is no history of hormone exposure in 25% of cases.** These tumors were initially thought to be associated with mesonephric rests, and were termed ***mesonephromas*,** but electron microscopy has clearly demonstrated that most cases are of müllerian origin (180). Treatment should be similar to that for other adenocarcinomas. **Unlike clear cell carcinoma of the endometrium, which carries a much worse prognosis, clear cell adenocarcinoma of the cervix has a prognosis comparable to that of other adenocarcinomas** (179).

Glassy Cell Carcinoma

In 1956, Glucksman and Cherry (181) defined "glassy cell" carcinoma of the cervix as **a poorly differentiated adenosquamous carcinoma, the cells of which had a moderate amount of cytoplasm and a typical "ground glass" appearance.** Survival was poor, regardless of the mode of therapy. In 1982, Maier and Norris (182) suggested that **poorly differentiated large cell, nonkeratinizing squamous carcinomas have a similar histologic appearance.** Subsequently, Tamimi et al. (183) reviewed their experience with undifferentiated large cell nonkeratinizing carcinomas of the cervix at the University Hospital in Seattle, Washington, and reported 29 cases over an 8-year period. The mean age of the patients was 31 years, and all cases were stage IB. All but one case was treated by radical hysterectomy, and the survival rate was 55%. In all but one case, the interval to recurrence was less than 8 months. They concluded that **the poor prognosis ascribed to the classically defined glassy cell carcinoma also holds true for this extended group of large cell undifferentiated cervical cancers that display similar histologic features.**

Villoglandular Papillary Adenocarcinoma

This uncommon lesion tends to occur in younger women, and to have a more favorable prognosis. Young and Scully (184) reviewed their consultation files to report 13 cases. The patients' ages ranged from 23 to 54 years (average, 33 years). Two of the patients were pregnant. Both were asymptomatic, both had a grossly abnormal-appearing cervix, and one had an abnormal Pap smear. Treatment ranged from cone biopsy for very superficial cases to radical hysterectomy and pelvic lymphadenectomy. With follow-up of 2 to 14 years, no recurrences were seen.

In the largest reported series by Jones et al. (185), none of 24 cases had lymph vascular invasion or lymph node metastases, and all patients remained free of disease with 7 to 77 months of follow-up. A review of seven cases by Kaku et al. (186) revealed lymph vascular invasion in two patients, both of whom had pelvic lymph node metastasis. One of the two had recurrence at 30 months and died at 46 months.

Small Cell Carcinoma

Small cell cancers are a rare, heterogeneous group of tumors, representing 0.5% to 5% of all invasive cervical cancers (187). In a thorough evaluation of 2,201 invasive cervical cancers at the University of Kentucky Medical Center, Van Nagell et al. (121) noted 25 cases (1.1%) of small cell carcinoma. They were characterized by a nuclear area of 160 μm^2 or less, and a maximum nuclear diameter of 16.2 µm. **Thirty-three percent of the small cell carcinomas stained positively for the neuroendocrine markers (neuron-specific enolase and chromogranin), whereas the remainder stained only for epithelial markers such as cytokeratin and epithelial membrane antigen. Both types of small cell cancers had a higher frequency of lymph-vascular space invasion, a significantly higher rate of recurrence, particularly to extrapelvic sites, and a lower survival rate.**

The neuroendocrine tumors arise from the argyrophil cells in the cervix (187). The cells have the ability to synthesize and store amines (polypeptides) and decarboxylate certain amino acids to form amines, and hence have been called APUD cells (**a**mine **p**recursor **u**ptake and **d**ecarboxylation). None of the neuroendocrine tumors in the Kentucky series had clinical signs of a paraendocrine syndrome, **although these tumors may sometimes present with carcinoid syndrome and the patients have elevated levels of 5-hydroxy-indoleacetic acid in the urine.**

Because of their propensity for early systemic spread, chemotherapy is usually advocated in addition to surgery and/or radiation therapy. The group at the Chang Gung Memorial Hospital in Taiwan administered adjuvant chemotherapy to 23 consecutive patients with stage IB to II small cell cervical cancer who had been treated primarily with radical hysterectomy (188). Ten of 14 patients (71.4%) who received a combination of *vincristine*, *doxorubicin*, and *cyclophosphamide* alternating with *cisplatin* and *etoposide (VAC/PE)* had no evidence of disease during a median follow-up of 41 months, whereas only 3 of 9 (33.3%) who received *cisplatin, vinblastine*, and *bleomycin (PVB)* survived. The survival rate was 70% for patients with negative lymph nodes and 35% for those with positive nodes (p =0.05). All patients who died of disease had extrapelvic metastases.

Sarcoma

A literature review by Rotmensch et al. (189) in 1983 identified 105 reported cases of cervical sarcomas. They classified them as shown in Table 9.13. A variety of therapies had been used in the management of cervical sarcomas, and the overall prognosis was poor except for the adenosarcomas. They concluded that more rigid criteria for diagnosis were needed to allow evaluation of the various therapies.

Tumor Type	*No. Reported*	*Average Age (yr)*
I Leiomyosarcoma	18	47
II Stromal sarcoma		
A Homologous	12	54
B Heterologous (liposarcoma)	1	59
C Sarcoma botryoides	61	27
D Adenosarcoma	4	31
E Malignant mixed müllerian tumor	9	54

Modified from Rotmensch J, Rosenshein NB, Woodruff JD. Cervical sarcoma: a review. Obstet Gynecol Surv 1983;38:456–468, with permission.

Table 9.13 Classification of Cervical Sarcomas

Sarcoma Botryoides In 1988, Daya and Scully (190) reviewed 13 cases of this rare tumor. The patient ages ranged from 12 to 26 years, with a mean of 18 years. All had polypoid lesions and presented with vaginal bleeding, “something” protruding from the introitus, or both. The patients were treated with a variety of operative procedures, with or without adjuvant chemotherapy, the operative procedures ranging from cervical polypectomy to hysterectomy with pelvic and paraaortic node dissection. Twelve of the 13 patients (92%) were alive and well 1 to 8 years after surgery. From their own experience and a review of the literature, Daya and Scully (190) concluded that there was **no evidence that chemotherapy or radiation therapy, which are known to be effective in the treatment of rhabdomyosarcomas at other sites, could improve the prognosis for cervical lesions that were adequately excised.**

The Intergroup Rhabdomyosarcoma Study Group reported five patients 14 to 15 years of age with localized cervical tumors (191). Four of the five were treated with polypectomy and adjuvant chemotherapy (*vincristine* and *dactinomycin*, with or without *cyclophosphamide*), and all were alive from 3 years to 6.5 years after surgery.

Patients with more advanced disease should be treated initially with chemotherapy, and surgical excision should attempt to conserve the function of the bladder, rectum, vagina, and ovaries, if possible. The role of radiation is unclear, and it is no longer recommended for localized disease (192).

Lymphoma

Cervical lymphomas are rare. Of 9,500 women with lymphomas reported by the Armed Forces Institute of Pathology, only 6 (0.06%) had primary cervical lesions (193).

Patients usually present with abnormal vaginal bleeding, and clinically the cervix is expanded by a subepithelial mass, without ulceration or fungation.

Histologic diagnosis is difficult; Harris and Scully (194) reported that only 15 of 25 cases (55%) referred for consultation were correctly diagnosed by the referring pathologist. Komaki et al. (195) emphasized the importance of distinguishing malignant lymphoma from undifferentiated carcinoma or sarcoma because **cervical lymphoma can be successfully treated in spite of locally advanced disease.**

Perren et al. (196) reviewed the literature in 1992, and found 72 cases of lymphoma of the cervix or upper vagina reported since 1963. Interpretation of the data was hindered by outdated methods of histologic classification in approximately half the cases. Staging information, if given, tended to be reported according to the FIGO classification rather than according to the Ann Arbor classification used routinely in lymphoma practice.

They concluded that outcome for cervical and vaginal lymphomas was unpredictable, and that excellent results could be achieved even if the tumor was high grade, bulky, or extensive. **They stressed the need for thorough staging, including CT scan of the chest, pelvis, and abdomen, bone marrow aspiration, hematologic analysis, and biochemistry.**

Regarding treatment, they **found no evidence that radical gynecologic surgery was advantageous** (196). For localized (Ann Arbor stage IE) and nonbulky disease (FIGO stage I and II) of low and intermediate grade, they recommended pelvic radiation therapy or modern combination chemotherapy. For more extensive disease (stage IIE), bulky locally advanced disease (FIGO stages III and IV), or disease of high grade, they recommended modern chemotherapy, possibly in conjunction with radiation therapy.

Verrucous Carcinoma

The term *verrucous carcinoma* was first used by Ackerman (197) in 1948 to describe a slow-growing, locally aggressive, papillomatous lesion in the oral cavity. The first cervical lesion was reported in 1972 (198).

In a literature review in 1988, Crowther et al. (199) reported 34 cases of cervical verrucous carcinoma, although they believed that some of these should be considered papillomas that had undergone malignant change to squamous cell carcinomas. The age of the women ranged from 30 to 84 years (average, 51 years), and only two had a past history of genital warts. Symptoms included vaginal discharge (42%) and abnormal bleeding (50%), whereas 35% had an abnormal Pap smear. **Colposcopy was not helpful because the lesion looked like a large condyloma acuminatum.** The lesions were confined to the cervix in 41% of cases and involved the vagina in 36% and the parametrium in 23%. One case invaded the bladder.

Radical surgery is the mainstay of treatment. Radicality of surgery varied in the cases reviewed by Crowther et al. (199), but of 14 patients having radical hysterectomy (with vaginectomy in 3 cases), recurrence occurred in 6 (43%). Three of the recurrences were salvaged with radiation therapy or exenterative surgery. **Radiation therapy was used as a primary or secondary treatment in 17 cases, and failures occurred in 10 of these (59%).** Anaplastic change was not noted. Schwade et al. (200) reported anaplastic transformation and rapid clinical deterioration in 10.7% of verrucous carcinomas, but suggested that many of these lesions were large and may have already contained occult areas of squamous cell carcinoma. Lymph node metastases were found in two patients and pulmonary metastases in a third, but at autopsy careful histologic evaluation showed nests of classic squamous carcinoma cells invading the stroma in two of these cases.

Overall, recurrent or persistent disease was noted in 21 cases (62%), with 82% of relapses occurring within 8 months.

Melanoma

Malignant melanoma of the cervix is a rare entity, and it is important to exclude a metastatic lesion. Literature reviews and case studies have been reported by Mordel et al. (201) in 1989 and Santosa et al. (202) in 1990. These tumors have in general been reported to occur in the seventh and eighth decades of life, and most lesions present with abnormal vaginal bleeding. **Macroscopically, the tumors are strongly colored, polypoid masses, and most patients have FIGO stage I or II disease at diagnosis.** Recommended treatment is usually radical hysterectomy with or without pelvic lymphadenectomy. **Adjuvant radiation may improve local control if the surgical margins are close.** The 5-year survival rate is poor, not exceeding 40% for stage I disease and reaching only 14% in stage II (201).

Metastatic Carcinoma

Metastasis of malignant epithelial tumors to the uterine cervix is a rare occurrence. Lemoine and Hall (203) reviewed the surgical pathology files of the London Hospital for the 65 years from 1919 to 1984 and found only 33 acceptable cases. Cases that involved direct extension from a primary site, such as the endometrium or rectum, were excluded. They also reviewed the literature for individual case reports and small series. Documented primary sites of diseases included stomach (25 cases), ovary (23), colon (21), breast (14), kidney (1), renal pelvis (1), carcinoid (1), and pancreas (1).

The patients almost invariably present with vaginal bleeding, and the histologic features of the cervical biopsy lead to a search for an asymptomatic primary tumor.

Special Problems

Cervical Cancer in Pregnancy

There is no standard definition in the literature for cervical cancer associated with pregnancy. Some authors report only cases diagnosed during pregnancy (204), whereas others have included cases diagnosed within the first 12 months postpartum (205). In a series from the University of Southern California in which only cases diagnosed during pregnancy were reported, the incidence of invasive cervical cancer was 1.2 cases per 10,000 pregnancies, or 1 in 8,333 pregnancies (204). In a literature review that included cases diagnosed up to 12 months postpartum, Hacker et al. (206) reported an incidence of invasive cancer of 4.54 cases per 10,000 pregnancies, or 1 in 2,205 pregnancies. One in 34 cases of cervical cancer was diagnosed during or within 12 months of pregnancy.

Symptoms Symptoms include vaginal bleeding, vaginal discharge, postcoital bleeding, and pelvic pain, but approximately 20% of patients are asymptomatic. It is easy to disregard abnormal bleeding in pregnancy and attribute it to a pregnancy-related cause, so delayed diagnosis is common.

Diagnosis Definitive diagnosis is made on the basis of a punch biopsy of a gross cervical lesion, proper evaluation of an abnormal smear, or colposcopic evaluation of a symptomatic patient. **Cone biopsy should be used only if strictly indicated because of the problems of hemorrhage and abortion or premature labor.** A suggested algorithm for investigation of an abnormal Pap smear in pregnancy is shown in Fig. 9.13.

Figure 9.13 Algorithm for the management of an abnormal Pap smear in pregnancy. Consideration may be given to colposcopic observation without biopsy for low-grade lesions during pregnancy because of the risk of hemorrhage. CIN, cervical intraepithelial neoplasia.

Distribution by Stage and Gestational Age Because pregnant patients are under medical surveillance, and because a Pap smear should be a routine part of antenatal testing, most patients diagnosed during pregnancy have early-stage disease. Hacker et al. (206) reported that 64.3% of patients diagnosed in the first trimester and 60.6% of those diagnosed in the second trimester had stage IB disease. Unfortunately, because symptoms are often ignored, 51.6% of cases were not diagnosed until the postpartum period. **The later the diagnosis is made, the more likely is the cancer to be in an advanced stage.**

Staging Staging of cervical cancer in pregnancy is complicated by the desire to protect the fetus from exposure to x-rays, and the typical edematous softening of the cervix and pelvic connective tissues makes clinical evaluation of the cervix and parametrium inaccurate. **MRI may be used during pregnancy to determine tumor volume, to identify spread beyond the cervix, and to detect lymph node enlargement** (207).

Management A suggested algorithm for the management of cervical cancer in pregnancy is shown in Fig. 9.14. **All management decisions should be made only after full discussion with the mother (and preferably the father) about the risks involved to both mother and fetus.** Some patients are prepared to take significant risks themselves to procure a live infant, and their wishes must be respected.

Figure 9.14 Algorithm for the management of invasive cervical cancer in pregnancy.

In general, if stage IA1 disease is diagnosed on cervical conization with clear surgical margins, it is reasonable to follow the pregnancy until term and anticipate vaginal delivery.

For more advanced disease, management is influenced by the stage of disease and the duration of the pregnancy. **For patients diagnosed before 20 weeks, the recommendation should be to treat without delay, whereas for those diagnosed after 30 weeks, the recommendation should be to await fetal viability.**

The dilemma arises for patients diagnosed between 20 and 30 weeks' gestation. There does not seem to be any significant impairment of prognosis with planned treatment delays, at least for patients with small stage IB tumors (204,208), but it is impossible to offer a precise risk estimate for any individual patient. **If a mother with locally advanced disease refuses to sacrifice her pregnancy, consideration may be given to using neoadjuvant chemotherapy in an attempt to prevent disease progression while allowing time for the fetus to achieve viability** (209). If the decision is made to delay treatment in the interests of the unborn child, it is important to ensure that the fetus is apparently normal and that sufficient delay occurs to ensure viability. These cases should be managed in conjunction with an obstetrician and a neonatal pediatrician.

Unless the lesion has been removed by conization, the recommended mode of delivery is classical cesarean section. However, from several retrospective studies, there is no evidence that vaginal delivery adversely affects prognosis (206).

If the patient's cancer is suitable for surgery, radical hysterectomy and pelvic lymphadenectomy should be performed, either with the fetus *in situ* (before fetal viability) or after classic cesarean section.

If radiation therapy is considered the treatment of choice, and treatment is planned before fetal viability, it is usual to commence with external-beam therapy. Spontaneous abortion usually occurs after an average of approximately 33 days during the first trimester, and 44 days during the second (210). If it has not occurred at the time of intracavitary therapy, hysterotomy should be performed, at which time nodal evaluation can be undertaken.

Outcome After a review of the literature in 1982, Hacker et al. (206) concluded that the overall prognosis for all stages of cervical cancer in pregnancy, as well as for stage I disease, was similar to that in nonpregnant women. The favorable overall prognosis was related to the greater proportion of pregnant patients with stage I disease. For more advanced disease, pregnancy had an adverse effect on prognosis. More recently, **matched, controlled studies have demonstrated identical survivals for pregnant and nonpregnant patients** (211,212).

Cancer of the Cervical Stump

Subtotal hysterectomy is less commonly performed today than in the past, but when invasive cancer arises in a cervical stump, the principles of treatment are the same as those for an intact uterus. The technique for radical trachelectomy is essentially the same as for radical hysterectomy, the only difficulty being the maintenance of adequate traction on the stump. Sometimes the bladder may be drawn up over the stump, necessitating careful dissection. **The ability to deliver an adequate dose of radiation to patients with advanced disease depends on the length of the cervical canal, and is compromised if the canal is less than 2 cm long.** Although 5-year survival rates compare favorably to those in patients with an intact uterus, complication rates are higher because of the previous surgery and the sometimes compromised methods of radiation therapy (213).

Invasive Cancer Found after Simple Hysterectomy

When invasive cervical cancer is discovered after simple hysterectomy, **the treatment options include full pelvic radiation or radical surgery consisting of radical parametrectomy, upper vaginectomy, and pelvic lymphadenectomy.**

Our preference is to obtain a chest radiograph and pelvic and abdominal CT scan. If enlarged nodes are found, they are removed by an extraperitoneal approach and the patient treated with radiation therapy. If there is no evidence of metastatic disease, reoperation is carried out as long as there is no indication for postoperative radiation on the basis of the hysterectomy specimen (i.e., surgical margins clear, tumor not deeply infiltrating, and no prominent vascular space invasion).

The operation is considerably more difficult than a radical hysterectomy, the main difficulty being the identification of the bladder, which is usually adherent over the vaginal vault. Operating in the low lithotomy position to allow use of a metal instrument (e.g., narrow malleable retractor) to push up on the vault from below facilitates identification of the bladder boundaries. Kinney et al. (214) from the Mayo Clinic reported 27 patients undergoing reoperation. Ureterovaginal fistulas developed in 2 of the 27 (7%), but the 5-year absolute survival rate was 82%.

Hopkins et al. (215) reported 92 patients who were treated by primary radiation therapy. Prognosis was similar to that for patients treated initially by radical surgery or radiation therapy for squamous lesions. Fifty-seven patients with stage I squamous cell carcinoma had a 5-year survival rate of 85%, whereas 27 patients with stage I adenocarcinoma had a 5-year survival rate of 42%. They suggested that alternative approaches should be investigated for adenocarcinomas.

Coexistent Pelvic Mass

A pelvic mass may be identified clinically or on a staging CT scan of the pelvis and abdomen. Solid masses of uterine origin are usually leiomyomas and do not need further investigation.

Coexistent adnexal masses must be explored, and a histologic diagnosis obtained. Benign adnexal masses can be surgically excised. Inflammatory masses can be excised, and an omental carpet used to prevent bowel adhesions. Malignant masses require surgical staging or cytoreductive surgery, depending on the individual case.

If the preferred treatment is radiation, any coexistent pyometra/hematometra must be drained, if necessary using ultrasonic guidance. Repeated dilatation of the cervix and aspiration of pus may be necessary every 2 to 3 days if there is ultrasonic evidence of a further collection. Broad-spectrum antibiotics should be used to cover *Bacteroides*, anaerobic *Streptococcus*, and aerobic coliforms. **Active infection decreases the response to radiation and may be exacerbated into a systemic infection if brachytherapy rods are packed into the uterus.**

Cervical Bleeding

Torrential bleeding may occasionally follow biopsy or pelvic examination, particularly with friable, advanced cancer. **A wide gauze bandage, soaked in Monsel's solution (ferric subsulfate) and tightly packed against the cervix, usually controls the bleeding.** It should be changed after 48 hours. If control of the bleeding is not achieved, consideration should be given to embolization of the hypogastric or uterine arteries (216), although this approach may increase tumor hypoxia, thereby decreasing radiosensitivity.

Commencement of external-beam therapy controls the bleeding within a few days. Daily fractions may be increased to 300 to 500 cGy for 2 or 3 days, or transvaginal orthovoltage treatment may be given if a suitable machine is available.

Ureteric Obstruction at Presentation

An uncommon problem at presentation is bilateral ureteric obstruction and renal failure. Other patients may have partial ureteric obstruction at presentation but become anuric while receiving pelvic radiation. A decision regarding active or palliative management must be made after open discussion with the patient and her family. Information about the likely outcome is helpful in making an informed decision.

Taylor and Anderson (217) reported 18 patients with oliguric renal failure and untreated cervical cancer. Five patients were treated palliatively, and they survived an average of 25 days. The 13 patients who completed pelvic radiation after medical or surgical management of their renal failure survived an average of 16.9 months. No patient survived beyond 34 months. Of the eight patients managed with peritoneal or hemodialysis, six experienced spontaneous resolution of their oliguria before the completion of radiation.

Recurrent Cervical Cancer

Treatment of recurrent disease depends on the mode of primary therapy and the site of recurrence. **If the disease recurs in the pelvis after primary radiation therapy, most patients require some type of pelvic exenteration** (see Chapter 21), although an occasional patient may be salvaged by radical hysterectomy. **Late, solitary distant metastases are very uncommon, but should they occur (e.g., in the lung), consideration should be given to surgical resection** (158).

With pelvic recurrence after primary surgery, radiation therapy is the treatment of first choice. External-beam therapy is used initially to shrink the tumor, and patients with a vaginal vault recurrence may then respond to vaginal ovoids or interstitial radiation. A 25% survival rate can be expected for radiation treatment of a postsurgical recurrence (218).

Radical Hysterectomy for Recurrence

Selected patients with limited persistent or recurrent disease in the cervix after primary radiation therapy may be suitable for radical hysterectomy, with or without partial resection of bowel, bladder, and/or ureter. The morbidity rate is high, but some patients can be cured without the need for a stoma.

Terada and Morley (219) reported 14 patients with recurrent disease after primary radiation who underwent radical hysterectomy. Six patients had regional, macroscopic metastatic disease, and all died of recurrent tumor. For the remaining eight patients, the 5-year survival rate was 54%. Complications requiring major surgical intervention occurred in 29% of patients, and included three urinary tract fistulas. Most recurrences were in the pelvis, and the authors believed that the lesser operation compromised these patients.

Rutledge et al. (220) from London, Ontario, reported data on 41 patients who underwent conservative surgery for postradiation recurrent or persistent cervical cancer. Thirteen patients who initially had FIGO stage IB or IIA disease underwent radical abdominal or radical vaginal hysterectomy. The 5-year survival rate for this group was 84%, and major morbidity occurred in 31% of cases. A second group of 20 patients had more advanced initial disease, and all underwent radical abdominal hysterectomy. This group had a 49% 5-year survival rate and a major morbidity rate of 50%. A third group of eight patients required an extended Wertheim's operation to encompass locally advanced disease involving the bladder base and/or parametrium. This group had a 5-year survival rate of 25%, but experienced a 75% rate of major morbidity, including two treatment-related deaths. Fistula formation occurred in 26% of patients overall.

It would appear that conservative surgery is realistic only for patients with small disease confined to the cervix, preferably detected on biopsy 4 to 6 months after primary radiation for bulky stage IB or IIA cervical cancer. For patients whose initial disease extended into the parametrium, there is a high failure rate in the pelvis, and such patients cannot be salvaged by further exenterative surgery.

Chemotherapy

For recurrent or metastatic disease, the role of chemotherapy is merely palliative (i.e., to produce an objective response), which in most instances is accompanied by relief of symptoms and prolongation of life. Complete responses are unusual, and generally limited to patients with lung metastases, where the dose of drug delivered to the disease is better than that delivered to the irradiated, fibrotic pelvis (221).

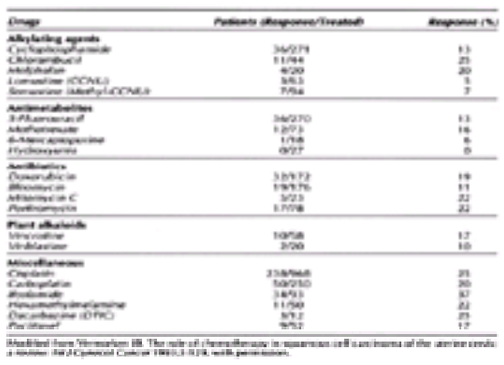
Vermorken (222) has reviewed the literature on chemotherapy for squamous cell carcinoma of the cervix and concluded that **current data do not show any significant survival benefit for combination chemotherapy, compared with single-agent *cisplatin*, although identification of subsets of patients who may benefit remains a challenge.** Very limited data are available on chemotherapy for glandular lesions, but their response to drugs does not seem to be different from that in squamous cases (223).

***Cisplatin* is considered the single most active agent, and its preferred schedule of administration is 50 to 100 mg/m^2 every 3 weeks, intravenously.** Doses above 50 mg/m^2 have not been shown to improve response duration, progression-free interval, or survival (224,225). The duration of response remains disappointing (4 to 6 months), although we have seen two long-term responses (>5 years), one in a patient with multiple pulmonary metastases and the other in a patient with a supraclavicular lymph node metastasis, diagnosed on fine-needle aspiration cytologic testing.

A report on the use of a short and dose-intensive regimen of *cisplatin* may offer promise (226). *Cisplatin*, 50 mg/m^2, was given weekly for four cycles, then second weekly for four cycles. The overall response rate for the 36 patients was 47%, and 56% in patients with recurrence in an irradiated pelvis. All but one response was seen within 4 weeks of commencing treatment. Three patients (9%) had a complete response, although in two cases this was of short duration. Median survival was 32 weeks, and the 18-month survival rate was 13%.

A report on *paclitaxel* from the GOG revealed an overall response rate of 17% (9 of 52) with a complete response rate of 3.8% (227). Patients were all chemotherapy naive, and the *paclitaxel* dose was 170 mg/m^2 over 24 hours, repeated every 3 weeks. If the patient had received prior radiation therapy, the dose was 135 mg/m^2.

Response rates for single agents and combination chemotherapy in squamous cell carcinoma of the cervix are shown in Table 9.14 and Table 9.15.



Drugs	Patients (Response/Treated)	Response (%)
Alkylating agents		
Cyclophosphamide	36/271	13
Chlorambucil	11/94	23
Melphalan	4/20	20
Lomustine (CCNU)	3/63	5
Semustine (Methyl-CCNU)	7/94	7
Antimetabolites		
5-Fluorouracil	36/270	13
Methotrexate	11/73	15
6-Mercaptopurine	1/58	6
Hydroxyurea	0/27	0
Antibiotics		
Doxorubicin	13/173	11
Mitomycin C	5/23	22
Plicamycin	1/198	22
Plant alkaloids		
Vincristine	10/58	17
Vinblastine	3/26	10
Miscellaneous		
Cisplatin	23/67	35
Carboplatin	5/20	30
Procarbazine	3/93	37
Hexamethylmelamine	11/50	22
Dacarbazine (DTIC)	5/12	25
Pentamustine	9/52	17

Modified from Vermorken JB: The role of chemotherapy in squamous cell carcinoma of the uterine cervix: a review. Int J Gynecol Cancer 1993;3:1-19, with permission.

Table 9.14 Single Conventional Agent Chemotherapy in Cervical Carcinoma

Regimen	Patients (Response/Treated)	Response (%)
Non-cisplatin-based combinations		
DOX/MTX	66/169	39
DOX/BLM	5/52	10
DOX/CTX ± 5FU	17/94	18
DOX (other)	48/186	26
BLM/MTX ± VCR	24/85	28
BLM/MMC	83/200	42
VRC/BLM/MMC	80/180	44
Cisplatin-based combinations		
2-drug	142/368	39
3-drug	174/416	42
4-drug	131/313	42

DOX, doxorubicin; MTX, methotrexate; CTX, cyclophosphamide; 5FU, 5-fluorouracil; BLM, bleomycin; VCR, vincristine; MMC, mitomycin-C.
Cumulative data.
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VIP, CBE, ADRIAMC	50/180	44
Cisplatin-based combinations		
2-drug	142/368	39
3-drug	174/416	42
4-drug	131/313	42

DOX, doxorubicin; MTX, methotrexate; CTX, cyclophosphamide; 5FU, 5-fluorouracil; BLM, bleomycin; VCR, vincristine; MMC, mitomycin C.
[a]Cumulative data.
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Table 9.15 Combination Chemotherapy in Cervical Carcinoma[a]

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10 Uterine Cancer

Neville F. Hacker

Endometrial carcinoma is the most common malignancy of the female genital tract in the United States. For 2000, 36,100 new cases and 6,500 deaths were anticipated (1). It is predominantly a disease of affluent, obese, postmenopausal women of low parity, although an increasing proportion of younger patients with endometrial cancer has been reported (2). **In the United States, black women have approximately a 40% lower risk for development of cancer of the corpus uteri, but approximately a 54% greater risk of dying of the disease, mainly because of late diagnosis** (3).

Over the last few decades, age-standardized incidence rates have risen in most countries and in urban populations. Developing countries and Japan have incidence rates four to five times lower than Western industrialized nations, with the lowest rates being in India and south Asia (4).

Since the mid-1980s, careful surgical staging has more accurately defined patterns of spread and has allowed more individualization of treatment, particularly with respect to adjuvant radiation.

Any factor that increases exposure to unopposed estrogen (e.g., hormone replacement therapy, obesity, anovulatory cycles, estrogen-secreting tumors) increases the risk of endometrial cancer, whereas factors that decrease exposure to estrogens or increase progesterone levels (e.g., oral contraceptives or smoking) tend to be protective (4). The impact of these factors differs in various populations, and in northern Italy, established risk factors account for only approximately 50% of the cases (5).

Screening of Asymptomatic Women

The ideal method for outpatient sampling of the endometrium has not yet been devised, and no blood test of sufficient sensitivity and specificity has been developed. Therefore, mass screening of the population is not practical. However, screening for endometrial carcinoma or its precursors is justified for certain high-risk people, including those shown in Table 10.1.

1. Postmenopausal women on exogenous estrogens without progestins
2. Women from families with hereditary nonpolyposis colorectal cancer
3. Premenopausal women with anovulatory cycles, such as those with polycystic ovarian disease

Table 10.1 Patients for Whom Screening for Endometrial Cancer Is Justified

Only approximately 50% of women with endometrial cancer have malignant cells on a Papanicolaou (Pap) smear (6,7). However, compared with patients who have normal cervical cytologic findings, patients with suspicious or malignant cells are more likely to have deeper myometrial invasion, higher tumor grade, positive peritoneal cytologic findings, and a more advanced stage of disease (8).

The appearance of normal- as well as abnormal-appearing endometrial cells in cervical smears taken in the second half of the menstrual cycle or in postmenopausal women should alert the clinician to the possibility of endometrial disease. **Approximately 6% of postmenopausal patients with *normal* endometrial cells in cervical smears have endometrial carcinoma, and approximately 13% have endometrial hyperplasia** (9). **If morphologically abnormal endometrial cells are present, approximately 25% of women have endometrial carcinoma** (10). The likelihood of endometrial carcinoma being present increases with the patient's age (11).

The unsatisfactory results obtained with conventional Pap smears are due to the indirect sampling of the endometrium, and several commercially available devices have been developed to allow direct sampling (e.g., Pipelle, Gyno Sampler, Vabra aspirator). A satisfactory endometrial biopsy specimen also may be obtained in the office with the Karman cannula or a small curette, such as a Novak or Kevorkian (Fig. 10.1).

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Figure 10.1 Devices used for sampling endometrium. From top to bottom: Serrated Novak, Novak, Kevorkian, Explora (Mylex), and Pipelle (Unimar).

With these devices, an endometrial smear may be made for cytologic evaluation and a cell block may be prepared for histologic examination. Even in experienced hands, endometrial smears are difficult to interpret, and optimal information is obtained by the combined use of endometrial smears and cell blocks (12). All of these office techniques for endometrial sampling cause the patient some discomfort, and in approximately 8% of patients it is not possible to obtain a specimen because of a stenotic os. This failure rate increases to approximately 18% for women older than 70 years of age (12). Although the accuracy of endometrial sampling has not been definitively determined, it is probably in the order of 90% (13). The clinician should be comfortable with one of these techniques.

In the 1990s, transvaginal ultrasonography with or without color flow imaging has been investigated as a screening technique (14). **There is a strong association between the thickness of the endometrial strip and endometrial disease, with normal endometrium being usually less than 5 mm thick.** In a large, multiinstutional study of 1,168 women, all 114 women with endometrial cancer and 95% of the 112 women with endometrial hyperplasia had an endometrial thickness of 5 mm or more (15). One indication for this screening technique would be postmenopausal women who are receiving unopposed estrogen, but Bourne et al. (16) reported an 11% false-positive rate for this group.

Tamoxifen **increases the risk of endometrial cancer twofold to threefold** (17), **and produces a sonographically unique picture of an irregularly echogenic endometrium that is attributed to cystic glandular dilatation, stromal edema, and edema and hyperplasia of the adjacent myometrium** (18). Transvaginal ultrasonography should be interpreted with caution in *tamoxifen*-treated women because the detection of a thickened endometrium may lead to overtreatment and mismanagement (18).

Patients taking *tamoxifen* should be informed of the increased risk of endometrial cancer and told to report any abnormal bleeding or spotting immediately. Any bleeding or spotting must be investigated by biopsy. A retrospective review of *tamoxifen*-treated women who underwent dilatation and curettage found that uterine cancer was found only in those with vaginal bleeding (18).

Clinical Features

Symptoms

Endometrial carcinoma should be excluded in all patients shown in Table 10.2. Ninety percent of patients with endometrial carcinoma have abnormal vaginal bleeding, most commonly postmenopausal bleeding. The usual causes of postmenopausal bleeding are shown in Table 10.3. **Intermenstrual bleeding or heavy prolonged bleeding in perimenopausal or anovulatory premenopausal women should arouse suspicion. The diagnosis may be delayed unnecessarily in these women because the bleeding is usually ascribed to "hormonal imbalance."** A high index of suspicion also is needed to make an early diagnosis in women younger than 40 years of age.

1. All patients with postmenopausal bleeding
2. Postmenopausal women with a pyometra
3. Asymptomatic postmenopausal women with endometrial cells on a Papanicolaou smear
4. Perimenopausal patients with intermenstrual bleeding or increasingly heavy periods
5. Premenopausal patients with abnormal uterine bleeding, particularly if there is a history of anovulation

Table 10.2 Patients in Whom a Diagnosis of Endometrial Cancer Should Be Excluded

Factor	*Approximate Percentage*
Exogenous estrogens	30
Atrophic endometritis/vaginitis	30
Endometrial cancer	15
Endometrial or cervical polyps	10
Endometrial hyperplasia	5
Miscellaneous (e.g., cervical cancer, uterine sarcoma, urethral caruncle, trauma)	10

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Table 10.3 Etiology of Postmenopausal Bleeding

Occasionally, vaginal bleeding does not occur because of cervical stenosis, particularly in thin, elderly, estrogen-deficient patients. In some patients with cervical stenosis a hematometra develops, and a small percentage have a purulent vaginal discharge resulting from a pyometra.

Signs

Physical examination commonly reveals an obese, hypertensive, postmenopausal woman, although approximately 35% of patients are not obese and show no signs of hyperestrogenism (19). Abdominal examination is usually unremarkable except in advanced cases when ascites may be present, and hepatic or omental metastases may be palpable. Occasionally, a hematometra appears as a large, smooth midline mass arising from the pelvis. On pelvic examination, it is important carefully to inspect and palpate the vulva, vagina, and cervix to exclude metastatic spread or other causes of abnormal vaginal bleeding. The uterus may be bulky, but often it is not significantly enlarged. Rectovaginal examination should be performed to evaluate the fallopian tubes, ovaries, and cul-de-sac. Endometrial carcinoma may metastasize to these sites or, alternatively, coexistent ovarian tumors such as a granulosa cell tumor, thecoma, or epithelial ovarian carcinoma may be noted.

Diagnosis

All patients suspected of having endometrial carcinoma should have an endocervical curettage and an office endometrial biopsy. A histologically positive endometrial biopsy allows the planning of definitive treatment.

Because there is a false-negative rate of approximately 10%, a negative endometrial biopsy in a symptomatic patient must be followed by a fractional curettage under anesthesia. A diagnosis of endometrial hyperplasia on endometrial biopsy does not obviate the need for further investigation. Hysteroscopy may provide information on benign endometrial disease, but it has not been shown to increase the yield in the diagnosis of endometrial cancer and it increases the cost of the initial evaluation (20).

Fractional Curettage

While the patient is under anesthesia, careful bimanual rectovaginal examination is performed, a weighted speculum is placed in the vagina, and the cervix is grasped with a tenaculum. The endocervical canal is curetted before cervical dilatation, and the tissue is placed in a specially labeled container. The uterus then is sounded, the cervix dilated, and the endometrium systematically curetted. The tissue is placed in a separate container so that the histopathologic status of the endocervix and endometrium can be determined separately.

Preoperative Investigations

Routine preoperative investigations for early-stage endometrial carcinoma are shown in Table 10.4. If a fractional curettage has not been performed, an endocervical curettage should be performed to evaluate the endocervix.

Full blood count
Serum creatinine and electrolytes
Liver function tests
Blood sugar
Urinalysis
Electrocardiogram
Chest radiograph

Table 10.4 Routine Preoperative Investigations for Early-Stage Endometrial Carcinoma

Nonroutine tests are sometimes indicated, particularly for more advanced cases. **Cystoscopy** and **sigmoidoscopy** are necessary only if bladder or rectal involvement is suspected clinically (21). A **barium enema** should be performed if there is occult blood in the stool or a recent change in bowel habits because concomitant colon cancer occasionally occurs, particularly if there is a family history of bowel cancer. A **pelvic and abdominal computed tomography (CT) scan** may be helpful to determine the extent of metastatic disease in the following circumstances:

1. Abnormal liver function test results
2. Clinical hepatomegaly
3. Palpable upper abdominal mass
4. Palpable extrauterine pelvic disease
5. Clinical ascites

Magnetic resonance imaging (MRI) was evaluated as a tool for preoperative staging in a National Cancer Institute cooperative study (22). Eighty-eight patients from five participating hospitals were entered in the study. For evaluating the depth of myometrial invasion, the overall accuracy was 66%, and the imaging was considered adequate for the evaluation of paraaortic lymph nodes in only 8% of the cases. Until image quality and techniques improve significantly, MRI is not a cost-effective method for the preoperative evaluation of patients with endometrial cancer.

Staging

The 1971 staging system for endometrial carcinoma devised by the International Federation of Gynecologists and Obstetricians (FIGO) is shown in Table 10.5. It was a **clinical staging,** based on examination under anesthesia, sounding of the uterus, and a limited number of investigations such as endocervical curettage, hysteroscopy, cystoscopy, proctoscopy, and radiographic examinations of the lungs and skeleton. This staging system is still used if a patient is considered unsuitable for surgery.

Stage 0	Carcinoma in situ
Stage I	The carcinoma is confined to the corpus
Stage IA	The length of the uterine cavity is 8 cm or less
Stage IB	The length of the uterine cavity is more than 8 cm
Stage I cases should be subgrouped with regard to the histologic grade of the adenocarcinoma as follows:	
Grade 1	Highly differentiated adenomatous carcinoma
Grade 2	Moderately differentiated adenomatous carcinoma with partly solid areas
Grade 3	Predominantly solid or entirely undifferentiated carcinoma
Stage II	The carcinoma has involved the corpus and the cervix but has not extended outside the uterus
Stage III	The carcinoma has extended outside the uterus but not outside the true pelvis
Stage IV	The carcinoma has extended outside the true pelvis or has obviously involved the mucosa of the bladder or rectum. A bullous edema as such does not permit a case to be allocated to stage IV.
Stage IVA	Spread of the growth to adjacent organs
Stage IVB	Spread to distant organs

FIGO, International Federation of Gynecology and Obstetrics.

Table 10.5 1971 FIGO Clinical Staging for Endometrial Carcinoma

Several studies in the literature demonstrated significant understaging when patients were subjected to adequate surgical evaluation (23,24,25,26,27 and 28). Therefore, in 1988, the Cancer Committee of FIGO introduced a **surgical staging** system (Table 10.6).

Stage IA G1,2,3	Tumor limited to endometrium
Stage IB G1,2,3	Invasion to less than one-half the myometrium
Stage IC G1,2,3	Invasion to more than one-half the myometrium
Stage IIA G1,2,3	Endocervical glandular involvement only
Stage IIB G1,2,3	Cervical stromal invasion
Stage IIIA G1,2,3	Tumor invades serosa and/or adnexa, and/or positive peritoneal cytology
Stage IIIB G1,2,3	Vaginal metastases
Stage IIIC G1,2,3	Metastases to pelvic and/or paraaortic lymph nodes
Stage IVA G1,2,3	Tumor invasion of bladder and/or bowel mucosa
Stage IVB G1,2,3	Distant metastases, including intra-abdominal and/or inguinal lymph nodes
Histopathology—degree of differentiation:	
Cases of carcinoma of the corpus should be classified or graded according to the degree of histologic differentiation, as follows:	
G1: ≤ 5% or less of a nonsquamous or nonmorular solid growth pattern	
G2: 6%—50% of a nonsquamous or nonmorular solid growth pattern	
G3: > more than 50% of a nonsquamous or nonmorular solid growth pattern	
Notes on pathological grading:	
1. Variable nuclear atypia, inappropriate for the architectural grade, raises the grade of a grade 1 or a grade 2 tumor by 1.	
2. In serous adenocarcinomas, clear cell adenocarcinomas, and squamous cell carcinomas, nuclear grading takes precedence.	
3. Adenocarcinomas with squamous differentiation are graded according to the nuclear grade of the glandular component.	
Rules related to staging:	
1. Because corpus cancer is now staged surgically, procedures previously used for determination of stages are no longer applicable, such as the findings from fractional dilatation and curettage to differentiate between stage I and stage II.	
2. It is apparent that there may be a small number of patients with corpus cancer who will be treated primarily with radiation therapy. If that is the case, the clinical staging adopted by FIGO in 1971 would still apply, but designation of that staging system would be optional.	
3. Ideally, width of the myometrium should be measured along with the width of tumor invasion.	

FIGO, International Federation of Gynecology and Obstetrics. Reproduced from International Federation of Gynecology and Obstetrics, Annual report on the results of treatment in gynecological cancer, with permission.

Table 10.6 1988 FIGO Surgical Staging for Endometrial Carcinoma

Although more accurate information should be obtained if thorough surgical staging is carried out on all patients, this is unlikely to happen; therefore, staging reports lack uniformity. Routine lymphadenectomy is unlikely to be performed for a number of reasons:

1. Many patients with endometrial carcinoma are treated in the community, where the necessary surgical skills may not be available to perform a lymphadenectomy.
2. Many patients are obese and not suitable for extensive nodal resections.
3. Patients with early tumors do not justify a routine lymphadenectomy, but a few have positive nodes.

In addition, the extent of the lymphadenectomy has not been defined (i.e., random sampling of pelvic and paraaortic nodes, complete pelvic and/or paraaortic lymphadenectomy, or resection of any enlarged nodes).

The distribution of endometrial carcinoma by surgical stage at initial presentation is shown in Table 10.7.

Stage	No.	Percent
I	3,839	72.8
II	574	10.9
III	694	13.2
IV	166	3.1
Total	5,273	100.0

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Table 10.7 Carcinoma of the Endometrium: Distribution by Surgical Stage for Patients Treated in 1990 to 1992

Spread Patterns

Endometrial carcinoma spreads by the following routes:

1. Direct extension to adjacent structures
2. Transtubal passage of exfoliated cells
3. Lymphatic dissemination
4. Hematogenous dissemination

Direct Extension Direct extension is the most common route of spread, and it results in penetration of the myometrium and eventually the serosa of the uterus. The cervix and fallopian tubes and ultimately the vagina and parametrium may be invaded. Tumors arising in the upper corpus may involve the tube or serosa before involving the cervix, whereas tumors arising from the lower segment of the uterus involve the cervix early. The exact anatomic route by which endometrial cancer involves the cervix has not been clearly defined, but it probably involves a combination of contiguous surface spread, invasion of deep tissue planes, and lymphatic dissemination (29,30).

Transtubal Dissemination The presence of malignant cells in peritoneal washings and the development of widespread intraabdominal metastases in some patients with early-stage endometrial cancer strongly suggest that cells may be exfoliated from the primary tumor and transported to the peritoneal cavity by retrograde flow along the fallopian tubes. Although this is probably the most common mechanism of spread, other mechanisms also must have some role because positive peritoneal washings have been reported in patients who have had a prior tubal ligation (31).

Lymphatic Dissemination Lymphatic dissemination is clearly responsible for spread to pelvic and paraaortic lymph nodes. **Although lymphatic channels pass directly from the fundus to the paraaortic nodes through the infundibulopelvic ligament, it is rare to find positive paraaortic nodes in the absence of positive pelvic nodes.** However, it is quite common to find microscopic metastases in both pelvic and paraaortic nodes, suggesting simultaneous spread to pelvic and paraaortic nodes in some patients. This is in contrast to cervical cancer, where paraaortic nodal metastases are always secondary to pelvic nodal metastases.

It seems likely that vaginal metastases also result from lymph-vascular spread. They commonly occur in the absence of cervical involvement (32), excluding direct spread as the mechanism, and may occur despite preoperative sterilization of the uterus with intracavitary radiation, excluding implantation of cells at the time of surgery as the mechanism (33).

Hematogenous Spread Hematogenous spread most commonly results in lung metastases, but liver, brain, bone, and other sites are involved less commonly.

Prognostic Variables

Although stage of disease is the most significant prognostic variable, a number of factors have been shown to correlate with outcome in patients with the same stage of disease. These prognostic variables are summarized in Table 10.8. Knowledge of them is essential if appropriate treatment programs are to be devised.

Age
Histologic type
Histologic grade
Nuclear grade
Myometrial invasion
Vascular space invasion
Tumor size
Peritoneal cytology
Hormone receptor status
DNA ploidy
Type of therapy (surgery vs. radiation)

FIGO: International Federation of Gynecology and Obstetrics.

Table 10.8 Prognostic Variables in Endometrial Cancer Other than FIGO Stage

Age

Age appears to be an independent prognostic variable. The Gynecologic Oncology Group (GOG) reported 5-year relative survival rates of 96.3% for 28 patients no older than 40 years of age, 87.3% for 261 patients 51 to 60 years, 78% for 312 patients 61 to 70 years, 70.7% for 119 patients 71 to 80 years, and 53.6% for 23 patients older than 80 years of age ($p < 0.001$) (34). All patients had clinical stage I or occult stage II disease. Using proportional hazards modeling of relative survival time, and taking 45 years of age as the arbitrary reference point, the relative risks for death from disease were as follows: 2.0 at 55 years, 3.4 at 65 years, and 4.7 at 75 years of age. It is important to review carefully the histologic characteristics of well differentiated lesions in young women because Crissman et al. (35) have reported overdiagnosis of atypical endometrial hyperplasias in 41% of 54 cases.

Histologic Type

A retrospective review of 388 patients treated at the Mayo Clinic recorded an uncommon histologic subtype in 52 patients (13%). There were 20 adenosquamous, 14 serous papillary, 11 clear cell, and 7 undifferentiated carcinomas (36). In contrast to the 92% survival rate among patients with endometrioid carcinoma, the overall survival rate for these patients was only 33%. At the time of surgical staging, 62% of the patients with an unfavorable histologic subtype had extrauterine spread of disease.

The prognostic significance of squamous elements in endometrial carcinoma has been debated for decades (37). Zaino et al. (38) investigated the prognostic significance of squamous differentiation in 456 patients with typical adenocarcinomas and 175 women with areas of squamous differentiation who had been entered into a GOG clinicopathologic study of stage I and II disease. They reported that the biologic behavior of these tumors reflected the histologic grade and depth of invasion of the glandular component. Although prognostically valuable information was provided by dividing these tumors into adenoacanthomas and adenosquamous carcinomas, more information was gained when they were stratified by the histologic grade of the glandular component. Zaino et al. (38) recommended that the terms *adenoacanthoma* and *adenosquamous carcinoma* be replaced by the simple term *adenocarcinoma with squamous differentiation.*

Papillary serous carcinomas have a poor prognosis even in the absence of deep myometrial invasion. They disseminate widely (39,40 and 41), with a particular predilection for recurrence in the upper abdomen (42,43).

Sherman et al. (41) studied 13 pure uterine papillary serous carcinomas (UPSC), 19 tumors consisting of UPSC admixed with other types of endometrial carcinomas, and 9 UPSCs confined to, or associated with, an endometrial polyp. Only cases in which at least 25% of the tumor consisted of UPSC were included. Survival rates were similar for the three groups, with more than 80% of the patients either dead of disease or alive with residual or recurrent tumor.

The mechanisms that have been proposed to explain the characteristic intraabdominal dissemination of these tumors include transtubal spread, vascular-lymphatic invasion, and multifocal disease. Sherman et al. (41) made the interesting observation that “intraepithelial serous carcinoma” was present in the endocervix in 22% of their cases, in the fallopian tube in 5%, on the surface of the ovary in 10%, and on peritoneal surfaces or omentum in 25%. More recently, Sherman et al. (44) have suggested that in contrast to the slow, estrogen-driven pathway leading to the biologically more indolent endometrioid carcinoma, a rapid, p53-driven pathway may lead to the aggressive serous carcinoma.

Clear cell carcinomas represent fewer than 5% of endometrial carcinomas, although clear cell elements are commonly present in papillary serous tumors (41). **Vascular space invasion is more common in these lesions** (45). In a review of 181 patients with clear cell endometrial carcinoma treated between 1970 and 1992, Abeler et al. (46) reported 5- and 10-year actuarial disease-free survival rates of 43% and 39%, respectively. Pathologic stage, clinical stage, age, and myometrial invasion were the only significant prognostic variables. Two thirds of the relapses were outside the pelvis, most frequently in the upper abdomen, liver, and lungs.

When papillary serous or clear cell carcinomas are limited to the curettings, with no adverse features in the hysterectomy specimen, prognosis may not be impaired (47).

Squamous cell carcinomas of the endometrium are rare. In a review of the literature, Abeler et al. (48) estimated that the survival rate for patients with clinical stage I disease was 36%.

Histologic Grade and Myometrial Invasion

There is a strong correlation between histologic grade, myometrial invasion, and prognosis. **Increasing tumor grade and myometrial penetration are associated with an increasing risk of pelvic and paraaortic lymph node metastases, adnexal metastases, positive peritoneal cytologic findings, local vault recurrence, and hematogenous spread** (42).

The GOG reported the surgical pathologic features of 621 patients with stage I endometrial carcinoma (28). The frequency of positive pelvic and paraaortic nodal metastases in relation to histologic grade and depth of myometrial invasion is shown in Table 10.9 and Table 10.10. When grade 1 carcinomas are confined to the inner third of the myometrium, the incidence of positive pelvic nodes is less than 3%, whereas when grade 3 lesions involve the outer third, the incidence of positive pelvic nodes is 34%. For aortic nodes, the corresponding figures are less than 1% and 23%, respectively.

	Histologic Grade		
Depth of Myometrial Invasion	*G1 (N = 180)*	*G2 (N = 288)*	*G3 (N = 153)*
Endometrium only (N = 86)	0/44 (0%)	1/31 (3%)	0/11 (0%)
Inner third (N = 281)	3/96 (3%)	7/131 (5%)	5/54 (9%)
Middle third (N = 115)	0/22 (0%)	6/68 (9%)	1/24 (4%)
Outer third (N = 139)	2/18 (11%)	11/57 (19%)	22/64 (34%)

Reproduced from Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. *Cancer* 1987;60:2035–2041, with permission.

Table 10.9 Grade, Depth of Invasion, and Pelvic Node Metastasis of Endometrial Carcinoma

	Histologic Grade		
Depth of Myometrial Invasion	*G1 (N = 180)*	*G2 (N = 288)*	*G3 (N = 153)*
Endometrium only (N = 86)	0/44 (0%)	1/31 (3%)	0/11 (0%)
Inner third (N = 281)	1/96 (1%)	5/131 (4%)	2/54 (4%)
Middle third (N = 115)	1/22 (5%)	0/69 (0%)	0/24 (0%)
Outer third (N = 139)	1/18 (6%)	8/57 (14%)	15/64 (23%)

Reproduced from Creasman WT, Morrow CP, Bundy BN, et al. Surgical pathologic spread patterns of endometrial cancer: a Gynecologic Oncology Group study. *Cancer* 1987;60:2035–2041, with permission.

Table 10.10 Grade, Depth of Invasion, and Aortic Node Metastasis of Endometrial Carcinoma

It is difficult to correlate accurately the risk of local recurrence with histologic grade and depth of myometrial invasion because of the prophylactic value of adjuvant radiation. The risk of distant metastases in relation to histologic grade and myometrial invasion is shown in Table 10.11 (49).

Variable	*Number*	*Metastases*	*Percent*
Histologic grade			
Grade 1	93	2	2.2
Grade 2	88	9	10.2
Grade 3	41	16	39.0
Myometrial invasion			
None	92	4	4.3
Inner third	80	8	10.0
Middle third	17	2	11.8
Outer third	33	13	39.4

*Gynecologic Oncology Group data.
Reproduced from DiSaia PJ, Creasman WT, Boronow RC, et al. Risk factors and recurrent patterns in stage I endometrial cancer. *Am J Obstet Gynecol* 1983;111:1059–1065, with permission.

Histologic grade			
Grade 1	93	2	2.2
Grade 2	88	9	10.2
Grade 3	41	16	39.0
Myometrial invasion			
None	92	4	4.3
Inner third	80	8	10.0
Middle third	17	2	11.8
Outer third	33	13	39.4

*Gynecologic Oncology Group data.
Reproduced from DiSaia PJ, Creasman WT, Boronow RC, et al. Risk factors and recurrent patterns in stage I endometrial cancer. Am J Obstet Gynecol 1983;151:1009–1015, with permission.

Table 10.11 Clinical Stage I Endometrial Carcinoma: Distant Metastases Versus Histologic Grade and Myometrial Invasion[a]

Vascular Space Invasion

Vascular space invasion appears to be an independent risk factor for recurrence and for death from endometrial carcinoma of all histologic types (50,51 and 52). Aalders et al. (50) reported recurrences and deaths in 26.7% of patients with stage I disease who had vascular space invasion compared with 9.1% of those without vessel invasion ($p < 0.01$). Abeler et al. (51) reviewed 1,974 cases of endometrial carcinoma from the Norwegian Radium Hospital and reported an 83.5% 5-year survival rate for patients without demonstrable vascular invasion compared with 64.5% for those in whom invasion was present (51).

The overall incidence of lymph-vascular invasion in stage I endometrial carcinoma is approximately 15%, although it increases with increasing myometrial invasion and decreasing tumor differentiation. Hanson et al. (52) reported vascular space invasion in 5% of patients with invasion limited to the inner one third of the myometrium compared with 70% of those with invasion to the outer one third. Similarly, it was present in 2% of grade 1 carcinomas and 42% of grade 3 lesions. Ambros and Kurman (53), using multivariate analysis, reported that only depth of myometrial invasion, DNA ploidy, and vascular invasion–associated changes correlated significantly with survival for patients with stage I endometrioid adenocarcinomas. Vascular invasion–associated changes were defined as vascular invasion by tumor, and/or the presence of myometrial perivascular lymphocytic infiltrates. In the GOG study, vascular space invasion carried a relative risk of death of 1.5 (34).

Peritoneal Cytologic Results

The significance of a positive peritoneal cytologic result is controversial (54). The incidence of positive cytologic findings in stage I disease is shown in Table 10.12. **Positive washings are most common in patients with grade 3 histologic type, metastases to the adnexa, deep myometrial invasion, and/or positive pelvic or paraaortic nodes** (28,54,55,56,57,58,59,60 and 61).

Author	*Cases*	*Positive Cytology*	*Percent*
Creasman et al., 1981 (55)	167	26	15.6
Szpak et al., 1981 (56)	54	12	22.2
Yazigi et al., 1983 (57)	93	10	10.8
Creasman et al., 1987 (28)	621	76	12.2
Haroutny et al., 1988 (58)	276	47	17.0
Hirai et al., 1989 (59)	173	25	14.4
Lurain et al., 1989 (60)	157	30	19.1
Total	1,541	226	14.7

Table 10.12 Incidence of Positive Peritoneal Cytology in Clinical Stage I Endometrial Carcinoma

Creasman et al. (55) reported that 6 of 13 patients (46%) with positive cytologic findings but no extrauterine disease died of disseminated intraperitoneal carcinomatosis, although a study by Kadar et al. (61) of 269 patients with clinical stage I and stage II endometrial cancer reported that if the disease was confined to the uterus, positive peritoneal cytologic results did not influence survival. If the disease had spread to the adnexa, lymph nodes, or peritoneum, positive peritoneal cytologic findings decreased the survival rate from 73% to 13% at 5 years, but all recurrences were at distant sites.

The GOG study reported by Morrow et al. (62) analyzed 697 patients with information on peritoneal cytologic results and adequate follow-up. Disease recurred in 25 of 86 patients (29.1%) with positive washings, whereas 64 of 611 patients (10.5%) with negative washings had recurrence. The authors noted, however, that 17 of the 25 recurrences were outside the peritoneal cavity. **The GOG estimated that the relative risk of death for patients with positive cytologic washings was 3** (34).

In a review of the literature concerning patients with clinical stage I endometrial cancer, Milosevic et al. (63) reported positive peritoneal cytologic results in 8.3%, 12.1%, and 15.9% of patients with grades 1, 2, and 3 histologic types, respectively. Superficial and deep myometrial invasion was associated with positive washings in 7.6% and 17.2% of the cases, respectively. They concluded that the poor prognosis associated with malignant washings was largely a reflection of other adverse prognostic factors. They suggested that a high technical false-positive rate made it difficult to determine the clinical usefulness of the test in patients with low-grade, superficially invasive tumors.

Hormone Receptor Status

In general, mean estrogen receptor (ER) and progesterone receptor (PR) levels are inversely proportional to histologic grade (64,65,66 and 67). However, **ER and PR content have been shown to be independent prognostic indicators for endometrial cancer; that is, patients whose tumors are positive for one or both receptors have longer survival than patients whose carcinoma lacks the corresponding receptors** (64,65 and 66,68,69). Liao et al. (65) reported that even for patients with lymph node metastases, the prognosis was significantly improved if the tumor was receptor positive. PR appears to be a stronger predictor of survival than ER and, at least for the ER, the absolute level of the receptors may be important: the higher the level, the better the prognosis (70).

Nuclear Grade

Nuclear grade is a significant prognostic indicator (70). Christopherson et al. (71) found nuclear grading to be a more accurate prognosticator than histologic grade.

The new FIGO grading system takes into account the nuclear grade of the tumor, and "nuclear atypia" inappropriate for the architectural grade raises the grade by 1. However, there is great variability in the literature regarding the criteria for nuclear grading, and intraobserver and interobserver reproducibility of nuclear grading are poor (72).

Tumor Size

In an analysis of 142 patients with clinical stage I endometrial carcinoma, Schink et al. (73) reported tumor size as an independent prognostic factor. Lymph node metastases occurred in 4% of the patients with tumors no more than 2 cm in diameter, 15% with tumors greater than 2 cm in diameter, and 35% with tumors involving the entire uterine cavity. The incidence of nodal metastases in relation to tumor size and depth of invasion is shown in Table 10.13.

	Tumor Size		
Depth of Invasion	*≤2 cm Diameter (%)*	*>2 cm Diameter (%)*	*Entire Surface (%)*
None	0/17 (0)	0/9 (0)	0/0 (0)
<½	0/27 (0)	5/41 (12)	2/9 (22)
≥½	2/9 (22)	6/23 (26)	4/8 (50)

Reproduced from Schink JC, Lurain JR, Wallemark CB, et al. Tumor size in endometrial cancer: a prognostic factor for lymph node metastasis. Obstet Gynecol 1987;70:314–319, with permission.

Table 10.13 Incidence of Lymph Node Metastasis in Endometrial Cancer by Tumor Size and Depth of Myometrial Invasion

DNA Ploidy and Other Biologic Markers

Approximately one fourth of patients with endometrial carcinomas have aneuploid tumors, which is a low incidence compared with many other solid tumors, including ovarian and cervical carcinomas. However, patients with aneuploid tumors are at significantly increased risk of early recurrence and death from disease (53,74,75). **The GOG estimated the relative risk to be 4.1 for disease-related death for patients with aneuploid tumors** (76). Mutations of the *p53* tumor suppressor gene and overexpression of the protooncogene HER-2/*neu* have been shown to have some prognostic significance, but the clinical implications of these biologic markers are not yet clear (77).

Method of Treatment

In contrast to cervical cancer, patients with endometrial cancer treated with hysterectomy alone or hysterectomy and radiation do significantly better than those treated with radiation alone (78,79 and 80). This appears to be related to the inability of radiation therapy effectively to eliminate disease in the myometrium (81,82). Grigsby et al. (79) reported on 116 patients with stage II endometrial carcinoma. Ninety were treated with combined radiation and surgery, whereas 26 received radiation alone. The results of treatment are shown in Table 10.14.

	No. of Patients	*Distant Metastases*	*Pelvic Recurrence*	*Five-Year Survival Rate*
Radiation and surgery	90	13.3%	8.9%	78%
Radiation alone	26	11.5%	34.6%	48%

Reproduced from Grigsby PW, Perez CA, Camel HM, et al. Stage II carcinoma of the endometrium: results of therapy and prognostic factors. Int J Radiat Oncol Biol Phys 1985;11:1915–1921, with permission.

Table 10.14 Clinical Stage II Carcinoma of the Endometrium: Comparison of Treatment Methods

Endometrial Hyperplasia

Classic teaching has been that endometrial hyperplasias represent a continuum of morphologic severity; the most severe form, termed *atypical adenomatous hyperplasia* or *carcinoma in situ*, was considered the immediate precursor of endometrial carcinoma (83,84 and 85).

Since the mid-1980s, this continuum concept has been challenged. Independent studies by Kurman et al. (86) and Ferenczy et al. (87) have suggested that

1. **Endometrial hyperplasia and endometrial neoplasia are two biologically different diseases.**
2. **The only important distinguishing feature is the presence or absence of cytologic atypia.**

Ferenczy et al. (87) suggested that the term ***endometrial hyperplasia*** be used for any degree of glandular proliferation devoid of cytologic atypia, and the term ***endometrial intraepithelial neoplasia*** **for lesions with cytologic atypia.** Using similar criteria in a long-term follow-up study of 170 patients with endometrial hyperplasia, Kurman et al. (86) reported a 1.6% risk of progression to carcinoma in patients devoid of cytologic atypia, compared with a 23% risk in patients with cytologic atypia.

Subsequently, Ferenczy and Gelfand (88) reported 85 menopausal women with endometrial hyperplasia. Sixty-five patients had no cytologic atypia, and 84% of this group responded to *medroxyprogesterone acetate (MPA)*. Four (6%) had recurrent hyperplasia after discontinuing the *MPA*, and none developed carcinoma, with a mean follow-up of 7 years. By contrast, 20 patients had cytologic atypia, and only 50% responded to *MPA*. Recurrent hyperplasia developed in five (25%), and adenocarcinoma in five (25%).

These data suggest that most women with endometrial hyperplasia respond to progestin therapy and are not at increased risk for development of cancer. Patients who do not respond are at a significantly increased risk for progressing to invasive cancer and should be advised to have a hysterectomy. Patients who are unlikely to respond can be identified on the basis of cytologic atypia. A suggested scheme of management is outlined in Fig. 10.2.

Figure 10.2 Management of endometrial hyperplasia.

Patients in whom endometrial carcinoma develops with concomitant hyperplasia are more likely to be younger, to have better-differentiated

Figure 10.2 Management of endometrial hyperplasia.

Patients in whom endometrial carcinoma develops with concomitant hyperplasia are more likely to be younger, to have better-differentiated tumors of lower surgical stage, and a better 5-year survival rate. However, the presence of endometrial hyperplasia does not appear to be an independent prognostic factor in multivariate analysis (89).

Treatment of Endometrial Cancer

The cornerstone of treatment for endometrial cancer is total abdominal hysterectomy and bilateral salpingo-oophorectomy, and this operation should be performed in all cases whenever feasible. In addition, many patients require some type of adjuvant radiation therapy to help prevent vaginal vault recurrence and to sterilize occult disease in lymph nodes. It is difficult to document that radiation actually improves survival rates (50,90), but the GOG study of surgery versus surgery plus adjuvant pelvic radiation for intermediate-risk endometrial cancer showed an improved disease-free survival rate for the radiation-treated group, but no improvement in overall survival rate (91). Failure to improve overall survival was related to the ability to cure most pelvic recurrences in the surgery-only arm once they occurred.

With the increasing emphasis on surgicopathologic staging, a more individualized approach to adjuvant radiation is now possible, and most centers no longer recommend preoperative radiation.

Stage I and Stage II Occult

Microscopic cervical involvement (positive endocervical curettage) is often designated (unofficially) stage II occult disease. For practical purposes, such patients can be managed in the same way as patients with stage I disease.

When the carcinomatous tissue obtained at endocervical curettage is completely separate from the endocervical tissue, it presumably represents contamination from the corpus, because the prognosis in such circumstances is similar to that of stage I disease (29,92). **False-positive rates of 40% to 50% have been reported for endocervical curettage** (78,92,93 and 94). Extension of endometrial carcinoma into the cervical stroma in the absence of involvement of the surface epithelium may be missed on endocervical curettage (95). If the cervix is firm and expanded and the endocervical curettage is negative, a wedge biopsy to include the underlying stroma may be necessary to determine cervical involvement.

A recommended treatment plan is shown in Fig. 10.3.

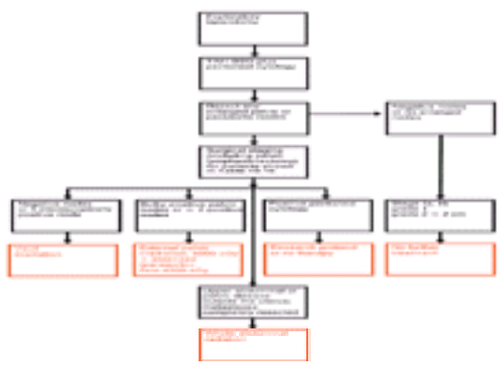

Figure 10.3 Management of patients with stage I and occult stage II endometrial carcinoma. TAH, total abdominal hysterectomy; BSO, bilateral salpingo-oophorectomy.

The initial approach for all medically fit patients should be total abdominal hysterectomy and bilateral salpingo-oophorectomy. Removal of a vaginal cuff is not necessary. The adnexa should be removed because they may be the site of microscopic metastases. In addition, patients with endometrial carcinoma are at increased risk for ovarian cancer. Such tumors sometimes occur concurrently (96). Surgical staging, including lymphadenectomy, should be performed in those patients listed in Table 10.15. The use of laparoscopically assisted vaginal hysterectomy is addressed in Chapter 20.

1. Patients with grade 3 lesions
2. Patients with grade 2 tumors >2 cm in diameter
3. Patients with adenosquamous, clear cell, or papillary serous carcinomas
4. Patients with greater than 50% of myometrial invasion
5. Patients with cervical extension

Table 10.15 Endometrial Carcinoma Stages I and Occult II: Patients Requiring Surgical Staging

Operative Technique

The laparotomy is best performed through a lower midline abdominal incision, although a Pfannenstiel incision is commonly used. The probability that this type of low transverse incision will be inadequate is substantial in the presence of a poorly differentiated carcinoma, an enlarged uterus, cervical extension, or an adnexal mass, because in these situations, omentectomy and removal of enlarged aortic nodes or abdominal metastases may be necessary (97). An alternative to this approach is to use a transverse, muscle-dividing incision (e.g., the Maylard or Cherney), as discussed in Chapter 19. In the presence of obesity and a large abdominal panniculus, which is not uncommon in patients with endometrial carcinoma, a lower midline incision may offer better exposure (98).

After the abdomen is opened, peritoneal washings are taken with 50 mL normal saline solution. Thorough exploration of the abdomen and pelvis is performed, with particular attention to the liver, diaphragm, omentum, and paraaortic nodes. Any suspicious lesions are excised or subjected to biopsy.

The uterus is grasped with clamps that encompass the round and ovarian ligaments and the fallopian tube. After the round ligaments are divided, the incision is carried anteriorly around the vesicouterine fold of peritoneum and posteriorly parallel and lateral to the infundibulopelvic ligaments. With a narrow Deaver retractor in the retroperitoneum providing gentle traction cephalad in the direction of the common iliac vessels, the iliac vessels and ureter are displayed. The pelvic lymph nodes can be visualized and palpated, and any enlarged nodes can be removed.

With each ureter under direct vision, the infundibulopelvic ligaments are divided and tied. The bladder is dissected off the front of the cervix, and then the uterine vessels are skeletonized and divided at the level of the isthmus. Straight Kocher clamps are used to secure the cardinal and uterosacral ligaments. The uterus, tubes, and ovaries are removed and the vaginal vault is closed. No vaginal cuff need be taken.

The specimen is opened on the operating table to determine the need for surgical staging in patients with grade 1 or 2 tumors (Fig. 10.4, Fig. 10.5). All patients with grade 3 tumors require surgical staging (Fig. 10.6). For grade 1 tumors, gross examination accurately predicts depth of myometrial invasion. In an analysis of 113 patients with surgical stage I endometrial carcinoma, Goff and Rice (99) reported that macroscopic examination of the fresh specimen correctly predicted depth of invasion in 55 of 63 grade 1 lesions (87.3%), 24 of 37 grade 2 lesions (64.9%), and 4 of 13 grade 3 lesions (30.8%). They recommended that frozen-section analysis should be done for patients with grade 2 or 3 tumors. An alternative approach we use is to measure tumor diameter for grade 2 lesions to determine the need for surgical staging. Schink et al. (73) reported a 22% incidence of lymph node metastases for grade 2 tumors greater than 2 cm in diameter (7 of 32). None of 19 grade 2 tumors less than 2 cm in diameter had nodal metastases.

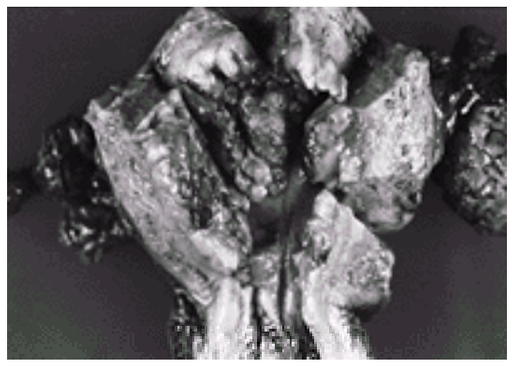

Figure 10.4 A small fundal grade 1 endometrial carcinoma. This patient does not require surgical staging.

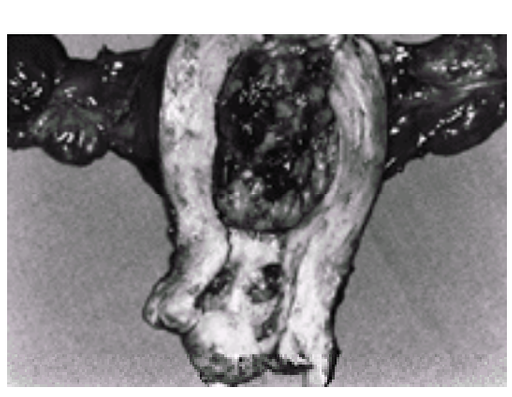

Figure 10.5 A grade 2 endometrial carcinoma occupying most of the corpus. A patient such as this should undergo surgical staging.

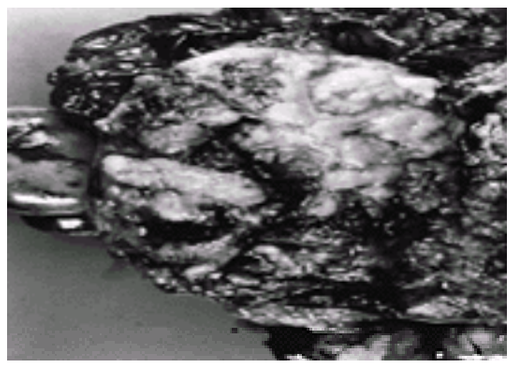

Figure 10.6 A patient with a grade 3 endometrial carcinoma invading the myometrium almost to the serosa and with extension to the upper endocervical canal.

Surgical staging requirements have not been detailed by the Cancer Committee of FIGO. If accurate surgical staging is to be obtained, full pelvic lymphadenectomy should be performed on all patients who meet the criteria in Table 10.15, and this is our current approach. The dissection includes removal of common iliac nodes and of the fat pad overlying the distal inferior vena cava. Any enlarged paraaortic nodes are also removed. If full pelvic lymphadenectomy is considered inadvisable because of the patient's general medical condition, which is uncommon, resection of any enlarged pelvic or paraaortic nodes should be performed. An omental biopsy specimen is also taken.

It is not our current approach to perform full paraaortic lymphadenectomy on patients with endometrial carcinoma. The GOG data (62) would suggest that **patients with positive paraaortic nodes are likely to have:**

1. **Grossly positive pelvic nodes**
2. **Grossly positive adnexa, or**
3. **Grade 2 or 3 lesions with outer-third myometrial invasion**

The pelvic peritoneum is not closed, and it usually is not necessary to place drains in the pelvis. The sigmoid colon is placed in the pelvis to help exclude loops of small bowel. The abdominal wound is best closed with a continuous Smead-Jones type of internal retention suture,

1. **Grossly positive pelvic nodes**
2. **Grossly positive adnexa, or**
3. **Grade 2 or 3 lesions with outer-third myometrial invasion**

The pelvic peritoneum is not closed, and it usually is not necessary to place drains in the pelvis. The sigmoid colon is placed in the pelvis to help exclude loops of small bowel. The abdominal wound is best closed with a continuous Smead-Jones type of internal retention suture, particularly if high-risk factors for postoperative wound dehiscence, such as obesity, are present.

Vaginal Hysterectomy **In selected patients with marked obesity and medical problems that place them at high risk for abdominal operations, vaginal hysterectomy should be considered.** Peters et al. (100) reported a 94% survival rate among 56 patients with stage I endometrial carcinoma who underwent vaginal hysterectomy. Seventy-five percent had grade 1 lesions, and 32 patients received adjuvant radiation, mainly brachytherapy. Others have reported a similar experience (101), and this approach is clearly preferable to treatment of these patients with radiation alone. Vaginal hysterectomy is particularly applicable to patients with grade 1 lesions. The diminished ability to remove the ovaries is an obvious shortcoming with the vaginal approach, although adnexectomy may be facilitated by laparoscopy.

Role of Lymphadenectomy

Pelvic lymphadenectomy, with or without paraaortic lymphadenectomy, plays an important role in the surgical staging of endometrial cancer, and thus provides more accurate prognostic information. The therapeutic role of lymphadenectomy and its ability to modify adjuvant therapy are less well understood, although several reports are provocative.

The therapeutic value of pelvic lymph node dissection was investigated by Kilgore et al. from Birmingham, Alabama, who reported on 649 surgically managed patients with adenocarcinoma of the endometrium (102). Two hundred twelve patients had multiple-site pelvic node sampling (mean number of nodes, 11), 205 had limited-site sampling (mean number of nodes, 4), and 208 had no node sampling. The decision regarding lymph node sampling was surgeon dependent, and prognostic features, including tumor grade, depth of invasion, adnexal metastasis, cervical involvement, and positive cytologic findings, were equally distributed between the three groups. All patients had adjuvant radiation therapy based on traditional prognostic factors. With a mean follow-up of 3 years, patients undergoing multiple-site pelvic node sampling had a significantly better overall survival ($p = 0.0002$) as well as a better survival for both low-risk and high-risk groups (low-risk, $p = 0.026$; high-risk, $p = 0.0006$).

The authors concluded that their results strongly suggested a therapeutic benefit to lymphadenectomy, but confirmation of this must await randomized studies. **If there is a therapeutic benefit, it must surely be related to the resection of bulky, positive nodes, which are unlikely to be sterilized with external-beam radiation therapy.**

The feasibility of using the results of pelvic lymphadenectomy to modify adjuvant radiation therapy has been addressed in several nonrandomized trials. **All reports would suggest that if the lymph nodes are negative, it may be reasonable to omit external-beam therapy, and rely on brachytherapy to prevent vault recurrence, thereby saving both treatment time and money** (103,104 and 105).

Mohan et al. (103) reported 159 evaluable patients who underwent total abdominal hysterectomy, bilateral salpingo-oophorectomy, complete pelvic lymphadenectomy, and vaginal brachytherapy. A mean of 33 lymph nodes were resected, and median follow-up was 8 years. For patients with surgical stage I disease, 10- and 15-year disease-free survival rates were 96% and 94%, respectively. Grade and myometrial invasion were not significant predictors of survival after complete node dissection.

In the COSA–New Zealand–United Kingdom study of pelvic lymphadenectomy for high-risk endometrial cancer, 207 patients with negative nodes underwent brachytherapy without external-beam therapy (104). There were two recurrences (1%) at the vaginal vault and seven (3.4%) in the pelvis. This study raises the question of the advisability of omitting external-beam therapy in patients with ultra–high-risk disease (grade 3 tumors invading the outer third of the myometrium) even if nodes are negative. Fanning and Firestein (106) reported a median additional operating time of 24 minutes to resect an average of 21 pelvic and 7 aortic lymph nodes. Blood loss and postoperative morbidity were minimal.

Adjuvant Radiation

Appropriate irradiation has been shown significantly to decrease the incidence of both pelvic and vaginal recurrences. Vault recurrences may be decreased by either external irradiation or intracavitary radium (26,107); pelvic recurrences may be decreased by external irradiation (108,109 and 110). Because approximately 5,000 cGy is probably necessary to sterilize micrometastases in lymph nodes, it seems unlikely that grossly enlarged nodes will be sterilized with the usual dose of adjuvant pelvic irradiation unless they are surgically resected initially.

Before the move toward surgicopathologic staging of endometrial carcinoma, preoperative intracavitary or external irradiation was usually given. The rationale was that the radiation would sterilize the malignant cells, impairing their implantability and thereby decreasing the likelihood of vaginal implantation or systemic dissemination at the time of uterine manipulation.

Truskett and Constable (33) reported a vaginal recurrence rate of 6.2% for patients with no residual disease in the operative specimen after preoperative radiation. Therapy was given with intrauterine Heyman capsules but without vault radium sources. This observation eliminates the risk of implantation as a rationale for preoperative irradiation and suggests that vaginal recurrences are due to lymphatic spread, which takes place before any surgical manipulation.

The remaining argument in favor of preoperative irradiation is the possibility of decreasing systemic dissemination. It seems unlikely that the manipulation associated with intracavitary therapy would be less likely to cause tumor dissemination than would surgical manipulation. Bean et al. (111) reported distant metastases in 4 of 130 patients treated with preoperative radiation, compared with 1 of 150 patients treated with primary surgery. Although this was not a properly randomized, prospective study, these data do suggest that primary surgery is associated with minimal risk of tumor dissemination.

With primary surgery, a significant number of patients are found to have such good-prognosis tumors that adjuvant radiation can be safely eliminated. For those patients who require postoperative radiation, the therapy can be better tailored to the needs of the individual patient. The proper role of adjuvant radiation for endometrial cancer will not be known until large, randomized studies with a control (no treatment) arm have been performed, but with our present state of knowledge, the options for postoperative management are as follows:

1. Observation
2. Vault irradiation
3. External pelvic irradiation
4. Extended-field irradiation
5. Whole abdominal irradiation
6. Intraperitoneal ^{32}P

Observation

Patients with stage IA or IB, grade 1 or 2 tumors have an excellent prognosis, and no adjuvant radiation is necessary for this group. Canadian workers reported 227 such patients who were followed without radiation, and the 5-year relapse-free survival rate was 95% (112). Elliot et al. (113) from Australia treated 308 patients with grade 1 or 2 lesions confined to the inner third of the myometrium with hysterectomy alone. There were ten vaginal recurrences (3.2%), eight at the vault, and one each in the middle and lower third. The Danish Endometrial Cancer Group (DEMCA) prospectively followed 641 patients with grade 1 and 2 tumors with no more than 50% myometrial invasion (stages IA and IB) who were treated by total abdominal hysterectomy and bilateral salpingo-oophorectomy without adjuvant radiation (114). With follow-up of 68 to 92 months, the disease-free survival rate was 93% (596 of 641). Fanning and colleagues (115) compared surgery and adjuvant radiation with surgery alone for patients with stage I, grade 2 adenocarcinomas of favorable histologic subtype and less than one-third myometrial invasion. The 5-year survival rate for surgery and radiation was 94% (128 of 136), and the recurrence rate was 2.2% (3 of 136). The 5-year survival rate for the surgery-alone group was 98% (51 of 52), and the recurrence rate was 1.9% (1 of 52). **If patients are treated without adjuvant therapy, they must be followed carefully so that vault recurrences can be diagnosed early, when they are eminently curable** (114,116).

Vaginal Radiation

Intracavitary vaginal radiation significantly reduces the incidence of vault recurrence. Lotocki et al. (26) reported that preoperative or postoperative vault radium decreased the incidence of vault recurrence from 14% to 1.7%. Morbidity is low, although vaginal stenosis and dyspareunia may be a problem for postmenopausal patients if there is no regular vaginal dilatation. Colpostats alone usually are used to deliver a surface dose of 5,500 to 6,000 cGy. We use vault cesium alone for intermediate and high-risk patients with negative lymph nodes

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External Pelvic Irradiation

With an increasing number of patients in cancer centers having pelvic lymphadenectomy as part of their primary surgery, the indications for external pelvic irradiation are decreasing. Patients with positive pelvic nodes are candidates for external pelvic radiation, if necessary combined with paraaortic radiation. It is also a reasonable option for high-risk patients who have not undergone surgical staging but have a negative chest radiograph, a negative pelvic and abdominal CT scan, and a normal CA125 titer.

The GOG reported results of a randomized study of adjuvant pelvic radiation after complete surgical staging for patients with intermediate-risk endometrial carcinoma (91). Eligible patients had surgical stage IB, IC, IIA (occult), or IIB (occult) disease, and were randomized to receive either no additional therapy or 5,040 cGy of pelvic radiation therapy. There were 390 eligible patients in the study, and median follow-up was 56 months. The 2-year progression-free survival rate was significantly higher in the group receiving adjuvant radiation (96% vs. 88%; $p = 0.004$). However, overall survival rates were not significantly different because there were more pelvic/vaginal recurrences in the no-treatment arm (17 vs. 3), and these were often effectively treated with second-line therapy.

External irradiation should be as effective as vaginal irradiation for sterilizing micrometastases at the vaginal vault; thus, there seems to be no reason to give both external and vault irradiation after surgery because morbidity will be significantly increased. Stokes et al. (118) reported a serious complication rate of 8.8% (7 of 79) when external irradiation and intracavitary radium were combined. Similarly, among 1,011 cases treated at the Radiumhemmet, there was a 1.8% incidence of late complications in the group receiving postoperative external irradiation, compared with 15.9% in the group treated with preoperative intrauterine radium plus postoperative whole-pelvic irradiation (119).

Extended-Field Radiation

Risk factors for pelvic lymph node metastases portend a lower but significant risk of paraaortic metastases, and failure rates of 15% to 20% in the paraaortic area have been reported for patients receiving pelvic radiation only (108,110). Fairly extensive experience with extended-field radiation in patients with cervical cancer indicates an approximately 25% 5-year survival rate for patients with positive paraaortic nodes (120). Limited information is available on extended-field radiation for patients with endometrial cancer, but workers at the University of Minnesota reported a 5-year survival rate of approximately 40% for 20 patients with surgically confirmed paraaortic spread (121). **Our current indications for extended-field radiation are patients with:**

1. **Biopsy-proven paraaortic nodal metastasis**
2. **Grossly positive pelvic nodes, or multiple positive pelvic nodes**

Tolerance to paraaortic radiation is limited to 4,500 to 5,000 cGy by the small bowel and spinal cord. Potish et al. (121) reported only 1 case of severe enteric morbidity in 48 patients, for a complication rate of 2%.

Whole Abdominal Radiation

Management of patients with positive peritoneal washings or adnexal or peritoneal metastases is controversial. Potish et al. (122) treated 27 patients with open-field external-beam abdominal irradiation. Nine patients had positive peritoneal cytologic findings only. Patients with spread to the adnexa, peritoneal fluid, or both had a 5-year relapse-free rate of 90%, whereas the disease recurred in all patients with macroscopic disease beyond the adnexa. Similar results have been reported with the moving-strip technique (123). **For patients with peritoneal or omental metastases that have been completely excised, it seems reasonable to use whole-abdomen radiation. In the presence of gross residual disease, systemic therapy should be offered.**

Intraperitoneal ^{32}P

Investigators at Duke University have reported favorable results with intraperitoneal ^{32}P for patients with malignant peritoneal cytologic findings (124). However, most patients with malignant washings are also at risk of vaginal vault and pelvic sidewall recurrences and thus require external pelvic irradiation. When the latter was combined with intraperitoneal ^{32}P, 5 of 17 patients (29%) had chronic intestinal morbidity necessitating surgical intervention (124). Other problems associated with ^{32}P include the uneven distribution of fluid commonly present and the potential for bowel injury from “hot spots.”

The significance of positive peritoneal washings in patients with endometrial cancer remains controversial. After reviewing the literature, Milosevic et al. (63) believed that routine adjuvant therapy for patients with malignant cytologic findings was not justified. Usually there are other adverse prognostic factors that necessitate adjuvant therapy in their own right.

Adjuvant Progestins

Although the role of progestins in the management of patients with advanced and recurrent endometrial cancer has been established, they have not been shown to be of value in an adjuvant setting (125,126 and 127). In a randomized study of 1,148 patients with clinical stage I or II endometrial cancer at the Norwegian Radium Hospital, death due to intercurrent disease, particularly cardiovascular disease, was actually more common in the progesterone-treated group ($p = 0.04$) (128). In 461 high-risk patients, a tendency toward fewer cancer-related deaths and a better disease-free survival rate in the treatment group was observed, but crude survival was unchanged. It was concluded that further studies were needed in high-risk patients but that the evidence suggested that prophylactic progestin therapy was not likely to be a cost-effective approach for patients with endometrial cancer unless the patient had a high-risk, receptor-positive tumor.

The COSA–New Zealand–United Kingdom trial of 1,012 patients with high-risk disease showed more relapses in the control group, but no difference in survival (129). Patients received *MPA* 200 mg twice daily for at least 3 years, or until recurrence. Steroid receptor status had no influence on outcome in either arm.

Clinical Stage II

When both the cervix and the endometrium are clinically involved with adenocarcinoma, it may be difficult to distinguish between a stage IB adenocarcinoma of the cervix and a stage II endometrial carcinoma. Histopathologic evaluation is not helpful in the differentiation of these two conditions, and the diagnosis must be based on clinical and epidemiologic features. The obese, elderly woman with a bulky uterus is most likely to have endometrial cancer, whereas the younger woman with a bulky cervix and a normal corpus is most likely to have cervical cancer.

The small number of cases in all reported series and the lack of randomized, prospective studies preclude dogmatic statements about the optimal mode of therapy. Patients with stage II endometrial cancer have approximately a 35% incidence of positive pelvic nodes (130); therefore, any treatment protocol should include treatment of these nodes. For optimal prognosis, the uterus also should be removed in all patients (79,131).

Two main approaches have been used for patients with stage II disease:

1. Radical hysterectomy, bilateral salpingo-oophorectomy, and bilateral pelvic lymphadenectomy
2. Combined radiation and surgery (i.e., preoperative external pelvic irradiation and intracavitary radium or cesium), followed in 6 weeks by total abdominal hysterectomy and bilateral salpingo-oophorectomy

Radical Surgery

Radical surgery allows accurate surgicopathologic information to be obtained, but many of these patients are obese, elderly, hypertensive, and diabetic and thus are unsuitable candidates for this approach. In addition, results are no better than with the combined approach. Rutledge (132) believed that radical hysterectomy should be limited to patients with anatomic problems or other conditions that conflict with the use of radiation.

Combined Radiation and Surgery

The most common approach is to use external and intracavitary radiation followed by extrafascial hysterectomy (82,131,132,133 and 134). The hysterectomy usually is performed approximately 6 weeks after irradiation to allow the inflammatory edema to settle. Preoperative external radiation optimizes the geometry of the intracavitary insertion, and there is less risk of fixed bowel in the pelvis. Nahhas et al. (81) reported no improvement in survival when radical hysterectomy was performed after the external radiation in lieu of intracavitary radium plus extrafascial hysterectomy.

Most studies on combined therapy report significant bowel morbidity. Workers at the Joint Center for Radiation Therapy in Boston reported significant morbidity in 5 of 55 patients (9%) (134). Rectovaginal fistulas developed in two patients, and three patients had small- or large-bowel obstructions requiring surgical intervention. Four required diverting colostomies.

A study from the M. D. Anderson Hospital of 83 patients with stage II endometrial cancer treated with a combined radiosurgical approach reported severe gastrointestinal or urologic complications in 10 patients (12%) (131). Complications included proctitis with rectal stricture (2), radiation enteritis (1), small bowel obstruction (3), rectovaginal fistula (1), recurrent hemorrhagic cystitis (3), bilateral ureteral obstruction (1), and enterovesicular fistula (2). Six patients required surgery, and three patients (4%) died of the complications.

Radiation Therapy Alone

Radiation therapy alone is reserved for patients with medical contraindications to surgery but may provide good pelvic control in patients with minimal myometrial invasion. These are usually patients with well differentiated lesions (135), particularly if the primary lesion is arising in the lower segment of the uterus.

Proposed Management

Although the incidence of metastases to the paraaortic lymph nodes, adnexal structures, and upper abdomen would be expected to be higher than for stage I lesions, there is limited staging information available on patients with clinically overt stage II disease; thus, the role of extended-field or whole-abdomen radiation for these patients has not been explored.

Our current approach to stage II endometrial carcinoma is to perform primary surgery and surgical staging, provided the patient is medically fit. The surgery, which should be performed only if the parametrial tissues are free of disease, is as follows:

1. Modified (type II) radical hysterectomy
2. Bilateral salpingo-oophorectomy
3. Pelvic and abdominal peritoneal washings for cytologic study
4. Pelvic lymphadenectomy to the aortic bifurcation
5. Resection of grossly enlarged paraaortic nodes
6. Omental biopsy
7. Biopsy of any suspicious peritoneal nodules

After surgery, adjuvant radiation is individualized. If lymph nodes are negative, vault cesium, without external-beam therapy, is given. Patients with multiple positive pelvic nodes or grossly positive pelvic nodes are given extended-field external-beam therapy, without vault cesium. Patients with completely resected upper abdominal disease receive whole-abdomen radiation. As at all centers, our experience with clinical stage II endometrial cancer is limited, and firm data to support this approach are not available.

Clinical Stage III

Patients with FIGO clinical stage III carcinoma of the endometrium usually have involvement of the parametrium, pelvic sidewall, or adnexal structures. Involvement of the vagina or cul-de-sac is less common (32). Because it usually is not possible to be certain of the nature of an adnexal mass without laparotomy, some cases have a lower surgicopathologic stage when benign adnexal disease is found. On the other hand, subclinical involvement of the adnexa occurs in approximately 5% to 10% of patients with stage I and II endometrial carcinoma, and these patients often are included in reports reviewing stage III endometrial cancer. Aalders et al. (136) reported a 5-year survival rate of 40% for patients with surgicopathologic stage III disease, compared with 16% for patients with clinical stage III. Bruckman et al. (137) reported a 5-year survival rate of 80% when only the ovary and/or fallopian tube were involved, compared with 15% when other extrauterine pelvic structures were involved.

Treatment for stage III endometrial carcinoma must be individualized but should aim to include total abdominal hysterectomy and bilateral salpingo-oophorectomy. In the presence of an adnexal mass, surgery usually should be performed initially to determine the nature of the mass and to remove the bulk of the diseased tissue. In the presence of parametrial extension, it usually is more appropriate to commence with external irradiation and intracavitary radium.

Surgical eradication of all macroscopic tumor is of major prognostic importance for all patients with clinical stage III disease (136). The surgery should include removal of any enlarged pelvic or paraaortic lymph nodes. If all gross disease can be removed from the pelvis, thorough surgical staging is warranted. This should include peritoneal washings from the paracolic gutters and subdiaphragmatic areas, paraaortic lymph node sampling, and biopsy of the omentum.

Genest et al. (138) reported that the site of first recurrence was limited to the abdominal cavity in 79% of their patients in whom treatment failed (23 of 29), suggesting a role for whole-abdomen radiation in stage III endometrial cancer, particularly in patients with positive peritoneal washings or demonstrable micrometastases to the upper abdomen. However, Mackillop and Pringle (32) noted that although abdominal failure was common, it was rarely the only site of failure. Morbid obesity or other general medical conditions may limit the use of whole-abdomen irradiation in these patients.

Systemic metastases are a major problem, but the value of adjuvant systemic therapy is unproven. These patients usually have tumors that are less well differentiated, so their hormone receptor content is usually low, making response to progestins unlikely. No chemotherapeutic agents have any apparent prophylactic value in endometrial cancer.

Stage IV

Stage IV endometrial carcinoma is uncommon, and results of therapy are in general poor. However, an occasional patient is seen with a well differentiated adenocarcinoma that has metastasized because of prolonged patient or physician delay, or because cervical stenosis has prevented the appearance of abnormal bleeding. Such tumors usually contain ER and PR, and prolonged survival may occur with progestin therapy followed later by total abdominal hysterectomy, bilateral salpingo-oophorectomy, and possibly radiation therapy.

In a series of 83 patients reported by Aalders et al. (139) from the Norwegian Radium Hospital, the lung was the main site of extrapelvic spread, with 36% of patients having lung metastases. Ballon et al. (140) reported 33 patients (2.3%) with pulmonary metastases among 1,434 patients who had endometrial cancer. Only 10 of the 33 patients had the lung metastases at initial presentation, and the lungs were the sole site of metastatic disease in only 8 of the 33 patients.

Treatment of stage IV disease must be individualized but usually involves a combination of surgery, radiation therapy, and progestins. The objective of the surgery is to try to achieve local disease control in the pelvis to help palliate bleeding, discharge, and complications involving the bowel and/or the bladder. Aalders et al. (139) reported that control of the pelvic disease could be achieved in 20 of 72 patients (28%) with radiation alone or in combination with surgery and/or progestins. If tumor is removed, it should be sent for ER and PR determination to help guide subsequent systemic therapy.

Pelvic exenteration may be considered in the occasional patient in whom disease extension is limited to the bladder and/or rectum.

Special Clinical Circumstances

Endometrial Cancer Diagnosed after Hysterectomy **This situation is best avoided by routinely opening the excised uterus in the operating room so that the adnexa can be removed and appropriate staging performed if unsuspected endometrial cancer is discovered.** When the diagnosis is made during the postoperative period, the following investigations are recommended:

1. A chest radiograph and a CT scan of the pelvis and abdomen
2. A serum CA125 titer

If there is any suggestion of metastatic disease on the chest radiograph, this should be investigated primarily. If the CA125 titer is elevated or if the CT scan reveals lymphadenopathy or other evidence of metastatic disease, laparotomy is usually indicated.

If all investigations are negative, the following approach is suggested:

1. Grade 1 or 2 lesions with less than one-half myometrial invasion: no further treatment, although laparoscopic prophylactic oophorectomy is advisable because of the risk of subsequent ovarian cancer. This is particularly important if there is any family history of breast, ovarian, or colon cancer (Lynch II syndrome).
2. All other lesions: further laparotomy with removal of adnexa, surgical staging, and appropriate postoperative radiation.

Synchronous Primary Tumors in the Endometrium and Ovary This is an uncommon but well recognized occurrence. In approximately half of the cases, both endometrial and ovarian tumors are of the endometrioid type. These patients are often premenopausal and have a favorable prognosis. Treatment should be determined on the premise that each represents a primary lesion, and many require surgery only, without adjuvant radiation (96,141). When more aggressive histologic subtypes are involved, or if the uterine and ovarian tumors are histologically dissimilar, the prognosis is much poorer, and adjuvant radiation therapy should be used.

Endometrial Carcinomas in Young Women **Adenocarcinomas of the endometrium occasionally occur in very young women (<30 years of age), usually in association with the polycystic ovarian syndrome. Approximately 90% of the lesions are well differentiated and limited to the endometrium** (142), although Zuckerman et al. (143) reported a healthy twin pregnancy after conservative management of a 26-year-old multipara with a moderately differentiated lesion. Pelvic MRI findings were within normal limits.

For the well differentiated lesions, a 2-month trial of progestins (e.g., *megestrol acetate* orally, 160 to 320 mg/day or *MPA* 200 to 500 mg/day) may be undertaken if childbearing capability is desired (144). If a repeat curettage shows no evidence of carcinoma, conservative treatment may continue. If the lesion persists, or if childbearing capability is not desired, hysterectomy is the treatment of choice. Hysterectomy should probably be performed once childbearing has been completed (143).

In our review of 254 patients with endometrial cancer at the Royal Hospital for Women in Sydney, synchronous ovarian malignancies were found in 5 of 17 patients (29.4%) younger than 45 years of age, compared with 11 of 237 patients (4.6%) older than 45 years ($p < 0.001$). Three other patients (17.7%) had secondary ovarian involvement (145). **In view of the efficacy of modern hormone replacement therapy, there seems little justification for retaining the ovaries, unless for psychological reasons.**

Endometrial Carcinoma after Endometrial Ablation **With increasing use of endometrial ablation as an alternative to hysterectomy for some women with dysfunctional uterine bleeding unresponsive to hormonal therapy, there have been several reports of the subsequent development of endometrial cancer.** Valle and Baggish (146) reviewed eight case reports and cautioned about the need for proper patient selection. They recommended that all patients should have a preablation biopsy showing a normal endometrium and that patients with persistent hyperplasia unresponsive to hormonal therapy should be recommended for hysterectomy. They also suggested that if endometrial ablation is performed in high-risk patients because of medical contraindications to laparotomy, vigorous follow-up, including periodic ultrasonography and endometrial sampling, is required. Hysteroscopy with biopsies of the endometrium should be done if bleeding occurs.

Endometrial Carcinoma Associated with Intrauterine Pregnancy Endometrial carcinoma associated with pregnancy is rare. Schammel et al. (147) reviewed the literature and found 17 reported cases since 1927, to which they added 5 additional cases. The patients ranged in age from 21 to 43 years, with a mean of 34 years. **The tumors were most commonly diagnosed at the time of dilatation and curettage after a spontaneous abortion, or for vaginal bleeding or irregular menses associated with an unsuspected pregnancy.** Four cases were diagnosed at the time of a live birth.

The tumors have been predominantly focal, noninvasive, or superficially invasive, well differentiated endometrioid adenocarcinomas with extensive squamous metaplasia in five cases. In four cases (18%), there was an associated ovarian cancer, three of which were considered to be synchronous endometrioid carcinomas of the endometrium and ovary.

Most patients underwent total abdominal hysterectomy, and prognosis has been excellent. One patient with cervical involvement died at 36 months (148), and a second patient with serous papillary carcinoma involving both endometrium and ovaries had only 7 months of follow-up (149).

Four patients with well differentiated lesions had conservative medical management, consisting of initial curettage, usually followed by progestin therapy and repeat curettage. Three of the conservatively managed patients had follow-up ranging from 7 to 58 months available, and all remained well. Two of them had each achieved two subsequent pregnancies.

Recurrent Disease

According to figures reported in the *Annual Report on the Results of Treatment in Gynecological Cancer* (volume 23), approximately 27% of patients treated for endometrial cancer die within 5 years (Table 10.16). **Serum CA125 titers are usually elevated in patients with recurrent disease, particularly if the recurrence is intraperitoneal** (150). Pastner et al. (151) reported that none of six patients with an isolated vaginal recurrence had elevated levels, but false-positive values may occur in the presence of severe radiation injury of the bowel.

		Overall Survival (%)		
Strata	Patients	1 yr	3 yr	5 yr
All subjects	7,350	92.1	80.0	73.4
IA	883	98.4	94.1	90.9
IB	2,011	98.0	92.7	86.2
IC	551	97.1	87.3	81.0
IIA	249	93.6	82.4	76.9
IIB	306	93.6	79.0	67.3
IIIA	453	87.3	66.7	60.3
IIIB	72	76.2	50.3	41.2
IIIC	369	78.4	44.5	31.7
IVA	41	58.5	24.2	20.8
IVB	126	58.2	17.8	5.3

Modified from Creasman W, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. Annual report on the results of treatment in gynecological cancer. *J Epidemiol Biostat* 1998;3:35–61, with permission.

Table 10.16 Carcinoma of the Corpus Uteri in Patients Treated in 1990 to 1992: Overall Survival and Survival Rates by FIGO Surgical Stage

The large series of 379 patients with recurrent disease reported by Aalders et al. (152) from the Norwegian Radium Hospital provides some important information. Local recurrence was found in 50% of the patients, distant metastases in 29%, and simultaneous local and distant metastases in 21%. The median time from primary treatment to detection of recurrence was 14 months for patients with local recurrence and 19 months for those with distant metastases. **Thirty-four percent of all recurrences were detected within 1 year and 76% within 3 years of primary treatment.** In 10% of the patients, recurrence was diagnosed more than 5 years after primary treatment. At the time of diagnosis, 32% of all patients were free of symptoms and the diagnosis was made on routine physical or radiologic examination. For patients with local recurrence, 36% were free of symptoms, 37% had vaginal bleeding, and 16% had pelvic pain.

Treatment of recurrent endometrial cancer must be individualized but usually begins with hormone therapy. If there is progressive disease, cytotoxic chemotherapy may be offered. However, the results of treatment with cytotoxic agents are poor (153).

Isolated vaginal metastases are the most amenable to therapy with curative intent. Phillips et al. (154) reported on 81 patients with vaginal recurrences and noted that 68% had an isolated vaginal recurrence, 23% had both vaginal and pelvic recurrences, and 9% had vaginal and extrapelvic recurrences. Among the 54 patients with isolated vaginal recurrences, 39 lesions (71%) recurred in the proximal half of the vagina, 9 (17%) recurred in the distal half, 3 (6%) recurred in the proximal and distal parts of the vagina, and in 3 patients (6%), the location of the vaginal recurrence was not recorded.

Patients with a vaginal recurrence require thorough investigation to detect any associated metastatic foci, and this should commence with a chest radiograph and pelvic and abdominal CT scan. Fine-needle aspiration cytologic testing may be used to make a definitive diagnosis of a suspicious nodule.

If no other foci are detected, patients who have had prior pelvic radiation may undergo exploratory laparotomy with a view to some type of pelvic exenteration, provided the disease is found to be central and there are no lymph node metastases. In patients who have received no prior pelvic irradiation, external irradiation plus some type of brachytherapy may be appropriate. **Surgical resection of the metastatic nodule before radiation may improve local control, particularly for lesions greater than 3 cm in diameter. Laparotomy has the advantage of allowing a thorough search of the pelvis and abdomen for other metastatic foci.** In the Danish endometrial cancer study in which low-risk patients were followed without radiation, 17 vaginal recurrences were reported, and 15 of these (88.2%) were salvaged with radiation therapy. By contrast, none of seven pelvic recurrences was salvaged (114).

Hormone Therapy

In 1961, Kelley and Baker (155) reported on the use of moderate doses of progesterone for 21 patients with recurrent endometrial cancer. Six objective responses were seen, ranging from 9 months to 4.5 years. Thigpen et al. (156) reported the GOG experience with 331 women with measurable disease treated with 150 mg of *MPA* daily. Only 32 complete responses (10%) and 26 partial responses (8%) were observed. The median progression-free interval was brief. Podratz et al. (157) reported similar findings from the Mayo Clinic—only 10% of patients had an objective response to therapy, and fewer than 50% were alive at 1 year.

The route of administration does not appear to influence response rate or survival (158) and the type of progestin seems to be of no significance (159). High-dose therapy (1,000 mg *MPA* daily) also seems to offer no advantage (160). Side effects are usually minor and include weight gain, edema, thrombophlebitis, headache, and occasionally hypertension.

Because of their low toxicity, progestins should be used initially in all patients with recurrent endometrial cancer, particularly those with positive hormone receptors. If an objective response is obtained, the progesterone should be continued indefinitely. Some responses may be sustained for several years. If no response is obtained within 2 months but PR are known to be present, a higher dose may be worth trying before therapy is changed.

The nonsteroidal antiestrogen, *tamoxifen*, has also been used to treat patients with recurrent endometrial cancer. It inhibits the binding of estradiol to uterine ER, presumably blocking the proliferative stimulus of circulating estrogens. Responses are usually seen in patients who have previously responded to progestins, but an occasional response may occur in a patient who is unresponsive to progestins (161,162). *Tamoxifen* may be administered orally in a dose of 10 to 20 mg twice daily and continued for as long as the disease is responding. In a review of the literature, Moore et al. (160) reported a pooled response rate of 22% for single-agent *tamoxifen.*

The potential for combined *tamoxifen–progestin* therapy has been explored because these two agents have been shown to have a synergism that may relate to the induction of increased levels of PR by the weak estrogenic action of *tamoxifen* (161). Results to date have been disappointing (160).

Cytotoxic Chemotherapy

Cytotoxic chemotherapy for endometrial cancer is of only palliative value, and the results are in general disappointing. *Doxorubicin* is the most active agent. The GOG reported an overall response rate of 38%, with 26% of the patients achieving a complete clinical response. Median survival for the complete responders was 14 months (163). Other single agents that show activity against endometrial cancer include *cisplatin, carboplatin, hexamethylmelamine, cyclophosphamide*, and *5-fluorouracil (5-FU).* The GOG conducted a trial to compare *melphalan, 5-FU*, and *megestrol acetate* with *doxorubicin, 5-FU, cyclophosphamide*, and *megestrol acetate*. The response rate in both arms of the trial was 36% (164), which is no better than that achieved with *doxorubicin* alone. However, the GOG did demonstrate that **the addition of *cisplatin* to *doxorubicin* significantly improved the response rate (66% vs. 35%) and the progression-free interval (6.2 vs. 3.9 months), but not the median survival** (165). **The GOG has also reported *paclitaxel* to have a 35% response rate in previously untreated women** (166). Uterine papillary serous carcinomas are histologically the same as ovarian serous tumors, but the reported response rate to *cisplatin*-containing combination chemotherapy has been disappointing (167). However, Rodriguez et al. (168) reported a complete response in 3 of 13 patients (23%) and a partial response in 8 of 13 (62%), to various platinum combinations, including *cisplatin/paclitaxel* in 3 patients. Median duration of response was 7.5 months (range, 1 to 30 months).

Hormone Replacement Therapy

Particularly for younger women, hormone replacement therapy is an important issue after treatment for endometrial cancer. **Patients with stage I disease have a good prognosis, and protection against osteoporosis and the cardiovascular effects of estrogen deficiency is important.** Although it has been frequently stated that estrogen replacement therapy is contraindicated in patients who have had endometrial cancer, Creasman et al. (169) have challenged this concept. In a nonrandomized study, they reported no deleterious effect from estrogen given to 47 patients with stage I endometrial cancer compared with 174 patients with similar risk factors who did not receive estrogen. In fact, the estrogen group experienced a significantly longer disease-free survival.

Our practice is to offer all patients a combination of conjugated estrogens *(Premarin)* 0.625 mg and *MPA (Provera)* 2.5 to 5 mg, both taken daily without interruption.

Prognosis

Although individual institutions may report superior results, the most comprehensive survival data are provided in the *Annual Report on the Results of Treatment in Gynecological Cancer* (170). Results for 1990 through 1992 are shown in Table 10.16 and Table 10.17. These data highlight the significance of histologic grade: **patients with stage II, grade 1 tumors have a better prognosis than patients with stage I, grade 3 lesions.**

	Overall 5-Year Survival Rates (%)			
	Stage I		Stage II	
Grade	No.	Percent	No.	Percent
1	1,816	91.7	212	86.0
2	1,327	86.7	216	68.8
3	496	73.6	106	53.9

Modified from Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. Annual report on the results of treatment in gynecological cancer. *J Epidemiol Biostat* 1998;3:35-61, with permission.

Table 10.17 Carcinoma of the Corpus Uteri in Patients Treated in 1990 to 1992: Survival Rates for Surgical Stage I and II by Histologic Grade

Survival in relation to grade and depth of myometrial invasion for stage I disease is shown in Table 10.18. The poor prognosis associated with adenosquamous, papillary serous, and clear cell carcinoma has been discussed earlier (see Table 10.19).

		Overall Survival Rates (%)		
Strata	Patients	1 yr	3 yr	5 yr
IA G1	543	99.3	96.7	93.6
IB G1	964	98.9	96.4	92.1
IC G1	309	98.7	91.2	86.9
IA G2	238	98.1	91.5	89.1
IB G2	733	98.2	92.5	87.4
IC G2	376	98.1	90.6	84.0
IA G3	79	93.5	84.2	82.7
IB G3	222	95.8	80.7	75.5
IC G3	194	94.7	77.2	67.9

Modified from Creasman W, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. Annual report on the results of treatment in gynecological cancer. *J Epidemiol Biostat* 1998;3:35-61, with permission.

Table 10.18 Carcinoma of the Corpus Uteri in Patients Treated in 1990 to 1992: Survival Rates in Stage I by Surgical Stage and Grade of Differentiation (N = 3,639)

Histologic Type	No.	Five-Year Survival Rate (%)
Endometrioid	6,162	76.3
Adenosquamous	443	68.2
Clear cell	169	51.0
Papillary serous	277	45.5

Modified from Creasman W, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. Annual report on the results of treatment in gynecological cancer. *J Epidemiol Biostat* 1998;3:35-61, with permission.

Table 10.19 Carcinoma of the Corpus Uteri in Patients Treated in 1990 to 1992: Survival Rates by Histologic Type

Uterine Sarcomas

Uterine sarcomas are rare mesodermal tumors that account for approximately 3% of uterine cancers (171). They are a heterogeneous group of tumors, and thus individual experience with each lesion is limited. Hence, treatment protocols are not standardized, and there are few controlled studies evaluating different therapeutic approaches.

Pelvic radiation is thought to predispose to the subsequent development of uterine sarcomas (172). Zelmanowicz et al. (173) reported that endometrial carcinomas and malignant mixed mullerian tumors have a similar risk factor profile, which is compatible with the hypothesis that the pathogenesis of these two tumors is similar.

Criteria for histopathologic classification are not standardized, particularly for the more borderline lesions. As a group, their behavior is characterized by rapid clinical progression and they carry a poor overall prognosis. **The number of mitoses per 10 high-power fields (HPF) seems to be the most reliable predictor of biologic behavior, but criteria for diagnosis of uterine sarcomas have varied between observers and over time.**

Classification

Mesodermal derivatives from which sarcomas may arise include uterine smooth muscle, endometrial stroma, and blood and lymphatic vessel walls. Uterine sarcomas can be divided basically into two types:

1. **Pure,** in which only malignant mesodermal elements are present (e.g., leiomyosarcoma, endometrial stromal sarcomas)
2. **Mixed,** in which malignant mesodermal and malignant epithelial elements are present (e.g., carcinosarcoma)

They also may be subdivided into **homologous** and **heterologous** tumors, depending on whether the malignant mesodermal elements are normally present in the uterus. Malignant smooth muscle and stroma represent homologous elements, whereas malignant striated muscle and cartilage represent heterologous elements.

A working classification, modified from the more extensive classifications of Ober (174) and Kempson and Bari (175), is shown in Table 10.20. For practical purposes, the three common malignant uterine sarcomas are leiomyosarcomas, endometrial stromal sarcomas, and mixed mesodermal sarcomas.

Type	*Homologous*	*Heterologous*
Pure	Leiomyosarcoma	Rhabdomyosarcoma
	Stromal sarcoma	Chondrosarcoma
	(i) Endolymphatic stromal myosis	Osteosarcoma
	(ii) Endometrial stromal sarcoma	Liposarcoma
Mixed	Carcinosarcoma	Mixed mesodermal sarcoma

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Table 10.20 Classification of Uterine Sarcomas

Staging

There is no official staging system for uterine sarcomas, but it is usual to use the FIGO system for corpus carcinoma (Table 10.6). More accurate prognostic information is obtained by surgical staging.

Spread Patterns

Like endometrial carcinomas, these tumors infiltrate the myometrium and extend locally. However, they have a propensity for early hematogenous spread, and lymphatic dissemination occurs in approximately 35% of the patients whose disease is clinically confined to the uterus and cervix (176).

Smooth Muscle Tumors

Leiomyosarcomas, which must be distinguished from the cellular leiomyomas and atypical leiomyomas (see Chapter 6), occur most commonly in the 45- to 55-year age group and account for 30% of uterine sarcomas. **They usually arise *de novo* from uterine smooth muscle, although rarely they may arise in a preexisting leiomyoma.** A review of 1,432 patients undergoing hysterectomy for presumed fibroids at the University of Southern California revealed leiomyosarcoma in the hysterectomy specimen in 10 patients (0.7%). The incidence increased steadily from the fourth to the seventh decades of life (0.2%, 0.9%, 1.4%, and 1.7%, respectively) (177). **Rapid enlargement of a fibroid is a possible sign of malignancy.**

Most leiomyosarcomas are accompanied by pain, a sensation of pressure, abnormal uterine bleeding, or a lower abdominal mass. A few patients may have signs of metastatic disease such as a persistent cough, back pain, or ascites. On physical examination, it is impossible to distinguish leiomyosarcomas from large leiomyomas or from other uterine sarcomas. Pap smears are unrewarding, and uterine curettings are diagnostic for only the 10% to 20% of tumors that are submucosal (175,178). Diagnosis usually is not made before surgery.

Intravenous leiomyomatosis is a rare, relatively benign uterine smooth muscle tumor in which much of the tumor is present in (and may arise from) veins (179). It may extend as rubbery cords beyond the uterus into the parametrium or occasionally into the vena cava. Some patients may survive for prolonged periods in spite of incomplete resection of diseased tissue. High levels of ER and PR are present in some tumors, and regression may occur after menopause.

Leiomyomatosis peritonealis disseminata is a condition in which numerous nodules of histologically benign smooth muscle are present on peritoneal surfaces (180). It is frequently associated with a term pregnancy or with the use of oral contraceptives, and regression may occur after termination of pregnancy.

Endometrial Stromal Tumors

Endometrial stromal tumors include the benign stromal nodule, the low-grade stromal sarcoma, and the frankly malignant endometrial stromal sarcoma (Table 10.21). **Endometrial stromal sarcomas constitute 15% to 25% of uterine sarcomas** (171). Most patients are in the age range of 42 to 53 years. More than half the patients are premenopausal, and young women and girls may be affected (171). Abnormal vaginal bleeding is the most common presenting symptom and abdominal pain and uterine enlargement may occur (181). **Although they may be intramural, most endometrial stromal sarcomas involve the endometrium, and uterine curettage usually leads to diagnosis.**

Tumor	*Malignant Potential*	*Cytologic Atypia*	*Mitoses/ 10 HPF*
Stromal nodule	None	Mild-moderate (pushing margins)	Less than 10; usually 0–3
Low-grade stromal sarcoma	Low to intermediate	Mild-moderate (infiltrating margins)	Less than 10; usually 1–3
Stromal sarcoma	High	Moderate-marked	10 or more

AFIP, Armed Forces Institute of Pathology; hpf, high-power field.
Reproduced from Zaloudek CJ, Norris HC. Mesenchymal tumors of the uterus. In: Fenoglio C, Wolff M, eds. Progress in surgical pathology, vol. 3. New York: Masson, 1981:1–35, with permission.

Table 10.21 AFIP Classification of Endometrial Stromal Tumors

Low-grade stromal sarcomas, which usually have fewer than five mitoses per 10 HPF, also have been termed *endometrial stromatosis* and *endolymphatic stromal myosis.* They have infiltrating margins and demonstrate venous and lymphatic invasion. Although their behavior is relatively indolent, recurrences and distant metastases have been documented, indicating that they are a form of malignant neoplasm (182). **The most frequent sites of recurrence for patients with stage I disease are the pelvis and abdomen** (183). Prolonged survival and even cure are not uncommon after surgical resection of recurrent or metastatic lesions.

Mixed Mesodermal Tumors

Mixed mesodermal tumors usually occur in an older age group, most patients being postmenopausal (184,185). The frankly malignant variants grow rapidly and usually are accompanied by postmenopausal bleeding, pelvic pain, a palpable lower abdominal mass, or symptoms of metastatic disease. **Most patients have an enlarged or irregular uterus, and the tumor protrudes through the cervical os like a polyp in approximately half the patients** (171). Uterine curettage usually detects malignant tissue in the uterus, although determination of the exact nature of the tumor may require histologic examination of the entire specimen.

Treatment

Surgery

The only treatment of any proven curative value for the frankly malignant uterine sarcomas is surgical excision. This typically involves total abdominal hysterectomy and bilateral salpingo-oophorectomy, although in young patients it may be reasonable to preserve the ovaries in a patient with a leiomyosarcoma, particularly if the tumor has arisen in a fibroid (186). Lissoni et al. (187) reported eight young patients with a diagnosis of leiomyosarcoma after myomectomy who were followed conservatively. All were nulliparous and all had no evidence of disease on ultrasonography, hysteroscopy, chest radiography, and pelvic and abdominal CT scan or MRI. The mean mitotic count of the leiomyosarcomas was 6 per 10 HPF, with a range of 5 to 33. With a median follow-up of 42 months, three live births were recorded, but one patient recurred and died. Surgical staging offers prognostic information, but there is no evidence that the information can be used to improve survival.

Radiation Therapy

Although the value of adjuvant radiation is controversial (188), most authors suggest that it improves tumor control in the pelvis without influencing final outcome (189,190). These findings are based on clinical staging and would be expected because of the high incidence of disease beyond the uterus at the time of laparotomy.

Two reports suggest that for patients with surgical stage I or II disease, pelvic radiation does improve survival. A report from Vienna suggested that pelvic radiation for all uterine sarcomas was an effective treatment with regard to disease-specific survival in patients with early-stage disease, and increased local control even in patients with advanced disease (191). A retrospective review of 43 patients with mixed mullerian tumors from Vanderbilt University revealed a significant survival advantage for patients with surgical stage I or II disease treated with surgery plus pelvic irradiation (192). This report noted that 29% of patients with clinical stage I or II disease were upstaged at laparotomy.

It is not known whether extended-field or whole-abdomen radiation after surgical staging can influence prognosis, although whole-abdomen radiation has been reported to prevent abdominal relapse (190).

Chemotherapy

A number of chemotherapeutic agents are active against uterine sarcomas, but **a large study of 1,042 patients with uterine sarcomas reported to the Cancer Registry of Norway from 1956 to 1992 reported no change in 5-year survival rate after the introduction of chemotherapy into the treatment protocols** (185).

The most important drugs are *doxorubicin, cisplatin*, and *ifosfamide*. Unfortunately, most responses are partial and of short duration. For *cisplatin* (50 mg/m^2 every 3 weeks), the GOG reported a complete response rate of 8% and a partial response rate of 11% among 63 patients with advanced or recurrent mixed mesodermal tumors who had received no prior chemotherapy (193). Among 33 patients with leiomyosarcomas, there was only 1 partial response (3%)By contrast, leiomyosarcomas appear to be more responsive to *doxorubicin.* In the GOG trials, the response rate for leiomyosarcomas was 25% (7 of 28), compared with 10% (4 of 41) for mixed mesodermal sarcomas (194). *Ifosfamide* also has good activity against mixed mesodermal sarcomas, the GOG demonstrating 9 responses among 28 patients (31.2%) (195). For leiomyosarcomas, the response rate for *ifosfamide* was 17.2% (6 of 35), and all responses were partial (196).

Peters et al. (197) treated 11 patients with advanced or recurrent uterine stromal sarcomas or mixed mesodermal tumors with *cisplatin* 100 mg/m^2 and *doxorubicin* 40 to 60 mg/m^2 every 3 to 4 weeks for six cycles and reported a response in eight patients (73%). Three patients had a negative second-look procedure and two were alive and free of disease for more than 24 months.

Because of the propensity for early hematogenous spread, adjuvant chemotherapy after hysterectomy to eliminate micrometastases is an attractive concept. However, in a randomized GOG study of *doxorubicin* after total abdominal hysterectomy and bilateral salpingo-oophorectomy for stage I or II uterine sarcoma, neither survival nor progression-free interval was prolonged by the adjuvant chemotherapy (198). In a nonrandomized study, Peters et al. (197) reported 17 patients with high-risk clinical stage I uterine stromal sarcomas or mixed mesodermal tumors who were treated with six cycles of *cisplatin* and *doxorubicin*, as described previously. Fourteen of the patients had invasion to the outer third of the myometrium, seven had documented lymph node metastases, and five had positive peritoneal washings. With a median follow-up of 34 months, there were only four recurrences, giving a projected 5-year survival rate of 75%. This combination certainly justifies further study in a phase III trial of adjuvant chemotherapy.

Prognosis

The frankly malignant uterine sarcomas usually have a poor prognosis. Surgical stage is the most important prognostic variable. **If the tumor is confined to the uterus at laparotomy (surgical stage I), the 5-year survival rate is approximately 50%.** If there is spread beyond the uterus, the 5-year survival rate is approximately 20%. **When corrected by stage, there is no significant difference in failure rates, spread patterns, or survival among the three main histologic variants** (189,191). For mixed mesodermal tumors, there is also no difference in patterns of recurrence or survival between homologous, heterologous, or undifferentiated sarcomatous elements, but tumors with components of serous or clear cell carcinomas have a less favorable prognosis (185). Leiomyosarcomas in premenopausal patients carry a better overall prognosis, but this relates to their earlier stage at diagnosis (178). If the leiomyosarcoma arises in a benign fibroid, the prognosis is improved (178,199), and tumor diameter is also important (200). Similarly, mixed mesodermal sarcomas and endometrial stromal sarcomas carry a worse overall prognosis, but this relates to the generally later stage at diagnosis (188,189,201).

Chang et al. (183) reported that for endometrial stromal sarcomas, stage and mitotic index were both independent predictors of overall and disease-free survival, but when only stage I patients were considered, mitotic index disappeared from the Cox model. However, these authors placed most high-grade sarcomas into the undifferentiated sarcoma category on the basis of anaplastic cells that had mitotic indices in excess of 20 per 10 HPF.

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11 Epithelial Ovarian Cancer

Jonathan S. Berek

Of all the gynecologic cancers, ovarian malignancies represent the greatest clinical challenge. Epithelial cancers are the most common ovarian malignancies, and, because they are usually asymptomatic until they have metastasized, patients present with advanced disease in more than two thirds of the cases. Ovarian cancer represents a major surgical challenge, requires intensive and often complex therapies, and is extremely demanding of the patient's psychological and physical energy. It has the highest fatality-to-case ratio of all the gynecologic malignancies. There are more than 23,000 new cases annually in the United States, and 14,000 women can be expected to succumb to their illness (1). Ovarian cancer is the sixth most common cancer in women in the United States, accounting for 4% of all female cancers and 25% of cancers of the female genital organs. A woman's risk at birth of having ovarian cancer sometime in her life is nearly 1.5%, and that of dying from ovarian cancer, almost 1% (2).

Classification

Approximately 90% of ovarian cancers are derived from tissues that come from the celomic epithelium or “modified mesothelium” (2). The cells are a product of the primitive mesoderm, which can undergo metaplasia. Neoplastic transformation can occur when the cells are genetically predisposed to oncogenesis and/or exposed to an oncogenic agent.

Pathology

Invasive Cancer

Approximately 75% to 80% of epithelial cancers are of the serous histologic type. Less common types are mucinous (10%), endometrioid (10%), clear cell, Brenner, and undifferentiated carcinomas, each of the latter three representing less than 1% of epithelial lesions (2). Each tumor type has a histologic pattern that reproduces the epithelial features of a section of the lower genital tract. For example, the serous or papillary pattern has an appearance similar to that of the glandular epithelium lining the fallopian tube. Mucinous tumors contain cells that resemble the endocervical glands, and the endometrioid tumors resemble the endometrium. More specific details of the histologic types are discussed in Chapter 6.

Borderline Tumors

An important group of tumors to distinguish is the *tumor of low malignant potential*, also called the *borderline tumor* (3,4 and 5). Borderline tumors are lesions that tend to remain confined to the ovary for long periods of time, occur predominantly in premenopausal women, and are associated with a very good prognosis. They are encountered most frequently in patients between the ages of 30 and 50 years, whereas invasive carcinomas are found more commonly between the ages of 50 and 70 years (2).

Although uncommon, metastatic implants may occur with borderline tumors. Such implants have been divided into noninvasive and invasive forms. The latter group has a higher likelihood of developing into progressive, proliferative disease in the peritoneal cavity, which can lead to intestinal obstruction and death (4,5).

Peritoneal Carcinoma

The primary malignant transformation of the peritoneum has been called *primary peritoneal carcinoma* or *primary peritoneal papillary serous carcinoma.* This disease has the appearance of a “mullerian” carcinoma and simulates ovarian cancer clinically. This phenomenon can produce a condition in which “ovarian cancer” can arise in a patient whose ovaries were surgically removed many years earlier (6,7 and 8). In such cases, there may be microscopic or small macroscopic cancer on the surface of the ovary and extensive disease in the upper abdomen, particularly in the omentum.

Clinical Features

The peak incidence of invasive epithelial ovarian cancer is at 56 years of age (2,9,10). The age-specific incidence of ovarian epithelial cancer rises precipitously from 20 to 80 years of age and subsequently declines (10). The average age of patients with borderline tumors is approximately 46 years (2,5). Eighty to 90% of ovarian cancers, including borderline forms, occur after the age of 40 years, whereas 30% to 40% of malignancies occur after the age of 65 years. The chance that a primary epithelial tumor will be of borderline or invasive malignancy in a patient younger than 40 years of age is approximately one in ten, but after that age it rises to one in three (2). Fewer than 1% of epithelial ovarian cancers occur before the age of 20 years, with two thirds of ovarian malignancies in such patients being germ cell tumors (2,10). Approximately 30% of ovarian neoplasms in postmenopausal women are malignant, whereas only approximately 7% of ovarian epithelial tumors in premenopausal patients are frankly malignant (2).

Etiology

Ovarian cancer has been associated with low parity and infertility (11). Although there have been a variety of epidemiologic variables correlated with ovarian cancer, such as talc use, galactose consumption, and tubal ligation (see Chapter 7), none has been so strongly correlated as prior reproductive history and duration of the reproductive career (11,12). Early menarche and late menopause increase the risk of ovarian cancer (12). These factors and the relationship of parity and infertility to the risk of ovarian cancer have led to the hypothesis that suppression of ovulation may be an important factor. Theoretically, the surface epithelium undergoes repetitive disruption and repair. It is thought that this process might lead to a higher probability of spontaneous mutations that can unmask germline mutations or otherwise lead to the oncogenic phenotype (see Chapter 1).

Prevention

Because parity is inversely related to the risk of ovarian cancer, having at least one child is protective of the disease, with a risk reduction of 0.3 to 0.4. Oral contraceptive use reduces the risk of epithelial ovarian cancer (11). Women who use oral contraceptives for 5 or more years reduce their relative risk to 0.5 (i.e., there is a 50% reduction in the likelihood of development of ovarian cancer). Women who have had two children and have used oral contraceptives for 5 or more years have a relative risk of ovarian cancer as low as 0.3, or a 70% reduction (13). **Therefore, the oral contraceptive pill is the only documented method of chemoprevention for ovarian cancer, and it should be recommended to women for this purpose. When counseling patients regarding birth control options, this important benefit of oral contraceptive use should be emphasized. This is also important for women with a strong family history of ovarian cancer** (see discussion later).

Fenretinide (4-hydroxy-retinoic acid), a vitamin A derivative, has been given to women with unilateral breast cancer in an effort to reduce the risk of contralateral breast cancer. In a prospective, randomized, placebo-controlled trial conducted in Italy (14), women with unilateral breast cancer were given either 6 months of *fenretinide* orally or a placebo. In the treatment group, no ovarian cancers developed, whereas there were six cases of ovarian cancer in the control group. A larger trial is planned in the United States in an attempt to verify these data.

The performance of a prophylactic oophorectomy reduces, but does not eliminate, the risk of ovarian cancer (7,8). Because the entire peritoneum is at risk, peritoneal carcinomas can occur even after prophylactic oophorectomy. Because the ovaries provide protection from cardiovascular and orthopedic diseases, prophylactic oophorectomy should not be routinely performed in premenopausal women at low risk for ovarian cancer.

Screening

The value of tumor markers and ultrasonography to screen for epithelial ovarian cancer has not been clearly established by prospective studies. A more complete discussion of tumor markers and screening is presented in Chapter 2.

Screening with transabdominal ultrasonography has been encouraging (15,16 and 17), but specificity has been limited. However, advances in transvaginal ultrasonography have been shown to have a very high (>95%) sensitivity for the detection of early-stage ovarian cancer, although this test alone might require as many as 10 to 15 laparotomies per ovarian cancer detected (15,16). Routine annual pelvic examinations are disappointing for the early detection of ovarian cancer (18). Transvaginal color flow Doppler to assess the vascularity of the ovarian vessels has been shown to be a useful adjunct to ultrasonography (19), but it has not been shown to be useful in screening.

Determination of CA125 levels can contribute to the early diagnosis of epithelial ovarian cancer (20,21,22,23,24,25,26, and 27). With regard to sensitivity, CA125 can detect 50% of patients with stage I disease, and 60% if patients with stage II disease are included (25). Data suggest that the specificity of CA125 is improved when the test is combined with transvaginal ultrasonography (24) or when the CA125 levels are followed over time (25,26). These data have encouraged the development of prospective screening studies in Sweden and the United Kingdom (22,23). In these studies, patients with elevated CA125 levels (>30 U/mL) have undergone abdominal ultrasonography, and 14 ovarian cancers have been discovered among 27,000 women screened. Approximately four laparotomies have been performed per cancer detected.

A randomized trial of nearly 22,000 women aged 45 years or older was performed in the United Kingdom (27). The patients were assigned to either a control group of routine pelvic examination (n = 10,977) or to a screening group (n = 10,958). The screening consisted of three annual screens that involved measurement of serum CA125, pelvic ultrasonography if the CA125 was 30 U/mL or higher, and referral for gynecologic examination if the ovarian volume was 8.8 mL or greater on the ultrasonography. Of the 468 women in the screened group with an elevated CA125, 29 were referred for surgery, 6 cancers were discovered, and 23 had false-positive screening results, yielding a positive predictive value of 20.7%. During a 7-year follow-up period, cancer developed in 10 additional women in the screened group, as it did in 20 women in the control group. Although the median survival of women in whom cancer developed in the screened group was 72.9 months, compared with 41.8 months in the control group ($p = 0.0112$), the number of deaths did not differ significantly between the control and screened groups [18/10,977 vs. 9/10,958; relative risk 2.0 (0.78 to 5.13)]. Therefore, these data show that a multimodal approach to ovarian cancer screening is feasible, but a larger trial is necessary to determine whether this screening approach affects mortality. Such a three-arm randomized trial is ongoing in the United Kingdom, and the anticipated accrual is approximately 50,000 women per study arm and 100,000 women in the control arm. The details of the study design are presented in Chapter 2.

Given the false-positive results for both CA125 and transvaginal ultrasonography, particularly in premenopausal women, these tests are not cost effective and should not be used routinely to screen for ovarian cancer. In the future, new markers or technologies may improve the specificity of ovarian cancer screening, but proof of this will require a large, prospective study (24,25). Screening in women who have a familial risk may have a better yield, but additional study is necessary (28,29).

Genetic Risk for Epithelial Ovarian Cancer

Ovarian cancers appear to arise from a single clone, that is, they are monoclonal, and thus they are initiated from a single mutation (see Chapter 1) (30). Conversely, there is evidence that peritoneal carcinomas may have a multiclonal origin (31).

Hereditary Ovarian Cancer

The risk of ovarian cancer is higher than that in the general population in women with certain family histories (32,33,34,35,36,37,38,39,40 and 41,). **Most epithelial ovarian cancer is sporadic, with familial or hereditary patterns accounting for 5% to 10% of all malignancies** (33).

BRCA1 and BRCA2 **Most hereditary ovarian cancer is associated with mutations in the BRCA1 gene, located on chromosome 17** (32). **A small proportion of inherited disease has been traced to another gene, BRCA2, located on chromosome 13** (34). Discovered through linkage analyses, these two genes are associated with the genetic predisposition to both ovarian and breast cancer. There may be other, yet undiscovered genes that predispose to ovarian and/or breast cancer (41).

In the past, it had been thought that there were two distinct syndromes associated with a genetic risk, *site-specific hereditary ovarian cancer* and *hereditary breast/ ovarian cancer syndrome.* However, it is now believed that these groups essentially represent a continuum of mutations with different degrees of penetrance within a given family (36,41). In addition, there is a higher-than-expected risk of ovarian and endometrial cancer in the *Lynch II syndrome*, known also as the *hereditary nonpolyposis colorectal cancer syndrome (HNPCC syndrome)* (42).

The mutations are inherited in an autosomal dominant fashion, and therefore a full pedigree analysis (i.e., both maternal and paternal sides of the family) must be carefully evaluated (36). There are numerous distinct mutations that have been identified on each of these genes, and the mutations have different degrees of penetrance that may account for the preponderance of either breast cancer, ovarian cancer, or both, in any given family. **Based on analysis of women who have a mutation in the BRCA1 gene and are from high-risk families, the lifetime risk of ovarian cancer may be as high as 28% to 44%, and the risk has been calculated to be as high as 27% for those women with a BRCA2 mutation** (33,34,40). **The risk of breast cancer in women with a BRCA1 or BRCA2 mutation may be as high as 56% to 87%.**

Hereditary ovarian cancers in general occur in women approximately 10 years younger than those with nonhereditary tumors (33). Because the median age of epithelial ovarian cancer is in the mid- to late 50s, a woman with a first- or second-degree relative who had premenopausal ovarian cancer may have a higher probability of carrying an affected gene.

Breast and ovarian cancer may exist in a family in which there is a combination of epithelial ovarian and breast cancers, affecting a mixture of first- and second-degree relatives. Women with this syndrome tend to have these tumors at a young age, and the breast cancers may be bilateral. If two first-degree relatives are affected, this pedigree is consistent with an autosomal dominant mode of inheritance (27,32).

Founder Effect There is a higher carrier rate of *BRCA1* and *BRCA2* mutations in women of Ashkenazi Jewish descent and in Icelandic women (38,39,41). There have been three specific mutations that are carried by the Ashkenazi population, 185delAG and 5382insC on *BRCA1*, and 6174delT on *BRCA2.* The total carrier rate for a patient of Ashkenazi Jewish descent to have at least one of these three mutations is one in 40 or 2.5%, and thus there is a substantial risk in this population. The increased risk is a result of the “founder effect,” that is, a higher rate of mutations that have occurred in a defined geographic area.

Pedigree Analysis **The risk of ovarian cancer depends on the number of first- and/or second-degree relatives with a history of epithelial ovarian carcinoma and/or breast cancer, and on the number of malignancies that occur at an earlier age. The degree of risk is difficult to determine precisely unless a full pedigree analysis is performed.**

1. In families with two first-degree relatives (i.e., mother, sister, or daughter) with documented premenopausal epithelial ovarian cancer, the risk that a female first-degree relative has an affected gene could be as high as 35% to 40% (34).
2. In families with a single first-degree relative and a single second-degree relative (i.e., grandmother, aunt, first cousin, or granddaughter) with epithelial ovarian cancer, the risk that a woman has an affected gene also may be increased. The risk may be twofold to tenfold higher than in those without a familial history of the disease (34).
3. In families with a single postmenopausal first-degree relative with epithelial ovarian carcinoma, a woman may not have an increased risk of having an affected gene because the case is most likely to be sporadic. However, if the ovarian cancer occurs in a premenopausal relative, this could be significant, and a full pedigree analysis should be undertaken.
4. Women with a primary history of breast cancer have twice the expected incidence of subsequent ovarian cancer (33).

Lynch II Syndrome (Hereditary Nonpolyposis Colorectal Cancer Syndrome, HNPCC Syndrome) This syndrome, which includes multiple adenocarcinomas, involves a combination of familial colon cancer (known as the Lynch I syndrome), a high rate of ovarian, endometrial, and breast cancers, and other malignancies of the gastrointestinal and genitourinary systems (42). The mutations that have been associated with this syndrome are *MSH2, MLH1, PMS1*, and *PMS2.* The risk that a woman who is a member of one of these families will develop epithelial ovarian cancer depends on the frequency of this disease in first- and second-degree relatives, although these women appear to have at least three times the relative risk of the general population. A full pedigree analysis of such families should be performed by a geneticist to determine the risk more accurately.

Management of Women at High Risk for Ovarian Cancer

The management of a woman with a strong family history of epithelial ovarian cancer must be individualized and depends on her age, her reproductive plans, and the extent of risk. In all of these syndromes, women at risk benefit from a thorough pedigree analysis. A geneticist should evaluate the family pedigree for at least three generations. Decisions about management are best made after careful study and, whenever possible, verification of the histologic diagnosis of the family members' ovarian cancer.

The value of testing for *BRCA1* and *BRCA2* has yet to be clearly established, although some guidelines for testing now exist (36,41,43). The importance of genetic counseling cannot be overemphasized because the decision is complex. The American Society of Clinical Oncology has offered guidelines that emphasize careful evaluation by geneticists, careful maintenance of medical records, and a clear understanding in a genetic screening clinic of how to counsel and manage these patients. Concerns remain over how the information should be used, the impact on insurability, how the results will be interpreted, and how the information will be used within a specific family (e.g., to counsel children).

Although there are some conflicting data, the behavior of breast cancers arising in women with germline mutations in *BRCA1* or *BRCA2* is comparable to that of sporadic tumors (35). Women with breast cancer who carry these mutations, however, are at a greatly increased risk of ovarian cancer as well as a second breast cancer.

Although recommended by the National Institutes of Health Consensus Conference on Ovarian Cancer (44), **the value of screening with transvaginal ultrasonography, CA125 levels, or other procedures has not been clearly established in women at high risk.** Bourne et al. (29) have shown that this approach can detect tumors approximately ten times more often than in the general population, and thus they recommend screening in high-risk women.

Data derived from a multiinstitutional consortium of genetic screening centers indicate that the use of the oral contraceptive pill is associated with a lower risk for development of ovarian cancer in women who have a mutation in either *BRCA1* or *BRCA2* (45). The risk reduction is significant: in women who have taken oral contraceptives for 5 or more years, the relative risk of ovarian cancer is 0.4, or a 60% reduction in the incidence of the disease.

The value of prophylactic oophorectomy in these patients is controversial (46,47). Although the risk of ovarian cancer is diminished, there remains the risk of peritoneal carcinoma, a tumor that may also have a higher predisposition in women who have mutations in *BRCA1* and *BRCA2.* Women at high risk for ovarian cancer who undergo prophylactic oophorectomy have a risk of harboring occult neoplasia: in one series of 42 such operations, 4 patients (9.5%) had a malignancy, 1 of which was noted at surgery and 3 that were microscopic; all were smaller than 5 mm (47).

Recommendations

Current recommendations for management of women at high risk for ovarian cancer are summarized as follows (43,44):

1. Women who appear to be at high risk for ovarian or breast cancer should undergo genetic counseling and, if the risk appears to be substantial, may be offered genetic testing for *BRCA1* and *BRCA2.*
2. Women who wish to preserve their reproductive capacity can undergo screening by transvaginal ultrasonography every 6 months, although the efficacy of this approach is not clearly established.
3. Oral contraceptives should be recommended to young women before they embark on a planned family.
4. Women who do not wish to maintain their fertility or who have completed their family may undergo prophylactic bilateral salpingo-oophorectomy. The risk should be clearly documented, preferably established by *BRCA1* and *BRCA2* testing, before oophorectomy. These women should be counseled that this operation does not offer absolute protection because peritoneal carcinomas occasionally can occur after bilateral oophorectomy (8,9).
5. In women who also have a strong family history of breast cancer, annual mammographic screening should be performed beginning at age 30 years.
6. Women with a documented HNPCC syndrome should undergo periodic screening mammography, colonoscopy, and endometrial biopsy (42).

Symptoms

Most women with epithelial ovarian cancer have no symptoms for long periods. When symptoms do develop, they are often vague and nonspecific (48). In early-stage disease, the patient may complain of irregular menses if she is premenopausal. If a pelvic mass is compressing the bladder or rectum, she may report urinary frequency or constipation. Occasionally, she may perceive lower abdominal distention, pressure, or pain, such as dyspareunia. Acute symptoms, such as pain secondary to rupture or torsion, are unusual.

In advanced-stage disease, patients most often have symptoms related to the presence of ascites, omental metastases, or bowel metastases. The symptoms include abdominal distention, bloating, constipation, nausea, anorexia, or early satiety. Premenopausal women may complain of irregular or heavy menses, whereas vaginal bleeding may occur in postmenopausal women.

Signs

The most important sign is the presence of a pelvic mass on physical examination. A solid, irregular, fixed pelvic mass is highly suggestive of an ovarian malignancy. If, in addition, an upper abdominal mass or ascites is present, the diagnosis of ovarian cancer is almost certain. Because the patient usually complains of abdominal symptoms, she may not be subjected to a pelvic examination, and the presence of a tumor may be missed.

In patients who are at least 1 year past menopause, the ovaries should have become atrophic and nonpalpable. Thus, any palpable pelvic mass in these patients should be considered suspicious. This situation has been referred to as the *postmenopausal palpable ovary syndrome* (49). This concept has been challenged because subsequent authors have reported that only approximately 3% of palpable masses measuring less than 5 cm are malignant in postmenopausal women (15,16).

Diagnosis

The diagnosis of an ovarian cancer requires an exploratory laparotomy. The preoperative evaluation of the patient with an adnexal mass is outlined in Fig. 11.1.

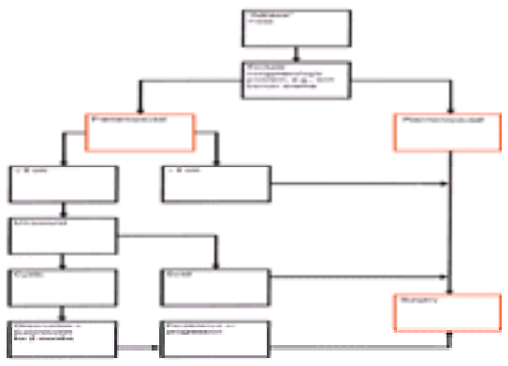

Figure 11.1 Preoperative evaluation of the patient with an adnexal mass.

In the premenopausal patient, a period of observation is reasonable, provided the adnexal mass is not clinically suspicious (i.e., it is mobile, mostly cystic, unilateral, and of regular contour). In general, an interval of no more than 2 months is allowed, a period during which hormonal suppression with an oral contraceptive may be used. If the lesion is not neoplastic, it should regress, as measured by pelvic examination and pelvic ultrasonography. If the mass does not regress or if it increases in size, it is presumed to be neoplastic and must be removed surgically.

The size of the lesion is important. If a cystic mass is greater than 10 cm in diameter, the probability that the lesion is neoplastic is increased, unless the patient has been taking *clomiphene citrate* or other agents to induce ovulation (13,14 and 15). Patients whose lesions are clinically suspicious (i.e., predominantly solid, relatively fixed, or irregularly shaped) should undergo laparotomy, as should postmenopausal patients with adnexal masses.

Before the planned exploration, the patient should undergo routine hematologic and biochemical assessments. A preoperative evaluation in a patient undergoing laparotomy should include a radiograph of the chest and an assessment of the urinary tract with an intravenous pyelogram. An abdominal and pelvic computed tomography (CT) or magnetic resonance imaging (MRI) scan is of no value in patients with a definite pelvic mass. Patients with ascites and no pelvic mass should have a CT or MRI scan to look particularly for liver or pancreatic tumors. The findings only rarely preclude laparotomy (50). If the hepatic enzymes are normal, the likelihood of liver disease is low. Liver–spleen, bone, and brain scans are unnecessary unless symptoms or signs suggest metastases to these sites.

The preoperative evaluation should exclude other primary cancers metastatic to the ovary. A barium enema or colonoscopy is indicated in some patients older than 45 years of age to exclude a primary colonic lesion with ovarian metastasis. Any patient who has evidence of occult blood in the stool or of intestinal obstruction should undergo this study. An upper gastrointestinal series or gastroscopy is indicated if there are symptoms indicating gastric involvement (51). Bilateral mammography is indicated if there is any breast mass because occasionally breast cancer metastatic to the ovaries can simulate primary ovarian cancer.

Cervical cytologic study should be performed, although its value for the detection of ovarian cancer is very limited. Patients who have irregular menses or postmenopausal vaginal bleeding should have an endometrial biopsy and an endocervical curettage to exclude the presence of uterine or endocervical cancer metastatic to the ovary.

Differential Diagnosis Ovarian epithelial cancers must be differentiated from benign neoplasms and functional cysts of the ovaries. A variety of benign conditions of the reproductive tract, such as pelvic inflammatory disease, endometriosis, and pedunculated uterine leiomyomata, can simulate ovarian cancer. Nongynecologic causes of a pelvic tumor, such as an inflammatory or neoplastic colonic mass, must be excluded (50). A pelvic kidney can simulate ovarian cancer.

Serum CA125 levels can be useful in distinguishing malignant from benign pelvic masses (52). In postmenopausal patients with an adnexal mass and a very high serum CA125 level (>95 U/mL), there is a 96% positive predictive value for malignancy. In premenopausal patients, however, the specificity of the test is low because the CA125 level tends to be elevated in common benign conditions.

Patterns of Spread

Ovarian epithelial cancers spread primarily by exfoliation of cells into the peritoneal cavity, by lymphatic dissemination, and by hematogenous spread.

Transcelomic The most common and earliest mode of dissemination is by exfoliation of cells that implant along the surfaces of the peritoneal cavity. The cells tend to follow the circulatory path of the peritoneal fluid. The fluid tends to move with the forces of respiration from the pelvis, up the paracolic gutters, especially on the right, along the intestinal mesenteries, to the right hemidiaphragm. Therefore, metastases are typically seen on the posterior cul-de-sac, paracolic gutters, right hemidiaphragm, liver capsule, the peritoneal surfaces of the intestines and their mesenteries, and the omentum. The disease seldom invades the intestinal lumen but progressively agglutinates loops of bowel, leading to a functional intestinal obstruction. This condition is known as *carcinomatous ileus.*

Lymphatic Lymphatic dissemination to the pelvic and paraaortic lymph nodes is common, particularly in advanced-stage disease (53,54,55 and 56). Spread through the lymphatic channels of the diaphragm and through the retroperitoneal lymph nodes can lead to dissemination above the diaphragm, especially to the supraclavicular lymph nodes (53). Burghardt et al. (55) performed systematic pelvic and paraaortic lymphadenectomy on 123 patients and reported that 78% of patients with stage III disease had metastases to the pelvic lymph nodes. In another series (54), the rate of positive paraaortic lymph nodes was 18% in stage I, 20% in stage II, 42% in stage III, and 67% in stage IV.

Hematogenous Hematogenous dissemination at the time of diagnosis is uncommon, with spread to vital organ parenchyma, such as the lungs and liver, in only approximately 2% to 3% of patients. Most patients with disease above the diaphragm at the time of presentation have a right pleural effusion. Systemic metastases are seen more frequently in patients who have survived for some years. Dauplat et al. (57) reported that distant metastasis consistent with stage IV disease ultimately occurred in 38% of patients whose disease was originally intraperitoneal. Malignt pleural effusion developed in one fourth of the patients, with a subsequent median survival of 6 months. Other sites and their median survivals were as follows: parenchymal lung metastasis in 7.1%, median survival 9 months; subcutaneous nodules in 3.5%, 12 months; malignant pericardial effusion 2.4%, 2.3 months; central nervous system 2%, 1.3 months; and bone metastases in 1.6%, 4 months. Significant risk factors for distant metastases were malignant ascites, peritoneal carcinomatosis, large metastatic disease in the abdomen, and retroperitoneal lymph node involvement at the time of initial surgery.

Prognostic Factors

The outcome of patients after treatment can be evaluated in the context of prognostic factors, which can be grouped into pathologic, biologic, and clinical factors. The survival of groups of patients based on prognostic factors is presented at the end of the chapter.

Pathologic Factors

The morphology and histologic pattern, including the architecture and grade of the lesion, are important prognostic variables (58,59,60,61,62 and 63).

In general, histologic type is not of prognostic significance, with the exception of clear cell carcinomas, which are associated with a worse prognosis than the other histologic types (61,62).

Histologic grade, as determined either by the pattern of differentiation or by the extent of cellular anaplasia and the proportion of undifferentiated cells, seems to be of prognostic significance (62,64). However, studies of the reproducibility of grading ovarian cancers have shown a high degree of intraobserver and interobserver variation (63). Because there is significant tumor heterogeneity and observational bias, the value of histologic grade as an independent prognostic factor has not been clearly established. Baak et al. (64) have presented a standard grading system based on morphometric analysis, and the system appears to correlate with prognosis, especially in its ability to distinguish low-grade or borderline patterns from other tumors.

Biologic Factors

Several biologic factors have been correlated with prognosis in epithelial ovarian cancer (65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86,87,88,89,90,91, 92,93,94,95,96,97,98 and 99). Using *flow cytometry*, Friedlander et al. (66) showed that ovarian cancers were commonly aneuploid. Furthermore, they and others showed that there was a high correlation between International Federation of Gynecology and Obstetrics (FIGO) stage and ploidy, in that low-stage cancers tend to be diploid and high-stage tumors tend to be aneuploid (65,66,67,68,69,70,71,72,73,74,75 and 76). In patients with stage I disease (Fig. 11.2), those with diploid tumors have a significantly longer 5 year survival than those with aneuploid tumors: 90% versus 60%, respectively (67). Multivariate analyses have demonstrated that ploidy is an independent prognostic variable and one of the most significant predictors of survival (68). *Flow cytometric analysis* also provides data on the cell cycle, and the proliferation fraction (S phase) determined by this technique has correlated with prognosis in some studies (69,70,78).

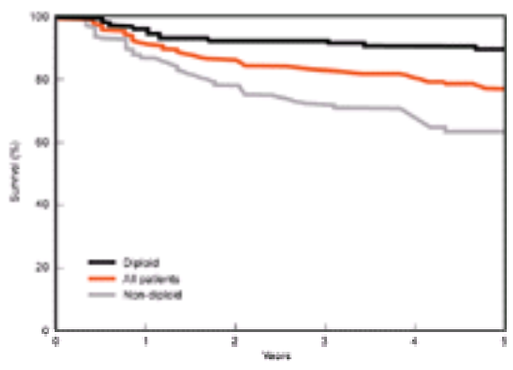

Figure 11.2 Survival of patients with stage I epithelial ovarian cancer based on ploidy evaluation. (From Tropé C, Kaern J, Vergote I. Adjuvant therapy for early-stage epithelial ovarian cancer. In: Gershenson DM, McGuire WP, eds. *Ovarian cancer: controversies in management.* New York: Churchill Livingstone, 1998:41–63, with permission.)

More than 100 *protooncogenes* have been identified, and studies have focused on the amplification or expression of these genetic loci and their relationship to the development and progression of ovarian cancer (79,80,81,82, 83,84,85,86, 87,88,89,90, 91,92, 93,94, 95 and 96). For example, Slamon et al. (81) reported that 30% of epithelial ovarian tumors expressed the HER-2/*neu* oncogene and that this group had a poorer prognosis, especially those patients with more than five copies of the gene. Berchuck et al. (82) reported a similar incidence (32%) of HER-2/*neu* expression. In their series, patients whose tumors expressed the gene had a poorer median survival (15.7 vs. 32.8 months). Others have not substantiated this finding (83), and a review of the literature by Leary et al. (84) revealed an overall incidence of HER-2/*neu* expression of only 11%. Thus the prognostic value of HER-2/ *neu* expression in ovarian cancer is unclear, and further study is required.

Additional prognostic variables include *p53, bcl-2*, k- *ras*, Ki67, interleukin-6, and platelet-derived growth factor (89,90,91,92,93,94,95 and 96). The relative prognostic value of individual factors is still undergoing evaluation. Further discussion of these molecular variables is presented in Chapter 1.

The *in vitro clonogenic assay* has been studied in ovarian cancer. A significant inverse correlation has been reported between clonogenic growth *in vitro* and survival (97,98 and 99). Multivariate analysis has found that clonogenic growth in a semisolid culture medium is a significant independent variable (99). Further study is needed to evaluate the clinical usefulness of this assay.

Clinical Factors

In addition to stage, the extent of residual disease after primary surgery, the volume of ascites, patient age, and performance status are all independent prognostic variables (100,101,102,103,104,105,106,107 and 108). Among patients with stage I disease, Dembo et al. (100) showed, in a multivariate analysis, that tumor grade and "dense adherence" to the pelvic peritoneum had a significant adverse impact on prognosis, whereas intraoperative tumor spillage or rupture did not. A subsequent study by Sjovall et al. (101) confirmed these findings. A multivariate analysis of these and several other studies was performed by Vergote (103), who found that for early-stage disease, poor prognostic variables were tumor grade, capsular penetrance, surface excrescences, and malignant ascites, but not iatrogenic rupture.

Initial Surgery for Ovarian Cancer

Staging

Ovarian epithelial malignancies are staged according to the FIGO system, and the staging system of 1987 is listed in Table 11.1. The FIGO staging system is based on findings at surgical exploration. A preoperative evaluation should exclude the presence of extraperitoneal metastases.

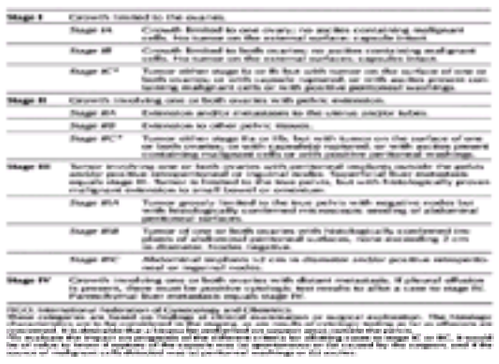

Table 11.1 FIGO Staging for Primary Carcinoma of the Ovary

A thorough surgical staging should be performed because subsequent treatment will be determined by the stage of disease. In patients in whom exploratory laparotomy does not reveal any macroscopic evidence of disease on inspection and palpation of the entire intraabdominal space, a careful search for microscopic spread must be undertaken.

In earlier series in which patients did not undergo careful surgical staging, the overall 5-year survival rate for patients with apparent stage I epithelial ovarian cancer was only approximately 60% (109,110). Since then, survival rates of 90% to 100% have been reported for patients who were properly staged and found to have stage IA or IB disease (110,111,112,113,114,115,116,117,118 and 119).

Technique for Surgical Staging

In patients whose preoperative evaluation suggests a probable metastatic malignancy, a midline or paramedian abdominal incision is recommended to allow adequate access to the upper abdomen. When a malignancy is unexpectedly discovered in a patient who has a lower transverse incision, the rectus muscles can be either divided or detached from the symphysis pubis to allow better access to the upper abdomen (see Chapter 19). If this is not sufficient, the incision can be extended on one side to create a "J" incision.

The ovarian tumor should be removed intact, if possible, and a frozen histologic section obtained. If ovarian malignancy is present and the tumor is apparently confined to the ovaries or the pelvis, thorough surgical staging should be carried out. This involves the following steps:

1. ***Any free fluid, especially in the pelvic cul-de-sac, should be submitted for cytologic evaluation.***
2. ***If no free fluid is present, peritoneal "washings" should be performed*** by instilling and recovering 50 to 100 mL of saline from the pelvic cul-de-sac, each paracolic gutter, and beneath each hemidiaphragm. Obtaining the specimens from under the diaphragms can be facilitated with the use of a red rubber catheter attached to the end of a bulb syringe.
3. ***A systematic exploration of all the intraabdominal surfaces and viscera is performed.*** This should proceed in a clockwise fashion from the cecum cephalad along the paracolic gutter and the ascending colon to the right kidney, the liver and gallbladder, the right hemidiaphragm, the entrance to the lesser sac at the paraaortic area, across the transverse colon to the left hemidiaphragm, down the left gutter and the descending colon to the rectosigmoid colon. The small intestine and its mesentery from the ligament of Trietz to the cecum should be inspected.
4. ***Any suspicious areas or adhesions on the peritoneal surfaces should be sampled for biopsy. If there is no evidence of disease, multiple intraperitoneal biopsies should be performed.*** The peritoneum of the pelvic cul-de-sac, both paracolic gutters, the peritoneum over the bladder, and the intestinal mesenteries should be sampled.
5. ***The diaphragm should be sampled either by biopsy or by scraping with a tongue depressor and making a cytologic smear.*** Biopsies of any irregularities on the surface of the diaphragm can be facilitated by use of the laparoscope and the associated biopsy instrument.
6. ***The omentum should be resected from the transverse colon, a procedure called an infracolic omentectomy.*** The procedure is initiated on the underside of the greater omentum, where the peritoneum is incised just a few millimeters away from the transverse colon. The branches of the gastroepiploic vessels are clamped, ligated, and divided, along with all the small branching vessels that feed the infracolic omentum. If the gastrocolic ligament is palpably normal, it does not need to be resected.
7. ***The retroperitoneal spaces should be explored to evaluate the pelvic lymph nodes.*** The pelvic retroperitoneal dissection is performed by incising the peritoneum over the psoas muscles. This may be done on the ipsilateral side only for unilateral tumors. Any enlarged lymph nodes should be resected and submitted for frozen-section analysis. If no metastases are present, a formal pelvic lymphadenectomy should be performed.
8. ***The paraaortic area should be explored.*** A vertical incision should be made cephalad in the paracolic gutter and an oblique incision across the posterior parietal peritoneum from the right iliac fossa to the ligament of Treitz. The right colon can then be mobilized and the paraaortic lymph nodes exposed. Any enlarged nodes should be removed and at least the nodes caudal to the inferior mesenteric artery resected (120).

Results

Metastases in apparent stage I and II epithelial ovarian cancer are summarized in Table 11.2. **As many as three in ten patients whose tumor appears confined to the pelvis have occult metastatic disease in the upper abdomen or the retroperitoneal lymph nodes** (54,113,114,115,116,117,118,119,120 and 121).

Ref.	Diaphragm	Aortic Lymph Nodes	Pelvic Nodes	Omentum	Positive Cytology
18		4/21 (19.0%)	2/21 (9.2%)		
21	2/58 (3.4%)	6/52 (11.5%)	1/11 (9.1%)	6/57 (10.5%)	
22	3/72 (4.2%)			7/79 (8.9%)	
23					7/26 (19.4%)
24	1/31 (3.2%)	0/5 (0%)		0/5 (0%)	8/31 (25.8%)
25		2/10 (20.0%)	0/10 (0%)		
26	7/16 (43.8%)				
27		5/26 (19.2%)	0/9 (0%)	1/23 (4.8%)	
28					16/44 (36.4%)
29					1/10 (10.0%)
Total	13/177 (7.3%)	17/114 (14.9%)	3/51 (5.9%)	14/162 (8.6%)	32/121 (26.4%)

Modified from Berek JS, Hacker NF. Staging and second-look operations in ovarian cancer. In: Piver MS, ed. Ovarian malignancies. Edinburgh: Churchill Livingstone, 1987:311, with permission.

Table 11.2 Site of Metastases in Patients with Apparent Stage I and II Ovarian Cancer

The importance of careful initial surgical staging is emphasized by the findings of a cooperative national study (110) in which 100 patients with apparent stage I and II disease who were referred for subsequent therapy underwent additional surgical staging. In this series, 28% of the patients initially thought to have stage I disease were “upstaged,” and 43% of those thought to have stage II disease had more advanced lesions. A total of 31% of the patients were upstaged as a result of additional surgery, and 77% were reclassified as having stage III disease. Histologic grade was a significant predictor of occult metastasis: 16% of the patients with grade 1 lesions were upstaged, compared with 34% with grade 2 disease and 46% with grade 3 disease.

Early-Stage Ovarian Cancer

The primary treatment for stage I epithelial ovarian cancer is surgical, that is, a total abdominal hysterectomy, bilateral salpingo-oophorectomy, and surgical staging (109,110). In certain circumstances, a unilateral oophorectomy may be permitted, as discussed later. Based on the prognostic variables outlined previously (59,68,100,101,102,103,104 and 105,107) early-stage epithelial ovarian cancer can be subdivided into low-risk and high-risk disease (Table 11.3).

Low Risk	High Risk
Low grade	High grade
Non-clear cell histologic type	Clear cell histologic type
Intact capsule	Tumor growth through capsule
No surface excrescenses	Surface excrescences
No ascites	Ascites
Negative peritoneal cytologic findings	Malignant cells in fluid
Unruptured or intraoperative rupture	Preoperative rupture
No dense adherence	Dense adherence
Diploid tumor	Aneuploid tumor

Table 11.3 Prognostic Variables in Early-Stage Epithelial Ovarian Cancer

Borderline Tumors

The principal treatment of borderline ovarian tumors is surgical resection of the primary tumor (122,123,124,125,126 and 127). **There are no prospective data to suggest that either adjuvant chemotherapy or radiation therapy improves survival** (128,129 and 130). After a frozen section has determined that the histologic type is borderline, premenopausal patients who wish to preserve ovarian function may be managed with a “conservative” operation (i.e., a unilateral oophorectomy) (122,123 and 125). In a study of patients who underwent unilateral ovarian cystectomy only for apparent stage I borderline serous tumors, Lim-Tan et al. (124) found that this conservative operation also was safe; only 8% of the patients had recurrences 2 to 18 years later, all with curable disease confined to the ovaries. Recurrence was associated with positive margins of the removed ovarian cyst (124). Thus, hormonal function and fertility can be maintained. In patients in whom an oophorectomy or cystectomy has been performed and a borderline tumor is later documented in the permanent pathology, no additional staging surgery is necessary.

Early-Stage Low-Risk Ovarian Cancer

In patients who have undergone a thorough staging laparotomy and in whom there is no evidence of spread beyond the ovary, an abdominal hysterectomy and bilateral salpingo-oophorectomy is appropriate therapy. The uterus and the contralateral ovary can be preserved in women with stage IA, low-risk disease who wish to preserve fertility. These women should be followed carefully with routine periodic pelvic examinations and determinations of the serum CA125 level. Usually, the other ovary and the uterus are removed at the completion of childbearing (see Treatment section, later).

Advanced-Stage Ovarian Cancer

The surgical management of all patients with advanced-stage disease is approached in a similar manner, with modifications made for the overall status and general health of the patient, as well as the extent of residual disease present at the time treatment is initiated. A treatment scheme is outlined in Fig. 11.3.

Figure 11.3 Treatment scheme for patients with advanced-stage ovarian cancer. ([a]Under selected circumstances or clinical trials.)

If the patient is medically stable, she should undergo an initial exploratory procedure with removal of as much disease as possible. The operation to remove the primary tumor as well as the associated metastatic disease is referred to as *debulking*, or *cytoreductive* surgery. Most patients subsequently receive combination chemotherapy for an empiric number of cycles. In some patients with completely resected disease, whole-abdominal radiation therapy may be used. In patients with no clinical evidence of disease and negative tumor markers at the completion of chemotherapy, a reassessment or *second-look laparotomy* may be performed in certain circumstances. In patients with persistent disease at second-look laparotomy, second-line therapy may be recommended because there are many options available.

Cytoreductive Surgery

Patients with advanced-stage epithelial ovarian cancer documented at initial exploratory laparotomy should undergo cytoreductive surgery (93,94,95,96,97,98,99 and 100). The operation typically includes the performance of a total abdominal hysterectomy and bilateral salpingo-oophorectomy, along with a complete omentectomy and resection of any metastatic lesions from the peritoneal surfaces or from the intestines. The pelvic tumor often directly involves the rectosigmoid colon, the terminal ileum, and the cecum (Fig. 11.4). In a minority of patients, most or all of the disease is confined to the pelvic viscera and the omentum, so that removal of these organs results in extirpation of all gross tumor, a situation that is associated with a reasonable chance of prolonged progression-free survival.

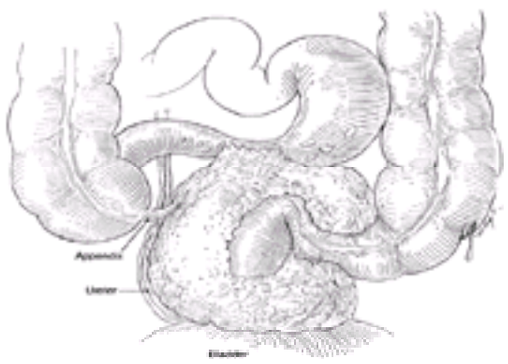

Figure 11.4 Extensive ovarian carcinoma involving the bladder, rectosigmoid, and ileocecal area. (From Heintz APM, Berek JS. Cytoreductive surgery for ovarian carcinoma. In: Piver MS, ed. *Ovarian malignancies.* Edinburgh: Churchill Livingstone, 1987:134, with permission.)

Theoretic Rationale

The rationale for cytoreductive surgery relates to three general theoretic considerations (131,132,133,134,135,136,137,138,139,140,141,142,143,144,145,146, and 147):

1. Physiologic benefits of tumor mass excision
2. Improved tumor perfusion and increased growth fraction, both of which increase the likelihood of response to chemotherapy or radiation therapy
3. Enhanced immunologic competence of the patient

Physiologic Benefits The removal of bulky tumor masses may reduce the volume of ascites present. Often, ascites completely disappear after removal of the primary tumor and a large omental “cake.” Also, removal of the omental cake often alleviates the nausea and early satiety that many patients experience. Removal of intestinal metastases may restore adequate intestinal function and lead to an improvement in the overall nutritional status of the patient, thereby facilitating the patient's ability to tolerate subsequent chemotherapy.

Tumor Perfusion and Cell Kinetics A large, bulky tumor may contain areas that are poorly vascularized, and such areas are exposed to suboptimal concentrations of chemotherapeutic agents. Similarly, these areas are poorly oxygenated, so radiation therapy, which requires adequate oxygenation to achieve maximal cell kill, is less effective. Thus, surgical removal of these bulky tumors may eliminate areas that are most likely to be relatively resistant to treatment.

In addition, larger tumor masses tend to be composed of a higher proportion of cells that are either nondividing or in the resting phase (i.e., G_0 cells, which are essentially resistant to the therapy). A *low growth fraction* is characteristic of bulky tumor masses, and cytoreductive surgery can result in smaller residual masses with a relatively higher growth fraction.

The *fractional cell kill hypothesis* of Skipper (144) postulates that a constant proportion of the tumor cells are destroyed with each treatment. This theory suggests that a given dose of a drug will kill a constant fraction of cells as long as the growth fraction and phenotype are the same. Therefore, a treatment that reduces a population of tumor cells from 10^9 to 10^4 cells also would reduce a population of 10^5 cells to a single cell. If the absolute number of tumor cells is lower at the initiation of treatment, fewer cycles of therapy should be necessary to eradicate the cancer, provided that the cells are not inherently resistant to the therapy.

The larger the initial tumor burden, the longer the necessary exposure to the drug and, therefore, the greater the chance of developing *acquired* drug resistance. However, because the spontaneous mutation rate of tumors is an inherent property of the malignancy, the likelihood of developing *phenotypic* drug resistance also increases as the size of the tumor increases. The chance of developing a clone of cells resistant to a specific agent is related to both the tumor size and its mutation frequency (144,145). This is one of the inherent problems with cytoreductive surgery for large tumor masses: phenotypic drug resistance may have already developed before any surgical intervention.

Immunologic Factors Larger tumor masses appear to be more immunosuppressive than smaller tumors. In addition to the nonspecific immunocompromise that occurs with large tumors, bulky tumors may be much less amenable to control by host defense mechanisms. The normal mechanisms of recognition of abnormal antigens may be overwhelmed and abrogated by the relatively large number of cancer cells. Excess tumor antigen can block the function of cytotoxic lymphocytes. Indeed, large tumors may result in the inherent production of immunologically suppressive substances as well as the induction of suppressor lymphocyte activity (146).

Goals of Cytoreductive Surgery

The principal goal of cytoreductive surgery is removal of all of the primary cancer and, if possible, all metastatic disease. If resection of all metastases is not feasible, the goal is to reduce the tumor burden by resection of all individual tumors to an “optimal” status. Griffiths (131) initially proposed that all metastatic nodules should be reduced to no greater than 1.5 cm in maximum diameter and showed that survival was significantly longer in such patients.

Subsequently, Hacker and Berek and colleagues (132,133 and 134,137,138,139 and 140) showed that patients whose largest residual lesions were no greater than 5 mm had a superior survival, and this was substantiated by Hoskins et al. (136), who presented data from the Gynecologic Oncology Group (GOG). The median survival of patients in this category was 40 months, compared with 18 months for patients whose lesions were less than 1.5 cm and 6 months for patients with nodules greater than 1.5 cm in diameter (Fig. 11.5). Clearly, those patients whose disease has been completely resected have the best prognosis, and approximately 60% of patients in this category were free of disease at 5 years (Fig. 11.6).

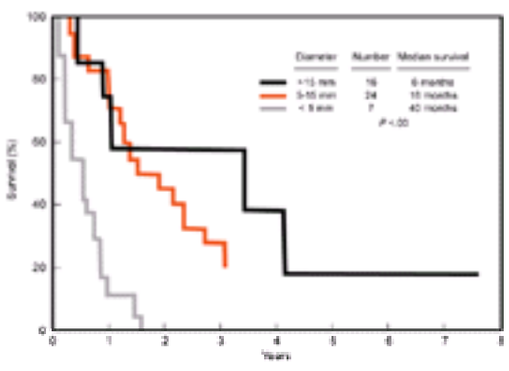

Figure 11.5 Survival versus diameter of largest residual disease. (From Hacker NF, Berek JS, Lagasse LD, Nieberg RK, Elashoff RM.

Figure 11.5 Survival versus diameter of largest residual disease. (From Hacker NF, Berek JS, Lagasse LD, Nieberg RK, Elashoff RM. Primary cytoreductive surgery for epithelial ovarian cancer. *Obstet Gynecol* 1983;61:413–420, with permission from the American College of Obstetrics and Gynecology.)

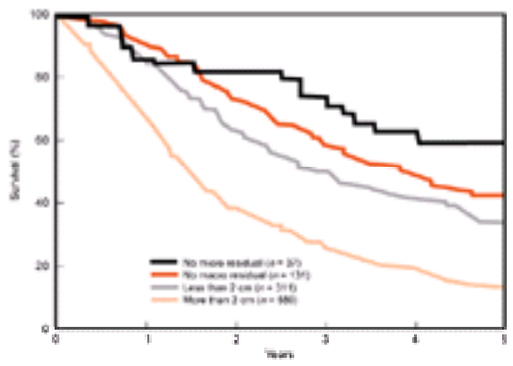

Figure 11.6 Survival of patients with stage IIIC epithelial ovarian cancer based on the maximum size of the residual tumor after exploratory laparotomy and tumor resection. (From Pecorelli S, Odicino F, Maisonneuve P, Creasman W, Shepard J, Sideri M, et al. Carcinoma of the ovary. Annual Report on the Results of Treatment of Gynaecological Cancer. *J Epidemiol Biostat* 1998;3:75–102, with permission.)

The resectability of the metastatic tumor is usually determined by the location of the disease. Optimal cytoreduction is difficult to achieve in the presence of extensive disease on the diaphragm, in the liver parenchyma, along the base of the small bowel mesentery, in the lesser omentum, or in the porta hepatis.

The ability of cytoreductive surgery to influence survival is limited by the extent of metastases before cytoreduction, presumably because of the presence of phenotypically resistant clones of cells in large metastatic masses (134,137). Patients whose metastatic tumor is very large (i.e., >10 cm before cytoreductive surgery) have a shorter survival than those with smaller areas of disease (134) (Fig. 11.7). Extensive carcinomatosis, the presence of ascites, and poor tumor grade, even with lesions that measure less than 5 mm, may also worsen survival (137,138,139 and 140).

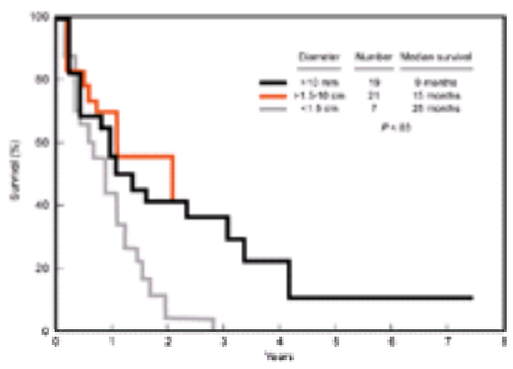

Figure 11.7 Survival versus diameter of largest metastatic disease before cytoreduction. (From Hacker NF, Berek JS, Lagasse LD, Nieberg RK, Elashoff RM. Primary cytoreductive surgery for epithelial ovarian cancer. *Obstet Gynecol* 1983;61:413– 420, with permission from the American College of Obstetrics and Gynecology.)

Exploration

The supine position on the operating table may be sufficient for most patients. However, for those with extensive pelvic disease for whom a low resection of the colon may be necessary, the low lithotomy position should be used. Debulking operations should be performed through a vertical incision to gain adequate access to the upper abdomen as well as to the pelvis.

After the peritoneal cavity is opened, ascitic fluid, if present, should be evacuated. In some centers, fluid is submitted routinely for appropriate *in vitro* studies, particularly the clonogenic assay. In cases of massive ascites, careful attention must be given to hemodynamic monitoring, especially in patients with borderline cardiovascular function. In such patients, monitoring of the central venous pressure alone may be inadequate, and a Swan-Ganz catheter may be used, as discussed in Chapter 17.

A thorough inspection and palpation of the peritoneal cavity and retroperitoneum are carried out to assess the extent of the primary tumor and the metastatic disease. All abdominal viscera must be palpated to exclude the possibility that the ovarian disease is metastatic, particularly from the stomach, colon, or pancreas. If optimal status is not considered achievable, extensive bowel and urologic resections are not indicated except to overcome a bowel obstruction. However, removal of the primary tumor and omental cake is usually both feasible and desirable.

Pelvic Tumor Resection

The essential principle in the removal of the pelvic tumor is to use the retroperitoneal approach (148). To accomplish this, the retroperitoneum is entered laterally, along the surface of the psoas muscles, which avoids the iliac vessels and the ureters. The procedure is initiated by division of the round ligaments bilaterally if the uterus is present. The peritoneal incision is extended cephalad, lateral to the ovarian vessels in the “infundibulopelvic ligament,” and caudally toward the bladder. With careful dissection, the retroperitoneal space is explored, and the ureter and pelvic vessels are identified. The pararectal and paravesicular spaces are identified and developed as described in Chapter 9.

The peritoneum overlying the bladder is dissected to connect the peritoneal incisions anteriorly. The vesicouterine plane is identified, and, with careful sharp dissection, the bladder is mobilized from the anterior surface of the cervix. The ovarian vessels are isolated, doubly ligated, and divided.

The hysterectomy, which is often not a “simple” operation, is performed. The ureters need to be carefully displayed to avoid injury. During this procedure, the uterine vessels can be identified. The hysterectomy and resection of the contiguous tumor are completed by ligation of the uterine vessels and the remainder of the tissues in the cardinal ligaments.

Because epithelial ovarian cancers tend not to invade the lumina of the colon or bladder, it is usually feasible to resect pelvic tumors without having to resect portions of the lower colon or the urinary tract (149,150,151 and 152). However, if the disease surrounds the rectosigmoid colon and its mesentery, it may be necessary to remove that portion of the colon to clear the pelvic disease (149,150) (Fig. 11.8). This is justified if the patient will be left with 'optimal” disease at the end of the cytoreduction. After the pararectal space is identified in such patients, the proximal site of colonic involvement is identified, the colon and its mesentery are divided, and the rectosigmoid is removed along with the uterus *en bloc.* A reanastomosis of the colon is performed, as described in Chapter 19.

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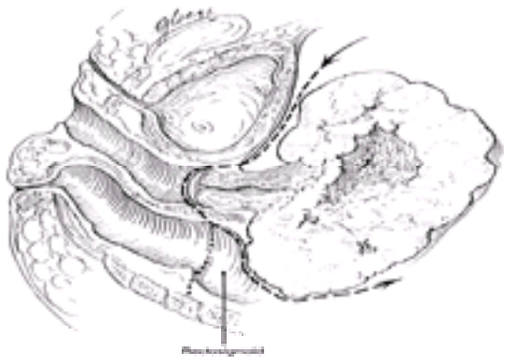

Figure 11.8 Resection of the pelvic tumor may include removal of the uterus, tubes, and ovaries, as well as portions of the lower intestinal tract. The *arrows* represent the plane of resection.

It is rarely necessary to resect portions of the lower urinary tract (151). Occasionally, resection of a small portion of the bladder may be required. If so, a cystotomy should be performed to assist in resection of the disease. Rarely, partial ureteric resection may be necessary, followed by primary reanastomosis (ureteroureterostomy), ureteroneocystostomy, or transureteroureterostomy, as described in Chapter 19.

Omentectomy

Advanced epithelial ovarian cancer often completely replaces the omentum, forming an omental cake. This disease may be adherent to the parietal peritoneum of the anterior abdominal wall, making entry into the abdominal cavity difficult. After freeing the omentum from any adhesions to parietal peritoneum, adherent loops of small intestine are freed by sharp dissection. The omentum is then lifted and pulled gently in the cranial direction, exposing the attachment of the infracolic omentum to the transverse colon. The peritoneum is incised to open the appropriate plane, which is developed by sharp dissection along the serosa of the transverse colon. Small vessels are ligated with hemoclips. The omentum is then separated from the greater curvature of the stomach by ligation of the right and left gastroepiploic arteries and ligation of the short gastric arteries (Fig. 11.9).

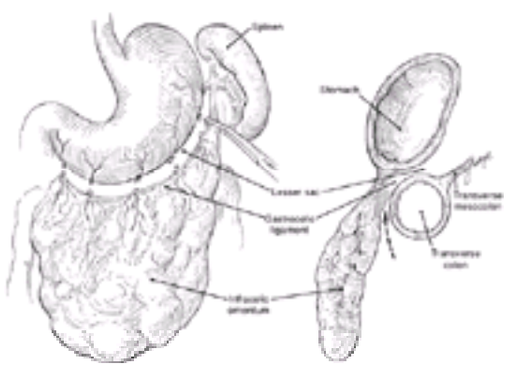

Figure 11.9 Separation of the omentum from stomach and transverse colon. (From Heintz APM, Berek JS. Cytoreductive surgery for ovarian carcinoma. In: Piver MS, ed. *Ovarian malignancies.* Edinburgh: Churchill Livingstone, 1987:134, with permission.)

The disease in the gastrocolic ligament can extend to the hilus of the spleen and splenic flexure of the colon on the left and to the capsule of the liver and the hepatic flexure of the colon on the right. Usually, the disease does not invade the parenchyma of the liver or spleen, and a plane can be found between the tumor and these organs. However, it occasionally is necessary to perform splenectomy to remove all the omental disease (152) (Fig. 11.10).

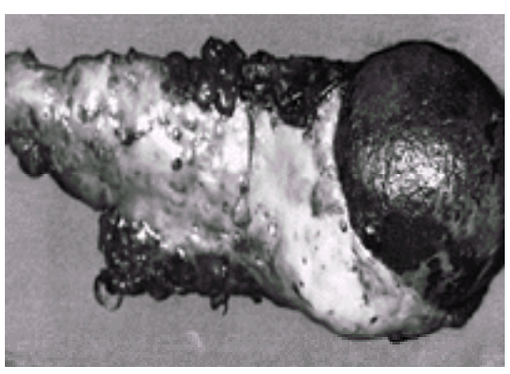

Figure 11.10 Omentum densely adherent to the spleen.

Intestinal Resection

The disease may involve focal areas of the small or large intestine, and resection should be performed if it permits the removal of all or most of the abdominal metastases. Apart from the rectosigmoid colon, the most frequent sites of intestinal metastasis are the terminal ileum, the cecum, and the transverse colon. Resection of one or more of these segments of bowel may be necessary (149,150,151 and 152).

Resection of Other Metastases

Other large masses of tumor that are located on the parietal peritoneum should be removed, particularly if they are isolated masses and their removal permits optimal cytoreduction. Resection of extensive disease from the surfaces of the diaphragm is usually neither practical nor feasible, although solitary metastases may be resected, the diaphragm sutured, and a chest tube placed for a few days (153,154). In patients with extensive tumor infiltration of the spleen, a splenectomy may need to be performed to facilitate the resection of all residual disease (155). The use of the CUSA (Cavitron Ultrasonic Surgical Aspirator), the argon laser, and the loop electrosurgical device may facilitate resection of small tumor nodules, especially those on flat surfaces (156,157 and 158).

Feasibility and Outcome

An analysis of the retrospective data available suggests that these operations are feasible in 70% to 90% of patients when performed by gynecologic oncologists (152). The major morbidity rate is in the range of 5%, and operative mortality in the range of 1% (159,160). Intestinal resection in these patients does not appear to increase the overall morbidity of the operation (152).

Feasibility and Outcome

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The performance of a pelvic and paraaortic lymphadenectomy in patients with stage IIIC to IV disease has been reported to prolong survival (56). In a nonrandomized trial, systematic pelvic and paraaortic lymphadenectomy performed in 60 optimally resected patients prior to chemotherapy was associated with an improved survival (2-year survival rate = 59%) compared with a combination of historical and concurrent control patients (N = 45; 2-year survival rate = 16%; $p < 0.001$). Verification of this awaits a prospective, randomized study.

Some have questioned the ability of cytoreductive surgery to improve the overall outcome of patients with ovarian cancer (147). Concern has been expressed that these operations are excessively morbid and that modern chemotherapies are sufficient. No randomized, prospective study has been performed to define the value of primary cytoreductive surgery. However, all retrospective studies indicate that the diameter of the largest residual tumor nodule before the initiation of chemotherapy is significantly related to progression-free survival in patients with advanced ovarian cancer. In addition, quality of life is likely to be significantly enhanced by removal of bulky tumor masses from the pelvis and upper abdomen.

The only prospective, randomized study of cytoreductive surgery was carried out by the European Organization for the Research and Treatment of Cancer (EORTC). A prospective trial of "interval" cytoreductive surgery (performed after three cycles of platinum-combination chemotherapy) demonstrated a survival benefit for those patients who had resection of their disease at that time compared with those who did not (142). **The risk of mortality was reduced by over 40% in the group that was randomized to a debulking operation as part of their therapy. Therefore, the performance of a debulking operation as early as possible in the course of the patient's treatment should be considered the standard of care** (143).

Treatment with Chemotherapy and Radiation

Early-Stage Low-Risk Ovarian Cancer

Guthrie et al. (121) studied the outcome of 656 patients with early-stage epithelial ovarian cancer. No untreated patients who had stage IA, grade 1 cancer died of their disease; thus, adjuvant radiation therapy and chemotherapy are unnecessary. Furthermore, the GOG carried out a prospective, randomized trial of observation versus *melphalan* for patients with stage IA and IB, grades 1 and 2 disease. **Five-year survival rates for each group were 94% and 96%, respectively, confirming that no further adjuvant treatment is needed for such patients.**

Early-Stage High-Risk Ovarian Cancer

In patients whose disease is high risk (e.g., more poorly differentiated or in whom there are malignant cells either in ascitic fluid or in peritoneal washings), additional therapy is indicated. Treatment options include chemotherapy or whole-abdominal radiation (161,162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178 and 179). Some comparisons of these modalities have been made and are summarized in the following sections.

Chemotherapy

Chemotherapy for patients with early-stage high-risk epithelial ovarian cancer can be either single agent or multiagent (161,162,163,164,165,166 and 167). Some researchers have questioned the wisdom of overly aggressive chemotherapy in women with early-stage disease, suggesting that the evidence for a durable impact on survival is marginal (168,169). Furthermore, the risk of leukemia with alkylating agents and platinol makes the administration of adjuvant therapy risky unless there is a significant benefit (162,163).

Because *cisplatin, carboplatin, cyclophosphamide (Cytoxan)*, and *paclitaxel (Taxol)* are active single agents against epithelial ovarian cancer, these drugs have been administered in various combinations. There are some series in which *cisplatin* and/or *cyclophosphamide* (PC) have been used to treat patients with stage I disease (170,171 and 172). In a GOG trial of three cycles of *cisplatin* and *cyclophosphamide* versus intraperitoneal ^{32}P in patients with stage I, grade 3 and II disease, the progression-free survival rate of women receiving the platinum-based chemotherapy was 31% higher than in those receiving the radiocolloid (172) (Fig. 11.11). Similar results for progression-free survival were reported by a multicenter trial performed in Italy by the Gruppo Italiano Collaborativo Oncologica Ginecologica (GICOG; Fig. 11.12A), although there was no overall survival advantage (Fig. 11.12B). *Carboplatin* can be substituted for *cisplatin* in the therapy of these patients (178), although it is unclear if there is any difference in survival. There is currently a GOG trial of three cycles of *carboplatin* and *paclitaxel* followed by a randomization between observation or 26 weeks of weekly low-dose (40 mg/m^2) *paclitaxel.*

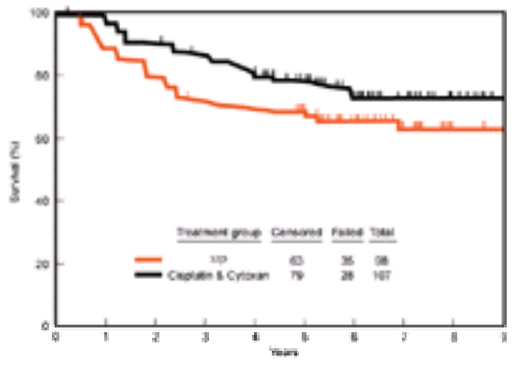


Figure 11.11 Progression-free survival of patients with stage I and II epithelial ovarian cancer treated with either *cisplatin* and *cyclophosphamide* or ^{32}P in Gynecologic Oncology Group Protocol 95. The recurrence rate on the cisplatin regimen is 36% lower than the ^{32}P regimen (relative risk = 0.641). [From Young RC, Brady MF, Nieberg RM, Long HJ, Mayer A, Lentz SS, et al. Randomized clinical trial of adjuvant treatment of women with early (FIGO I–IIA high risk) ovarian cancer: a Gynecologic Oncology Group study (GOG 95). *Proceedings of the American Society of Clinical Oncology* 1999;35:1376(abst), with permission.]

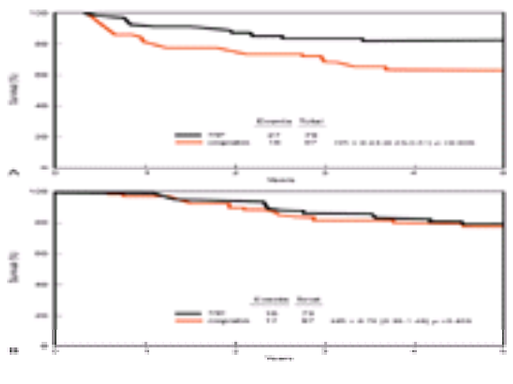
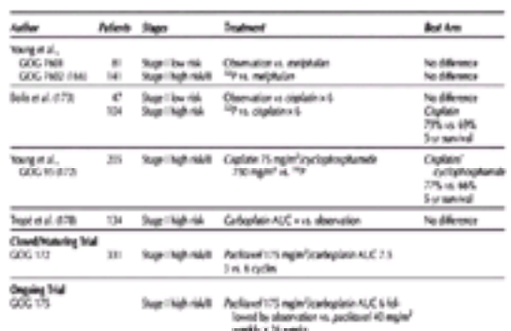
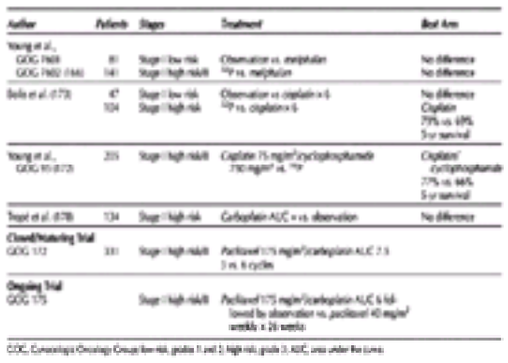


Figure 11.12 Progression-free (A) **and overall** (B) survival of patients with stage I high grade epithelial ovarian cancer treated with either *cisplatin or ^{32}P by the Gruppo Italiano Collaborativo Oncologica Ginecologica.* (From Bolis G, Colombo N, Pecorelli S, Torri V, Marsoni S, Bonazzi C, et al. Adjuvant treatment for early epithelial ovarian cancer: results of two randomized clinical trials comparing cisplatin to no further treatment or chromic phosphate (^{32}P). *Ann Oncol* 1995;6:887– 893, with permission.)

A summary of randomized phase III trials reported since 1995 for the treatment of patients with low-stage disease is presented in Table 11.4 (165,166,170,172 and 178).





Author	Patients	Stage	Treatment	Best Arm
Young et al., GOG 1988	81	Stage I low risk	Observation vs. melphalan	No difference
GOG 1988 (1-66)	141	Stage I high risk/II	^{32}P vs. melphalan	No difference
Bolis et al. (173)	47	Stage I low risk	Observation vs. cisplatin × 6	No difference
	104	Stage I high risk	^{32}P vs. cisplatin × 6	Cisplatin 79% vs. 69% 5-yr survival
Young et al., GOG 95 (172)	205	Stage I high risk/II	Cisplatin 75 mg/m²/cyclophosphamide 750 mg/m² vs. ^{32}P	Cisplatin/ cyclophosphamide 77% vs. 66% 5-yr survival
Trope et al. (178)	134	Stage I high risk	Carboplatin AUC = vs. observation	No difference
Closed/Maturing Trial				
GOG 132	331	Stage I high risk/II	Paclitaxel 175 mg/m²/carboplatin AUC 7.5 3 vs. 6 cycles	
Ongoing Trial				
GOG 175		Stage I high risk/II	Paclitaxel 175 mg/m²/carboplatin AUC 6 followed by observation vs. paclitaxel 40 mg/m² weekly × 24 weeks	

GOG, Gynecologic Oncology Group; low risk, grades 1 and 2; high risk, grade 3; AUC, area under the curve.

Table 11.4 Randomized Trials in Stage I Epithelial Ovarian Cancer (since 1995)

Radiation Therapy

There are two general approaches to the treatment of these low-stage epithelial cancers with radiation: intraperitoneal radiocolloids or whole-abdominal radiation therapy. In one retrospective trial of ^{32}P, the 5-year survival rate for patients thus treated was 85% (165). In a series of patients with stage I disease treated with whole-abdominal radiation (164), the 5-year relapse-free survival rate was only 78%, but many of these patients had high-risk variables (e.g., poor histologic grade).

A prospective trial was conducted by the GOG in patients with stage IB, grade 3, stage IC, or stage II with no residual disease. Twelve cycles of *melphalan* were compared with intraperitoneal ^{32}P; there was no difference in survival (166). However, in a multicenter Italian trial (173), a randomized comparison of six cycles of *cisplatin* as a single agent versus ^{32}P showed an 84% disease-free survival rate with *cisplatin* versus 61% with ^{32}P ($p < 0.01$). Although ^{32}P produces results similar to single-agent *melphalan* chemotherapy, platinum-based chemotherapy is preferable (Table 11.3). Pelvic radiation alone is not as effective as *melphalan* in these patients and should not be used in ovarian cancer (161).

Recommendation for Adjuvant Treatment of Early-Stage Ovarian Cancer

Low-Risk Early-Stage Disease (Stage IA and B, grades 1 and 2)

No adjuvant chemotherapy is recommended for these patients.

High-Risk Early-Stage Disease (Stage I, grade 3; stage II)

We recommend that:

1. **Patients with high-risk stage I epithelial ovarian cancer be given adjuvant chemotherapy. The type depends on the patient's overall health and status.**
2. **Treatment with *carboplatin and paclitaxel* chemotherapy for three to six cycles seems desirable in most patients, whereas a short course of a single agent, either *carboplatin* or *paclitaxel*, may be preferable for older women.**

Advanced-Stage Ovarian Cancer

Chemotherapy

Systemic chemotherapy is the standard treatment for metastatic epithelial ovarian cancer (180,181,182,183,184,185,186,187,188,189,190,191,192,193,194,195,196,197,198, 199,200,201,202,203,204,205,206,207,208,209 and 210). After the introduction of cisplatin in the latter half of the 1970s, platinum-based combination chemotherapy became the most frequently used treatment regimen in the United States. *Paclitaxel* become available in the 1980s, and this drug was incorporated into the combination chemotherapy in the 1990s (181,182,183,184,185,186 and 187). Comparative trials of *paclitaxel, cisplatin*, and *carboplatin* are summarized in the following sections.

For many years, oral single-agent alkylating therapy was used. The standard dose for the single alkylating agent, *melphalan*, is 0.2 mg/kg/day given for 5 consecutive days every 28 days. In three separate GOG studies of suboptimal stage III ovarian cancer, 193 patients were treated with this regimen. Sixty-two patients (33%) had a clinical response, with a 16% complete response rate and a 17% partial response rate (180). However, the median duration of response was only 7 months, and median survival was 12 months.

The use of single-agent chemotherapy for metastatic epithelial ovarian cancer is usually reserved for patients whose overall physical condition precludes the use of more toxic therapy. Either *carboplatin* or *paclitaxel* alone can be used in these patients.

Cisplatin Combination Chemotherapy

A variety of combination chemotherapeutic regimens have been tested in the treatment of advanced epithelial ovarian cancer. Combination chemotherapy has been shown to be superior to single-agent therapy in most patients with advanced epithelial ovarian cancer (192). After cisplatin became available for the treatment of ovarian cancer, a prospective study conducted in England showed that *cisplatin* was better than an alkylating agent, *cyclophosphamide*, as a single agent (193). Concurrently, *cisplatin* was tested in a variety of different combinations, and the platinum-containing regimens were shown to be superior (194). In a meta-analysis performed on studies of patients with advanced-stage disease, those patients given *cisplatin*-containing combination chemotherapy were compared with those treated with regimens that did not include *cisplatin* (191). Survival differences between the groups were seen from 2 to 5 years, with the *cisplatin* group having a slight survival advantage, but this difference disappeared by 8 years (Fig. 11.13).

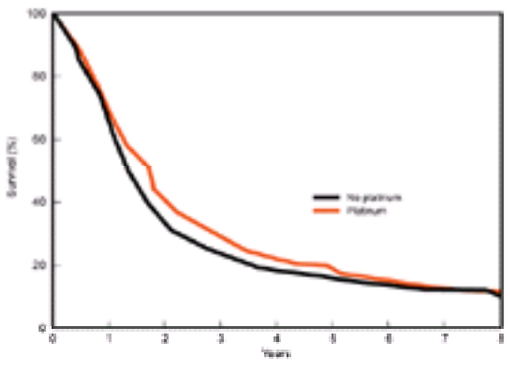
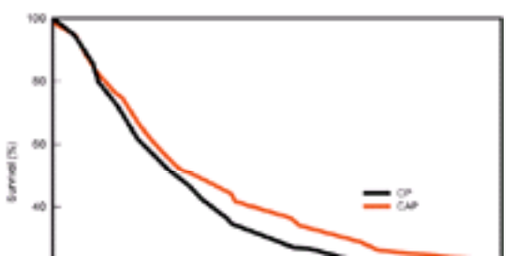


Figure 11.13 Survival of patients with advanced-stage ovarian cancer: a meta-analysis of multiple trials comparing cisplatin-containing combination chemotherapy with regimens without *cisplatin.* (From Advanced Ovarian Cancer Trialists Group. Chemotherapy in advanced ovarian cancer: an overview of randomized clinical trials. *BMJ* 1991;303:884, with permission.)

Cisplatin -combination chemotherapy became the treatment of choice for many years (191,192,193,194,195,196,197,198,199,200 and 201). Most studies using the PC or PAC [*cisplatin, doxorubicin (Adriamycin)*, and *cyclophosphamide*] regimen report similar survival rates. There have been several trials comparing PAC with PC (195,196,197,198,199 and 200). No study showed a significant difference in survival between treatment arms. The GOG's randomized, prospective comparison of equitoxic doses of PAC versus PC showed no benefit to the inclusion of *doxorubicin* in the combination (196). Although a meta-analysis of the combined data from these trials showed a 7% survival advantage at 6 years for those patients treated with the *doxorubicin*-containing regimen (200) (Fig. 11.14), the survival curves converge at 8 years.



advantage at 8 years for those patients treated with the *doxorubicin*-containing regimen (206) (Fig. 11.14), the survival curves converge at 8 years.

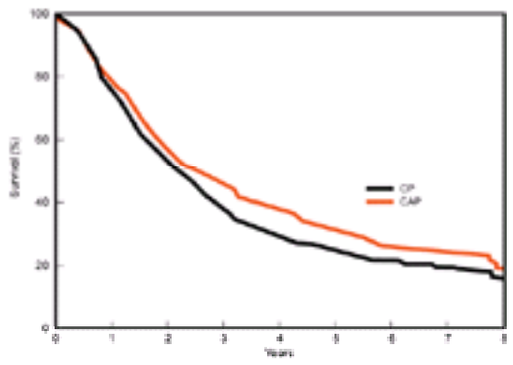


Figure 11.14 Survival of patients with advanced ovarian cancer: a meta-analysis of trials comparing PC (*cisplatin* and *cyclophosphamide*) to PAC (*cisplatin, doxorubicin*, and *cyclophosphamide*)chemotherapy. (From Ovarian Cancer Meta-Analysis Project. Cyclophosphamide plus cisplatin versus cyclophosphamide, doxorubicin, and cisplatin chemotherapy of ovarian carcinoma: a meta-analysis. J Clin Oncol 1991; 9:1668–1674, with permission.)

Paclitaxel

The next major advance in the treatment of advanced stage disease was the incorporation of *paclitaxel* into the chemotherapeutic regimens. A series of randomized, prospective clinical trials with *paclitaxel*-containing arms have defined the current recommended treatment protocol in advanced epithelial ovarian cancer (185,186,204,205). These studies are listed in Table 11.5.

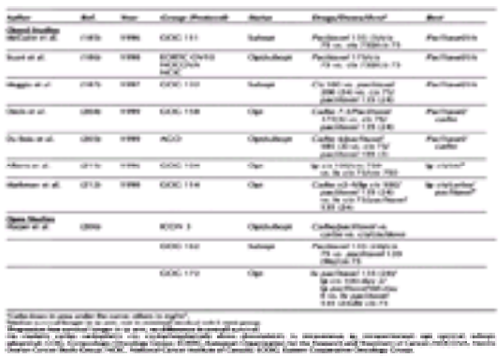


Table 11.5 Platinum and *Taxol* Chemotherapy Randomized Trials in Advanced-Stage Epithelial Ovarian Cancer

Paclitaxel was shown to be a very active agent in ovarian cancer (181,182,183,184,185,186 and 187,202). The overall response rate with *paclitaxel* in phase II trials was 36% in previously treated patients (183), which is a higher rate than was seen for *cisplatin* when it was first tested.

Reporting the GOG data (Protocol 111), McGuire et al. (185) showed that the combination of *cisplatin* (75 mg/m^2) and *paclitaxel* (135 mg/m^2) was superior to *cisplatin* (75 mg/m^2) and *cyclophosphamide* (600 mg/m^2), each given for six cycles (Table 11.5). In suboptimally resected patients, the *paclitaxel*-containing arm produced a 36% reduction in mortality (Fig. 11.15). These data were verified in a trial conducted jointly by the EORTC, the Nordic Ovarian Cancer Study Group (NOCOVA), and the National Cancer Institute of Canada (NCIC), in which patients with both optimal and suboptimal disease were treated (186). In this study the *paclitaxel*-containing arm produced a significant improvement in both progression-free interval and overall survival in both optimal and suboptimal groups (Fig. 11.16). **Based on these two studies, *paclitaxel* should be included in the primary treatment of all women with advanced-stage epithelial ovarian cancer, unless precluded by toxicity.**

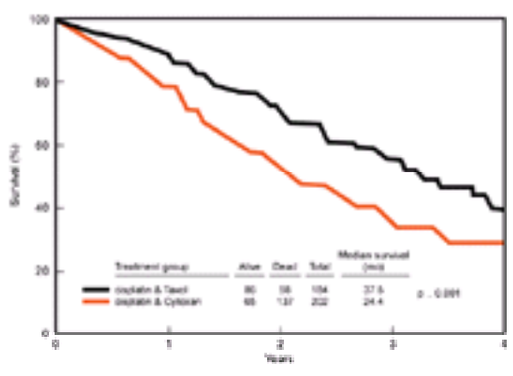


Figure 11.15 Survival of patients with suboptimal stage III and IV epithelial ovarian cancer treated with *paclitaxel* and *cisplatin* versus *cyclophosphamide* and *cisplatin:* results of the Gynecologic Oncology Group study (Protocol 111). From McGuire WP, Hoskins WJ, Brady MF, Kucera PR, Partridge EE, Look KY, et al. Cyclophosphamide and cisplatin compared with paclitaxel and cisplatin in patients with stage III and stage IV ovarian cancer. *N Engl J Med* 1996;334:1–6, with permission.)

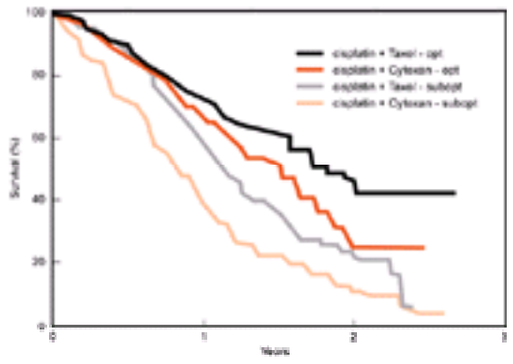


Figure 11.16 Survival of patients with stage III and IV epithelial ovarian cancer treated with *paclitaxel* and *cisplatin* or *cyclophosphamide* and *cisplatin*: results of a European cooperative group trials study. [From Stuart G, Bertelsen K, Mangioni C, Tropé C, James K, Kaye S, et al. Updated analysis shows a highly significant improved survival for cisplatin-paclitaxel as first line treatment of advanced stage epithelial ovarian cancer: mature results of the EORTC-GCCG, NOCOVA, NCIC CTG and Scottish Intergroup Trial. *Proceedings of the American Society of Clinical Oncology* 1998; 34:1394(abst), with permission.]

A three-arm comparison of *paclitaxel* (T) versus *cisplatin* (P) versus PT in suboptimal stage III and IV patients (GOG Protocol 132) showed

Proceedings of the American Society of Clinical Oncology 1998; 34:1394(abst), with permission.]

A three-arm comparison of *paclitaxel* (T) versus *cisplatin* (P) versus PT in suboptimal stage III and IV patients (GOG Protocol 132) showed equivalency in the three groups, but cross-over from one drug to the other was permitted (187). The study essentially showed that the combination regimen was better tolerated than the sequential administration of the agents in suboptimally resected patients.

Carboplatin

The second-generation platinum analog, *carboplatin*, was introduced and developed to have less toxicity than its parent compound, *cisplatin*. In early trials, *carboplatin* was shown to have lower overall toxicity (189). Fewer gastrointestinal side effects, especially nausea and vomiting, were observed than with *cisplatin*, and there was less nephrotoxicity, neurotoxicity, and ototoxicity. *Carboplatin* is associated with a higher degree of myelosuppression.

The initial studies showed that *carboplatin* and *cisplatin* had approximately a 4:1 equivalency ratio. Thus, a standard single-agent dose of approximately 400 mg/m^2 has been used in most phase II trials. **The dose is calculated by using the area under the curve (AUC) and the glomerular filtration rate according to the *Calvert formula*** (210), as discussed in Chapter 4. *The target AUC is 6 to 7.5 for untreated patients with ovarian cancer. Alternatively, a dose of approximately 350 to 450 mg/m^2 carboplatin* can be used initially in patients with a normal serum creatinine and adjusted to toxicity. A platelet nadir of approximately 50,000/mL is a suitable target (189).

Carboplatin and *Paclitaxel*

Two randomized, prospective clinical studies have compared the combination of *paclitaxel* and *carboplatin* versus *paclitaxel* and *cisplatin* (204,205) (Table 11.5). **In both studies, the efficacy and survival rates are similar, but the toxicity is more acceptable for the carboplatin-containing regimen.** In the first trial, GOG Protocol 158, the randomization was *carboplatin* AUC 7.5 and *paclitaxel* 175 mg/m^2 over 3 hours versus *cisplatin* 75 mg/m^2 and *paclitaxel* 135 mg/m^2 over 24 hours. The progression-free survival of the *carboplatin*-containing arm was 22 months, versus 21.7 months for the control arm (204). The gastrointestinal and neurotoxicity of the *carboplatin* arm were appreciably lower than in the *cisplatin* arm. A similar result was obtained in a large randomized trial in Germany (205), in which the dose of *carboplatin* was AUC = 6 and paclitaxel was 185 mg/m^2 over 3 hours compared with the same dose of *paclitaxel* and *cisplatin* 75 mg/m^2. **Thus, the preferred regimen in patients with advanced stage disease is the *paclitaxel* plus *carboplatin* combination** (121).

Ongoing trials are comparing the combination of *carboplatin* and *paclitaxel* with single-agent *carboplatin* or combination chemotherapy with the PAC regimen (206).

Dose Intensification

Intravenous Chemotherapy The issue of dose intensification of *cisplatin* was examined in a prospective trial conducted by the GOG (207). In this study, 243 patients with suboptimal ovarian cancer were randomized to receive either 50 mg/m^2 or 100 mg/m^2 *cisplatin* plus 500 mg/m^2 *cyclophosphamide.* There was no difference in response rates in those patients with measurable disease, and the overall survival times were identical. There was greater toxicity associated with the high-dose regimen. A Scottish group reported that patients who received 100 mg/m^2 *cisplatin* plus 750 mg/m^2 *cyclophosphamide* had a significantly longer median survival compared with those receiving 50 mg/m^2 *cisplatin* plus the same dose of *cyclophosphamide* (208). The overall median survival time was 114 weeks in the high-dose group and 69 weeks in the low-dose group (p = 0.0008), but this difference disappeared with longer follow-up (209). Therefore, the doubling of the dose of *cisplatin* does not improve the survival of these patients.

Dose escalations of *paclitaxel* and *carboplatin* require *granulocyte colony-stimulating factor (G-CSF)* because of the combined myelosuppressive effects, but there is no evidence to support a role for a more intensive course of either agent (203,211,212).

Intraperitoneal Chemotherapy A randomized, prospective trial of intraperitoneal *cisplatin* versus intravenous *cisplatin* (100 mg/m^2), each given with 750 mg/m^2 *cyclophosphamide*, has been performed jointly by the Southwest Oncology Group (SWOG) and the GOG in patients with minimal residual disease (213). The intraperitoneal *cisplatin* arm had a somewhat longer overall median survival than the intravenous arm (49 vs. 41 months, respectively, p = 0.03). In the patients with minimal residual disease (<0.5 cm maximum residual), however, there was no difference between the two treatments (51 vs. 46 months, p = 0.08).

In a follow-up trial (GOG Protocol 114), the dose-intense arm was initiated by giving a moderately high dose of *carboplatin* (AUC = 9) for two induction cycles followed by intraperitoneal *cisplatin* 100 mg/m^2 and intravenous *paclitaxel* 135 mg/m^2 over 24 hours, versus intravenous *cisplatin* 75 mg/m^2 and intravenous *paclitaxel* 135 mg/m^2 (214). The results in the dose-intense arm were slightly better—the disease progression–free median survival was 27.6 months, compared with 22.5 months for the control arm (p= 0.02). However, there was no difference in overall survival (52.9 vs. 47.6 months, p = 0.056). Thus, it is unclear if dose intensification with intraperitoneal *cisplatin* has a sustained long-term impact on the survival of these patients. Based on the GOG data of intraperitoneal *paclitaxel* (215), a randomized, prospective GOG study is comparing intraperitoneal *cisplatin* and *paclitaxel* versus intravenous *cisplatin* and *paclitaxel.*

Based on these two studies, the value of intraperitoneal chemotherapy in the primary treatment of optimally resected stage III ovarian cancer remains unclear.

Neoadjuvant Chemotherapy

Some authors have suggested that, for patients with suboptimal stage III and IV disease, chemotherapy may be given in lieu of debulking surgery. A series performed at Yale by Schwartz et al. (216) suggested that the survival of these patients treated with “neoadjuvant” or cytoreductive chemotherapy was comparable with that in patients historically treated with debulking surgery followed by conventional chemotherapy in the same institution. Because other authors have shown a benefit to debulking patients before chemotherapy (141), the issue would need to be resolved by a prospective clinical trial.

However, two or three cycles of chemotherapy before cytoreductive surgery may be helpful in patients with massive ascites and large pleural effusions. The chemotherapy may dry up the effusions, improve the patient's performance status, and decrease postoperative morbidity, particularly chest morbidity.

Chemotherapeutic Recommendation in Advanced Ovarian Cancer

For the treatment of advanced-stage epithelial ovarian cancer, we recommend (Table 11.6):

Drugs	Dose	Administration (hr)	Interval	No. of Treatments
Standard Regimens				
Paclitaxel *Carboplatin*	175 mg/m² AUC = 5–6	24	Every 3 weeks	Six cycles
Paclitaxel *Cisplatin*	135 mg/m² 75 mg/m²	3	Every 3 weeks	Six cycles
Alternative Drugs[a]				
(Can be given with platinum)				
Cyclophosphamide	600–750 mg/m²		Every 3 weeks	
Topotecan	1.0–1.25 mg/m²		Daily × 5 days every 3 weeks	
Gemcitabine	800–1000 mg/m²		Every 3 weeks	

AUC, area under the curve dose by Calvert formula (210).
[a]Drugs that can be substituted for paclitaxel if hypersensitivity to that drug occurs.

Table 11.6 Combination Chemotherapy for Advanced Epithelial Ovarian Cancer: Recommended Regimens

1. **Combination chemotherapy with *carboplatin* and *paclitaxel.* The recommended doses and schedule are *carboplatin* (starting dose AUC = 5 to 6) and *paclitaxel* (175 mg/m^2) given over 3 hours every 3 weeks for six cycles.**
2. **In patients who cannot tolerate the combination, single-agent *carboplatin* (AUC = 5 to 6) can be given.**
3. **In those who have a hypersensitivity to *paclitaxel*, an alternative active drug can be substituted (e.g., *cyclophosphamide* or *topotecan*).**
4. **In patients who cannot tolerate intravenous chemotherapy, an oral alkylating agent can be substituted.**

Administration of Chemotherapy and Amelioration of Toxicity

Paclitaxel The principal concern of combining *paclitaxel* and *carboplatin* is the potential for enhanced bone marrow toxicity. In general, shorter (e.g., 3-hour) infusions of *paclitaxel* tend to reduce the likelihood of bone marrow depression when the drug is combined with *carboplatin* (204). Conversely, when *paclitaxel* is combined with *cisplatin*, the principal concern is the potentiation of neurotoxicity. This toxicity can be minimized by using a slightly lower dose of *paclitaxel* given over a longer period of time (e.g., 135 mg/m^2 over 24 hours).

Carboplatin The renal and gastrointestinal toxicities of *carboplatin* are modest compared with *cisplatin*, and therefore patients do not require prehydration and outpatient administration is more feasible. *Carboplatin* does tend to have appreciable bone marrow toxicity, and growth factors such as *G-CSF* and *granulocyte-macrophage colony-stimulating factor* have facilitated the administration of drug combinations that have neutropenia as a dose-limiting toxicity. The combination of *carboplatin* with *paclitaxel* can produce considerable neutropenia, and the concomitant administration of 250 µg/m^2 of *G-CSF* given subcutaneously on days 1 to 10 of a treatment cycle may be protective (202,203). The use of growth factors is discussed more fully in Chapter 4.

Cisplatin *Cisplatin* combination chemotherapy is given every 3 to 4 weeks by intravenous infusion over 1 to 1.5 hours. *Cisplatin* requires appropriate hydration, and can be administered on either an inpatient or outpatient basis. Hydration is administered with one-half normal saline given intravenously at a rate of 300 to 500 mL/hour for 2 to 4 hours until the urinary output is greater than 100 mL/hour. It is preferable to place a Foley catheter to monitor the output. When the urinary output is satisfactory, the *cisplatin* is infused in normal saline; the intravenous fluid rate is decreased to 150 to 200 mL/hour for 6 hours and then is discontinued if the patient is stable.

The principal toxicities of this regimen are renal, gastrointestinal, hematologic, and neurologic. The renal and neurologic toxicities usually limit the duration of treatment to six cycles.

The acute gastrointestinal toxicity of *cisplatin* (i.e., nausea and vomiting) can be minimized with a strong antiemetic, *ondansetron*, given as a 32-mg intravenous bolus, followed every 4 to 6 hours with 10 mg intravenously. Alternative regimens include *diphenhydramine (Benadryl)*, 25 mg orally, and *lorazepam (Ativan)*, 2 mg sublingually, both given 1 hour before the initiation of treatment, followed by *lorazepam*, 2 mg sublingually every 3 hours, *metoclopramide (Reglan)*, 100 mg intravenously every 3 to 4 hours, and one dose of *dexamethasone (Decadron)*, 20 mg intravenously.

Radiation Therapy

An alternative to combination chemotherapy for selected patients with metastatic ovarian cancer is the use of whole-abdominal radiation therapy. Although this approach is not commonly used in the United States, it is standard treatment in some institutions in Canada for patients with no residual macroscopic tumor in the upper abdomen (164). The treatment involves a radiation field that extends from 1 to 2 cm above the level of the diaphragm to include the entire pelvis. Details of this approach are discussed in Chapter 5.

Whole-abdominal radiation appears useful in patients whose metastatic disease is microscopic or completely resected. The treatment has not been tested against combination chemotherapy. Radiation therapy has been compared with oral *chlorambucil* and appears to be superior (164). The available data suggest that whole-abdominal radiation is inappropriate for patients with macroscopic residual disease.

A trial of three cycles of high-dose *cisplatin* and *cyclophosphamide* induction chemotherapy followed by whole-abdominal radiation therapy to consolidate the initial response has been reported (217). No apparent benefit could be shown by adding whole-abdominal radiation after chemotherapy in patients with optimal disease (see Chapter 5).

Hormonal Therapy

There is no evidence that hormonal therapy alone is appropriate primary therapy for advanced ovarian cancer. The use of progestational agents in the treatment of recurrent, well differentiated endometrioid carcinomas is supported by the current data. In a study by Rendina et al. (218), 30 evaluable patients with recurrent epithelial cancers were treated; 17 (57%) had an objective response, with 3 (10%) of these achieving a complete response. All responding patients had well differentiated, estrogen receptor–positive tumors.

Immunotherapy

There have been various trials using nonspecific immunostimulants to treat patients with ovarian cancer. Most frequently, agents such as *Corynebacterium parvum* and *bacillus Calmette-Guerin (BCG)* have been used systemically in conjunction with cytotoxic chemotherapy. In trials of *C. parvum* given with *melphalan* and *BCG* given with PAC chemotherapy, the nonspecific immunostimulant did not provide any additional benefit (200). Although there is a great deal of interest in the use of biologic response modifiers in ovarian cancer, none as yet has demonstrated efficacy as primary treatment. The use of cytokines has been tested in a second-line setting, and the activity of *interferon*-a, *interferon*-g and *interleukin-2* has been demonstrated, as discussed later.

Trials of monoclonal antibodies directed toward ovarian cancer–associated antigens are being conducted. Antibodies directed toward CA125 and the human milk fat globulin (HMFG) tumor-associated antigens are underway. *Herceptin*, an antibody directed toward the extracellular protein produced when the HER-2/*neu* oncogene is overexpressed, has been used extensively in breast cancer, where it has been shown to improve the response rate to chemotherapy in selected patients. Trials of this antibody in HER-2/*neu*–overexpressing ovarian cancers are ongoing. Antibodies against the protein produced by the mutated *p53* tumor suppressor gene are also undergoing clinical studies. The rationale for the use of these agents in ovarian cancer is discussed in Chapter 1 and Chapter 3.

Treatment Assessment

Many patients who undergo optimal cytoreductive surgery and subsequent chemotherapy for epithelial ovarian cancer have no evidence of disease at the completion of treatment. Tumor markers and radiologic assessments have proved to be too insensitive to exclude the presence of subclinical disease. Therefore, a common technique used to evaluate these patients is the second-look operation (219,220,221,222,223,224,225,226,227,228,229, 230 and 231). Most often, patients undergo a formal reassessment laparotomy, although the laparoscope also is used in this circumstance (232,233 and 234).

Tumor Markers

Tumor markers are not reliable enough to predict accurately which patients with epithelial tumors have had their disease completely eradicated by a particular therapy.

The level of CA125, a surface glycoprotein associated with mullerian epithelial tissues, is elevated in approximately 80% of patients with epithelial ovarian cancers, particularly those with nonmucinous tumors. The levels frequently become undetectable after the initial surgical resection and one or two cycles of chemotherapy. A full discussion of tumor markers is presented in Chapter 2.

The levels of CA125 have been correlated with the findings at second-look operations. Positive levels are useful in predicting the presence of disease, but negative levels are an insensitive determinant of the absence of disease. In a prospective study (235), the predictive value of a positive test was shown to be 100%; that is, if the level of CA125 was positive (>35 U/mL), disease was always detectable in patients at the second look. The predictive value of a negative test was only 56%; that is, if the level was less than 35 U/mL, disease was present in 44% of the patients at the time of the second look. **A review of the literature suggests that an elevated CA125 level predicts persistent disease at second look in 97% of cases** (18), **but the CA125 level is not sensitive enough to exclude subclinical disease in many patients.**

Serum CA125 levels can be used during chemotherapy to follow those patients whose level was positive at the initiation of therapy (18,236). The change in level usually correlates with response. Those patients with persistently elevated titers after three cycles of treatment most likely have resistant clones. Rising levels on treatment almost invariably indicate treatment failure and suggest that continuation of the current regimen is futile.

Radiologic Assessment

In patients with stage I to III epithelial ovarian cancer, radiologic tests have in general been of limited value in assessing the response to therapy for subclinical disease. Ascites can be readily detected, but even quite large omental metastases can be missed on CT scan (237,238). If liver enzymes are abnormal, the liver can be evaluated with a CT scan or ultrasonography. A positive CT scan and fine-needle aspiration cytologic test indicating tumor persistence could obviate the need for second-look surgery, but the false-negative rate of a CT scan is approximately 45% (237).

Second-Look Operations

A second-look operation is one performed to determine the response to therapy on a patient who has no clinical evidence of disease after a prescribed course of chemotherapy.

Second-Look Laparotomy

The technique of the second-look laparotomy is essentially identical to that for the staging laparotomy. The operation should be performed through a vertical abdominal incision. The incision should be initiated below the level of the umbilicus, so that if pelvic disease is detected in the absence of any palpable upper abdominal disease, a smaller incision might suffice. The incision can be extended cranially as needed.

After multiple cytologic specimens have been obtained, biopsies of the peritoneal surfaces should be performed, particularly in any areas of previously documented tumor. These are the most important areas to sample for biopsy because they are most likely to give a positive result. Any adhesions or surface irregularities should be sampled. In addition, biopsy specimens should be taken from the pelvic sidewalls, the pelvic cul-de-sac, the bladder, the paracolic gutters, the residual omentum, and the diaphragm. A pelvic and paraaortic lymph node dissection should be performed in those patients whose nodal tissues have not been previously removed.

Approximately 30% of patients with no evidence of macroscopic disease have microscopic metastases (219). Also, in many patients with microscopic disease, it is detected only in the occasional biopsy or cytologic specimen. Therefore, a large number of specimens (20 to 30) should be obtained to minimize the “false-negative” rate of the operation. In selected patients in whom gross residual tumor is discovered at second-look surgery, resection of isolated masses may be performed. The removal of all macroscopic areas of disease might facilitate response to salvage therapies (239,240 and 241), and it also permits the collection of tissue for *in vitro* analyses.

Results

Second-look laparotomy has not been shown to influence patient survival, although the information obtained at second look is highly prognostic (229,230). **The operation should be performed selectively, such as in patients receiving therapy in a setting where second-line therapies are undergoing clinical trials.**

The findings at second look correlate with subsequent outcome and survival (219,220,221,222,223,224,225,226,227 and 228). Patients who have no histologic evidence of disease have a significantly longer survival than those in whom microscopic or macroscopic disease is documented at laparotomy (219,220,221,222,223 and 224).

The attainment of a negative second look is not tantamount to a cure (224,229,230). Indeed, the reported probability that a patient will have a recurrence after a negative second-look laparotomy ranges from 30% to 50% at 5 years. Clearly, it is not possible to sample every potential site of disease. In addition, disease can become clinically apparent in sites that are occult, such as the liver parenchyma (57). Most recurrences after a negative second-look laparotomy are in patients with poorly differentiated cancers (231).

Variables associated with the outcome of the second-look laparotomy are:

1. Initial stage
2. Tumor grade
3. The size of the residual tumor and the size of the largest metastatic tumor before treatment
4. The type of chemotherapy

No single variable or combination of variables is sufficiently accurate to predict the histopathologic findings at second-look laparotomy (231).

Stage Patients whose tumors are initially stage I and II have negative second-look laparotomy rates of 85% to 95% and 70% to 80%, respectively, whereas the rate for patients with stage III or IV disease is 30% to 45% (219,220,221,222,223,224,225,226,227,228,229, 230 and 231).

Grade Most patients with low-grade disease who have evidence of persistent disease at second-look operation have more poorly differentiated tumors. The likelihood of a negative second look in patients at all stages is approximately 60% to 70% for those with grade 1 tumors, 40% to 50% for those with grade 2, and only 20% for those with grade 3 (219,222,231).

Residual Tumor The maximum size of the residual tumor before therapy is an important predictor of outcome; that is, the probability of a negative second look is higher in those patients whose tumor burden before initiation of chemotherapy is smaller. Patients whose disease is microscopic or no larger than 5 mm at the start of therapy have a much higher likelihood of a complete pathologic remission than those patients with more extensive disease (219,226,227 and 228,231). Whereas smaller primary tumors seem to be associated with a poorer prognosis, those patients with very extensive metastatic tumors have little likelihood of a negative second look, regardless of the extent of tumor reduction.

Chemotherapy The likelihood of a negative second-look laparotomy is greater in patients who have been treated with a platinum and *paclitaxel* combination chemotherapy, compared with rates reported in those treated with non- *paclitaxel* regimens (185). In patients with optimally resected stage III disease treated with the platinum and *paclitaxel* regimen, the negative second-look rate is approximately 45% to 50% (204).

The second-look laparotomy has helped to define the number of cycles of chemotherapy necessary to achieve a complete response. Six cycles of *cisplatin*-containing combination chemotherapy produce approximately the same negative second-look laparotomy rate in patients with advanced-stage disease as do 10 to 12 cycles (200). These data suggest that epithelial carcinomas that are sensitive to the chemotherapy are likely to respond early in the course of treatment. Additional treatment beyond six cycles of a platinum therapy does not appear to increase the probability of achieving a complete pathologic remission and only increases the treatment-related toxicity. The use of prolonged treatment (3 to 6 months longer than conventional therapy) with *paclitaxel* is being investigated.

Second-Look Laparoscopy

The advantage of laparoscopy is that it is a less invasive operation; the disadvantage is that visibility may be limited by the frequent presence of intraperitoneal adhesions (232,233 and 234). The development of newer techniques for retroperitoneal lymph node dissection has potentially increased the utility of the endoscopic approach to second look. The morbidity and role of this technique are being studied by the GOG.

One technique that has been used for second look is “open” laparoscopy. This procedure allows placement of the laparoscope after a cut-down to the fascia of the rectus abdominis. The peritoneum is entered under direct vision, thus avoiding the blind insertion that can be associated with intestinal injury (232).

The laparoscope has been used immediately before a planned laparotomy. If gross disease is detected and secondary resection of the tumor is not possible, a laparotomy may be omitted (234).

The role of the laparoscope in patients with epithelial ovarian cancer is therefore still being defined. It may be used to stage disease in patients who have undergone a prior laparotomy for a tumor that was incompletely staged. Second-look laparoscopy may also be useful for patients on experimental treatment protocols, especially second-line treatments that require some evaluation of response.

Secondary Therapy

Secondary Cytoreduction

Patients with persistent or recurrent pelvic and abdominal tumors after primary therapy for ovarian cancer are occasionally candidates for surgical excision of their disease. This operation has been referred to as *secondary* cytoreductive surgery (239). Tumor resection under these circumstances should be restricted to carefully selected patients for whom resection has a reasonable chance of either prolonging life or significantly palliating symptoms, because most patients with persistent or progressive disease after primary therapy do not benefit (239,240,241 and 242). The patient in whom secondary cytoreduction might be appropriate should be in good general medical condition. Patients who had complete resection of disease at their primary operation, or those who experienced a disease-free interval of more than 12 months after primary operation, are most likely to benefit from a second operation in recurrent ovarian cancer (241). Patients should have clinical and radiologic evidence that the recurrent disease is reasonably localized (e.g., isolated pelvic recurrence).

The goal of secondary debulking is to remove all residual gross tumor, if possible, or to reduce the metastatic tumor burden to less than 5 mm maximum dimension. Some patients with minimal residual disease respond to second-line treatment. **Those patients in whom the residual disease is completely resected have a significantly longer survival than those who do not have complete resection** (240,241 and 242).

Second-Line Chemotherapy

If disease recurs or progresses after primary therapy, patients usually have been switched to a second-line chemotherapy. The response rates for second-line chemotherapies have been 15% to 35% for most drugs tested by the oral or intravenous route (243,244,245,246,247,248,249,250,251,252,253,254,255,256,257,258,259,260,261, 262,263,264 and 265) (Table 11.7). Active drugs that have been used as single agents include *cisplatin, carboplatin, paclitaxel, docataxel, topotecan, gemcitabine, etoposide (VP-16), doxorubicin (Doxil), navelbine, ifosfamide, 5-fluorouracil (5-FU)* with *leucovorin*, and *hexamethylmelamine*. Single-agent drugs are sometimes used for second-line chemotherapy because of their relative ease of administration and low toxicity.

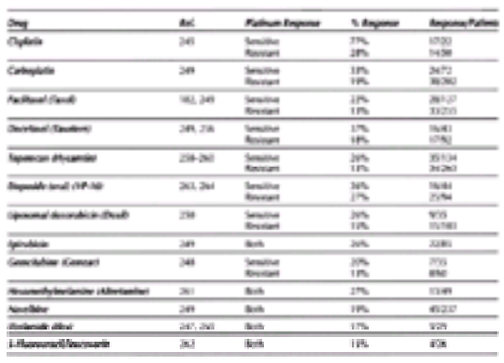


Table 11.7 Second-Line Chemotherapy in Recurrent/Persistant Epithelial Ovarian Cancer

Platinum Sensitive versus Platinum Resistant

Second-line therapies have been categorized by whether the patients responded to their initial platinum-based chemotherapy. Although this concept has been variously defined, platinum sensitivity has been related to a disease progression–free interval of 12 to 24 months (Table 11.7). Response rates after retreatment with *cisplatin* have been shown to be higher in patients whose time to clinical relapse after prior response to *cisplatin* is at least 12 to 24 months (243,244,245 and 246,249). *Carboplatin* is active as a second-line agent in patients who have responded to prior *cisplatin* treatment, and response rates in these patients have been 20% to 30% (244). The concepts of platinum sensitivity and *paclitaxel* sensitivity should influence the choice of second-line chemotherapy.

In patients who have platinum- or *paclitaxel*-sensitive tumors, retreatment with a platinum drug or *paclitaxel* is appropriate. Second-line responses to *paclitaxel, carboplatin*, and *cisplatin* in such patients have been observed in 25% to 50% of patients.

In *cisplatin*-refractory patients, response rates to second-line *carboplatin* are less than 10% (171,173). **In platinum-resistant disease, persistent disease is best treated with non–cross-resistant agents that have different anticancer mechanisms,** such as the topoisomerase inhibitors, *etoposide* and *topotecan*, an anthracycline (e.g., *doxorubicin*), an alkylating agent (e.g., *ifosfamide*), or other agents (e.g., *hexamethylmelamine*). These agents have resulted in second-line response rates of approximately 8% to 28% in platinum-resistant patients (247,248,249 and 250,256,257,258,259,260,261,262,263,264 and 265).

Several new combinations of chemotherapy are now being tested in advanced epithelial ovarian cancer. The rationale for this approach is that the two agents have complementary toxicities and mechanisms of action. Combinations such as *gemcitabine* and platinum and *topotecan* and platinum may have greater activity than either agent alone. Various neuroprotective and myelosuppressive “protectors,” such as *amifostine*, are being tested in *cisplatin* combination regimens.

Dose-Intense Chemotherapy

Intraperitoneal Chemotherapy In patients with minimal residual (£5 mm) or microscopic disease confined to the peritoneal cavity, consideration can be given to intraperitoneal chemotherapy or immunotherapy (266,267,268,269,270,271,272, 273,274,275,276,277,278,279,280,281 and 282). The failure of second-line intravenous chemotherapy to control residual disease has led to great interest in intraperitoneal therapies. Cytotoxic chemotherapeutic agents, such as *cisplatin, paclitaxel, 5-FU, etoposide (VP-16)*, and *mitoxantrone*, have been used as single agents in patients with persistent epithelial ovarian cancer (266,267,268,269,270 and 271), and complete responses have been seen in patients who start their treatment with minimal residual disease. The surgically documented response rates reported with this approach are approximately 20% to 40% for carefully selected patients, and the complete response rate is approximately 10% to 20%. Although *cisplatin* is an effective drug, the response rates appear to be enhanced by combining it with *etoposide, 5-FU, cytosine arabinoside*, or *thiotepa* (269,271,273 and 276). Although it has been suggested that this approach produces a significant subsequent improvement in survival (273), there are no prospective phase III data, and the patients so treated tend to be those with a more favorable prognosis regardless of subsequent therapy.

Intraperitoneal Immunotherapy Another approach is the use of intraperitoneal immunologic agents, such as *interferon* (274,275,276,277,278,279,280,281 and 282) (see Chapter 3). The latter has been found to have some activity in patients with minimal residual disease (274,275,276,277,278,279,280 and 281). Because of recombinant DNA technology, the cytokines in particular are becoming increasingly available for clinical testing. Trials of intraperitoneal *interferon*-a, *interferon*-g, *tumor necrosis factor*, and *interleukin-2* have been performed. The response rate for the intraperitoneal cytokines, *interferon*-a and *interferon*-g is the same as that for the cytotoxic agents, approximately 28% to 50% (274,275 and 276,279,281,). The intraperitoneal administration of *interferon*-a produced a 32% (9/28) surgically documented complete response rate and a 50% (14/28) total response rate in patients with minimal residual disease after primary combination chemotherapy with *cisplatin* (274). This experience was replicated in a multiinstitutional trial, where the surgically documented complete response rate was 28% in platinum-sensitive patients (275).

The interferons have been combined with cytotoxic agents in an effort to increase the overall response rates. The combination of *cisplatin* and *interferon*-a produced a 50% complete response rate, which was greater than that produced by either single agent alone (276). The alternating use of the two agents produced a response rate similar to that seen with each of the single agents used separately (278). Surgically documented responses to intraperitoneal therapy have been generally limited to patients with minimal residual disease (i.e., <5 mm maximum tumor dimension) and those whose tumors have been responsive to *cisplatin* chemotherapy (279).

Candidates for Intraperitoneal Therapy Intraperitoneal treatment is not suitable for all patients because it can be cumbersome, requiring catheters that remain functional. Patients with extensive intraperitoneal adhesions are not appropriate candidates, and neither are patients with extraperitoneal disease. Therefore, second-line intraperitoneal chemotherapy and immunotherapy should still be considered experimental.

High-Dose Chemotherapy and Autologous Bone Marrow Transplantation The use of high-dose chemotherapy and either autologous bone marrow transplantation (ABMT) or transplantation is being tested in patients with advanced ovarian cancer (283,284 and 285). In one trial of high-dose *carboplatin* with ABMT, 7 of the 11 patients with extensive refractory disease had an objective response. The maximum tolerated dose of high-dose *carboplatin* was 2 g/m^2 (283). In a retrospective analysis of 35 patients treated with high-dose *melphalan* and ABMT, 9 of 12 with evaluable residual disease had a measurable response (284). The morbidity of this approach is high, and the survival rate after this approach in a phase II trial (285) has been similar to that after second-line *paclitaxel.*

A prospective, randomized clinical trial of a combination of very high-dose chemotherapy supported with ABMT versus standard-dose chemotherapy with *paclitaxel* and *carboplatin* was initiated by the GOG, but the trial was discontinued because of poor accrual. The use of peripheral stem cell transplantation as an alternative to ABMT should be considered investigational.

Hormonal Therapy

Tamoxifen has been associated with response rates of 15% to 20% in well differentiated carcinomas of the ovary (286,287). The gonadotropin agonist, *leuprolide acetate (Lupron)*, has been shown to produce a response rate of 10% in one series (288). Trials combining *tamoxifen* and *leuprolide* and *tamoxifen* and combination chemotherapy are being conducted (289). Aromatase inhibitors [e.g., *anastrozole (Arimidex)*], which have been shown to have activity in metastatic breast cancer, are being studied in relapsed ovarian cancer (290).

Whole-Abdominal Radiation

Whole-abdominal radiation therapy given as a second-line treatment has been shown to be potentially effective in a small subset of selected patients with microscopic disease, but it is associated with a relatively high morbidity. The principal problem associated with this approach is the development of acute and chronic intestinal morbidity. Intestinal obstruction develops in as many as 30% of patients treated with this approach, necessitating potentially morbid exploratory surgery (291).

Intestinal Obstruction

Intestinal obstruction often develops in patients with epithelial ovarian cancer, either at the time of initial diagnosis or, more frequently, in association with recurrent disease (292,293,294,295,296,297 and 298). Obstruction may be related to a mechanical blockage or to carcinomatous ileus.

Correction of the intestinal blockage can be accomplished in most patients whose obstruction appears at the time of initial diagnosis (292). However, the decision to perform an exploratory procedure to palliate intestinal obstruction in patients with recurrent disease is more difficult. In patients whose life expectancy is very short (e.g., <2 months), surgical relief of the obstruction is not indicated (292,293). In those whose projected life span is longer, features that predict a reasonable likelihood of correcting the obstruction include young age, good nutritional status, and the absence of rapidly accumulating ascites.

For most patients with recurrent ovarian cancer who present with intestinal obstruction, initial management should include proper radiographic documentation of the obstruction, hydration, correction of any electrolyte disturbances, parenteral alimentation, and intestinal intubation. For the latter, a long gastrointestinal tube (e.g., Cantor tube) should be used, as discussed in Chapter 19. In some patients the obstruction may be alleviated by this conservative approach. A preoperative upper gastrointestinal series and a barium enema define possible sites of obstruction.

If exploratory surgery is deemed appropriate, the type of operation to be performed depends on (a) the site and (b) the number of obstructions. Multiple sites of obstruction are not uncommon in patients with recurrent epithelial ovarian cancer. More than one half of the patients have small bowel obstruction, one third have colonic obstruction, and one sixth have both (294,297). If the obstruction is principally contained in one area of the bowel (e.g., the terminal ileum), this area can either be resected or bypassed, depending on what is easier to accomplish safely. The techniques for these intestinal operations are discussed in Chapter 19. If multiple obstructions are present, resection of several segments of intestine in patients with recurrent disease is usually not indicated, and intestinal bypass and/or colostomy should be performed. A gastrostomy may also be useful in this circumstance (298).

Intestinal bypass is usually associated with less morbidity than resection, and in patients with recurrent, progressive cancer, the survival time after these two operations is the same (297). Most frequently, an enteroenterostomy or an enterocolostomy is performed (295,297). Colostomy may be necessary when there is a distal large bowel obstruction. Occasionally, the performance of an ileostomy or a jejunostomy is warranted when the large bowel is completely encased in tumor. In very advanced cases, a palliative gastrostomy may be used, and this can be placed percutaneously if there is no carcinomatosis around the stomach (298).

Among over 400 patients reported to have undergone operations for intestinal obstruction resulting from ovarian cancer, the operative mortality rate was approximately 10% and major complications were seen in approximately 30% of the patients (292,293,294,295,296 and 297). The need for multiple reanastomoses and prior radiation therapy increased the morbidity, which consisted primarily of sepsis and enterocutaneous fistulas.

The median survival time for patients who have undergone intestinal surgery for obstruction secondary to ovarian cancer ranges from 3 to 12 months, although approximately 20% of such patients survive longer than 12 months.

Survival

As discussed, the prognosis for patients with epithelial ovarian cancer is related to several clinical variables. Survival analyses based on the most commonly used prognostic variables are presented in the following sections (9,12,103,104,105,106,107 and 108).

Age Including patients at all stages, patients younger than 50 years of age have a 5-year survival rate of approximately 40%, compared with approximately 15% for patients older than 50 years (9,104,105,108).

Stage The 5-year survival rate for properly staged patients with stage I disease is 76% to 93%, depending on the tumor grade (9,103). The 5-year survival rate for stage II is 60% to 74%. The 5-year survival rate for stage IIIA is 41%, for stage IIIB approximately 25%, for stage IIIC 23%, and for stage IV disease 11% (9,108) (Note also the proportion of the stage of patients at the time of their diagnosis; Fig. 11.17.). The survival by substage is presented in Fig. 11.18.

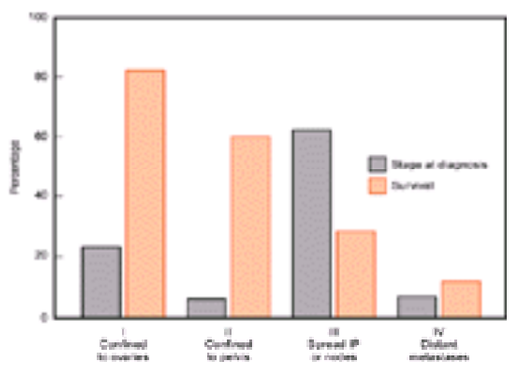


Figure 11.17 Survival of patients with epithelial ovarian cancer by stage. The percentage of patients diagnosed at a particular stage is shown next to the 5-year survival by stage. IP, intraperitoneal.

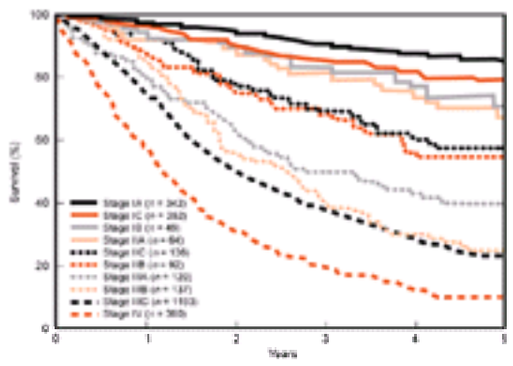


Figure 11.18 Survival of patients with epithelial ovarian cancer by substage. (From Pecorelli S, Odicino F, Maisonneuve P, Creasman W, Shepard J, Sideri M, et al. Carcinoma of the ovary. Annual Report on the Results of Treatment of Gynaecological Cancer. *J Epidemiol Biostat* 1998;3:75–102, with permission.)

An analysis of the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database reveals a trend toward improved survival for ovarian cancer in the United States during the last period of analysis (1988 to 1994). In this cohort, the survival rate for stage I was 93%, for stage II 70%, for stage III 37%, and for stage IV 25% (299). Compared with the interval 1983 to 1987, there was a statistically significant improvement in survival for stages I, III, and IV disease.

Grade The survival of patients with borderline tumors is excellent, with stage I lesions having a 98% 15-year survival rate (3). When all stages of borderline tumors are included, the 5-year survival rate is approximately 86% to 90% (3,9) (Fig. 11.19).

was 93%, for stage II 70%, for stage III 37%, and for stage IV 25% (299). Compared with the interval 1983 to 1987, there was a statistically significant improvement in survival for stages I, III, and IV disease.

Grade The survival of patients with borderline tumors is excellent, with stage I lesions having a 98% 15-year survival rate (3). When all stages of borderline tumors are included, the 5-year survival rate is approximately 86% to 90% (3,9) (Fig. 11.19).

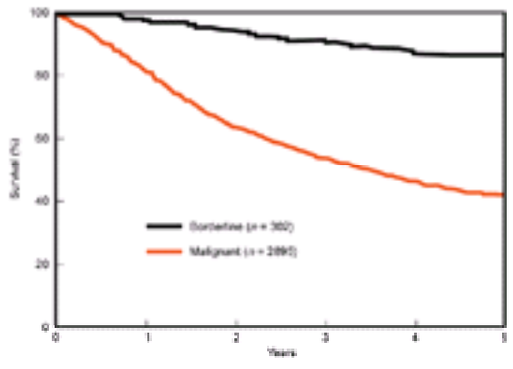


Figure 11.19 Survival of patients with borderline versus invasive epithelial ovarian cancer. (From Pecorelli S, Odicino F, Maisonneuve P, Creasman W, Shepard J, Sideri M, et al. Carcinoma of the ovary. Annual Report on the Results of Treatment of Gynaecological Cancer. *J Epidemiol Biostat* 1998;3:75–102, with permission.)

Regarding patients with invasive cancer, for stage I disease, the 5-year survival rate for grade 1 epithelial ovarian cancers is approximately 91%, compared with approximately 74% for grade 2 and 75% for grade 3 (9,67,71) (Fig. 11.20). For stage II disease, the survival rates are 69%, 60%, and 51%, respectively, for grades 1, 2, and 3. In patients with stage III to IV disease, the 5-year survival rates for grades 1, 2, and 3, respectively, are 38%, 25%, and 19% (Fig. 11.21).

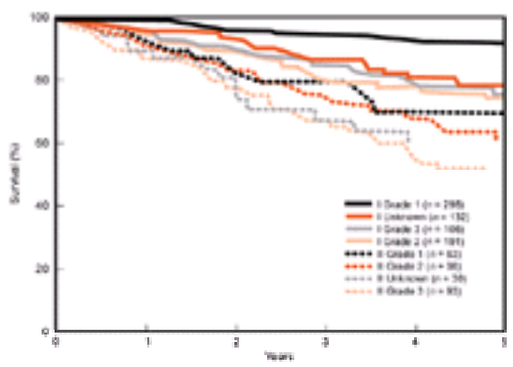


Figure 11.20 Survival of patients with FIGO stages I and II epithelial ovarian cancer by grade of the tumor. (From Pecorelli S, Odicino F, Maisonneuve P, Creasman W, Shepard J, Sideri M, et al. Carcinoma of the ovary. Annual Report on the Results of Treatment of Gynaecological Cancer. *J Epidemiol Biostat* 1998;3:75–102, with permission.)

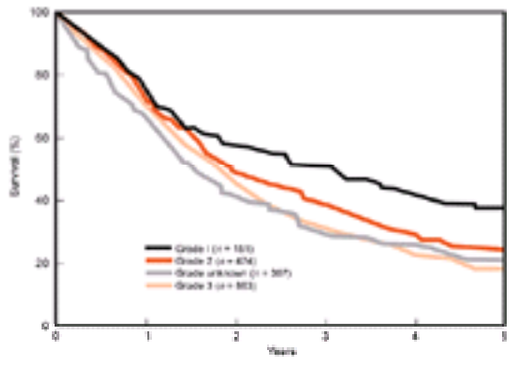


Figure 11.21 Survival of patients with FIGO stages III and IV epithelial ovarian cancer by grade of the tumor. (From Pecorelli S, Odicino F, Maisonneuve P, Creasman W, Shepard J, Sideri M, et al. Carcinoma of the ovary. Annual Report on the Results of Treatment of Gynaecological Cancer. *J Epidemiol Biostat* 1998;3:75–102, with permission.)

Residual Disease Patients with stage III disease with microscopic residual disease at the start of treatment have a 5-year survival rate of approximately 40% to 75%, compared with approximately 30% to 40% for those with optimal disease and only 5% for those with nonoptimal disease (134,135 and 138) (Fig. 11.6).

Second-Look Status Patients with stage III cancer without evidence of disease at second-look laparotomy have a 5-year survival rate of 50%, compared with approximately 35% for those with microscopic disease and approximately 5% for those with macroscopic disease (219,221,223,224).

Performance Status Patients whose Karnofsky's index (KI) is low (<70) have a significantly shorter survival than those with a KI greater than 70 (104,108).

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12 Nonepithelial Ovarian and Fallopian Tube Cancers

Jonathan S. Berek and Neville F. Hacker

Compared with epithelial ovarian cancers, other malignant tumors of the female genital adnexal structures are uncommon. Nonepithelial ovarian cancers include malignancies of germ cell origin, sex cord–stromal cell origin, metastatic carcinomas to the ovary, and a variety of extremely rare ovarian cancers (e.g., sarcomas, lipoid cell tumors). Fallopian tube carcinomas and sarcomas are also rare.

Nonepithelial malignancies of the ovary account for approximately 10% of all ovarian cancers (1,2). Although there are many similarities in the presentation, evaluation, and management of these patients, these tumors also have many unique qualities that require a special approach (1,2,3,4 and 5).

Germ Cell Malignancies

Germ cell tumors are derived from the primordial germ cells of the ovary. Their incidence is only approximately one tenth the incidence of malignant germ cell tumors of the testis, so most of the advances in the management of these tumors have been extrapolations from experience with the corresponding testicular tumors. Although malignant germ cell tumors can arise in extragonadal sites such as the mediastinum and the retroperitoneum, most germ cell tumors arise in the gonad from the undifferentiated germ cells. The variation in the site of these cancers is explained by the embryonic migration of the germ cells from the caudal part of the yolk sac to the dorsal mesentery before their incorporation into the sex cords of the developing gonads (1,2).

Classification

A histologic classification of ovarian germ cell tumors is presented in Table 12.1 (1). Both a-fetoprotein (AFP) and human chorionic gonadotropin (hCG) are secreted by some germ cell malignancies; therefore, the presence of circulating hormones can be clinically useful in the diagnosis of a pelvic mass and in monitoring the course of a patient after surgery. Placental alkaline phosphatase and lactate dehydrogenase (LDH) are commonly produced by dysgerminomas (up to 95% of patients with the diagnosis), and serial measurements of LDH may be useful for monitoring the disease. a_1-Antitrypsin can be detected rarely in association with germ cell tumors. When the histologic and immunohistologic identification of these substances in tumors is correlated, a classification of germ cell tumors emerges (6) (Fig. 12.1).

1. *Dysgerminoma*
2. *Teratoma*
A. Immature
B. Mature
(1) Solid
(2) Cystic
a. Dermoid cyst (mature cystic teratoma)
b. Dermoid cyst with malignant transformation
C. Monodermal and highly specialized
(1) Struma ovarii
(2) Carcinoid
(3) Struma ovarii and carcinoid
(4) Others
3. *Endodermal sinus tumor*
4. *Embryonal carcinoma*
5. *Polyembryoma*
6. *Choriocarcinoma*
7. *Mixed forms*

Reproduced from Serov SF, Scully RE, Robin IH. Histological typing of ovarian tumors. International histological classification of tumors, no. 9. Geneva: World Health Organization, 1973, with permission.

Table 12.1 Histologic Typing of Ovarian Germ Cell Tumors

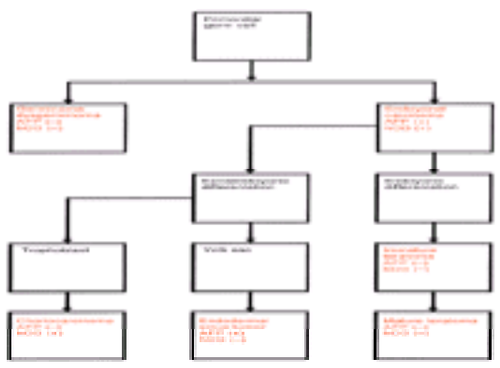

Figure 12.1 Relationship between examples of pure malignant germ cell tumors and their secreted marker substances.

In this scheme, embryonal carcinoma, which is a cancer composed of undifferentiated cells, synthesizes both hCG and AFP, and this lesion is the progenitor of several other germ cell tumors (4,6). More differentiated germ cell tumors, such as the endodermal sinus tumor (EST), which secretes AFP, and choriocarcinoma, which secretes hCG, are derived from the extraembryonic tissues; the immature teratomas derived from the embryonic cells have lost the ability to secrete these substances. Elevated hCG levels are seen in 3% of dysgerminomas (1).

Epidemiology

Although 20% to 25% of all benign and malignant ovarian neoplasms are of germ cell origin, only approximately 3% of these tumors are malignant (1). Germ cell malignancies account for fewer than 5% of all ovarian cancers in Western countries. Germ cell malignancies represent up to 15% of ovarian cancers in Asian and black societies, where epithelial ovarian cancers are much less common.

In the first two decades of life, almost 70% of ovarian tumors are of germ cell origin, and one third of these are malignant (1,2). Germ cell tumors account for two thirds of the ovarian malignancies in this age group. Germ cell cancers also are seen in the third decade, but thereafter they become quite rare.

Clinical Features

Symptoms

In contrast to the relatively slow-growing epithelial ovarian tumors, germ cell malignancies grow rapidly and often are characterized by subacute pelvic pain related to capsular distention, hemorrhage, or necrosis. The rapidly enlarging pelvic mass may produce pressure symptoms on the bladder or rectum, and menstrual irregularities also may occur in menarchal patients. Some young patients may misinterpret the early symptoms of a neoplasm as those of pregnancy, and this can lead to a delay in the diagnosis. Acute symptoms associated with torsion or rupture of the adnexa can develop. These symptoms may be confused with acute appendicitis. In more advanced cases, ascites may develop, and the patient can have abdominal distention (3).

Signs

In patients with a palpable adnexal mass, the evaluation can proceed as outlined in Chapter 11. Some patients with germ cell tumors are premenarchal and may require examination under anesthesia. If the lesions are principally solid or a combination of solid and cystic, as might be noted on an ultrasonographic evaluation, a neoplasm is probable and a malignancy is possible (Fig. 12.2). The remainder of the physical examination should search for signs of ascites, pleural effusion, and organomegaly.

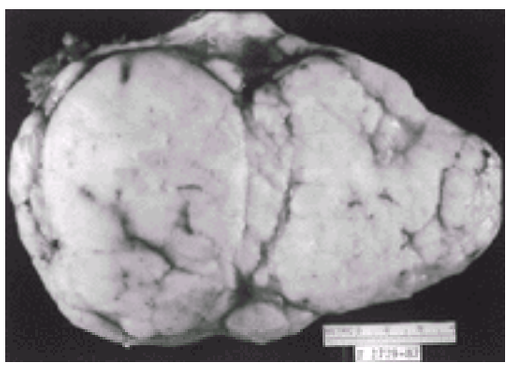

Figure 12.2 Dysgerminoma of the ovary. Note that the lesion is principally solid with some cystic areas.

Diagnosis

Adnexal masses measuring 2 cm or larger in premenarchal girls or complex masses 8 cm or larger in other premenopausal patients usually require surgical exploration (Fig. 12.3). In young patients, blood tests should include serum hCG and AFP titers, a complete blood count, and liver function tests. A radiograph of the chest is important because germ cell tumors can metastasize to the lungs or mediastinum. A preoperative karyotype should be obtained on all premenarchal girls because of the propensity of these tumors to arise in dysgenetic gonads (3,7). A preoperative computed tomography (CT) scan or magnetic resonance imaging may document the presence and extent of retroperitoneal lymphadenopathy or liver metastases; however, because these patients require surgical exploration, such extensive and time-consuming evaluation is unnecessary. If postmenarchal patients have predominantly cystic lesions up to 8 cm in diameter, they may undergo a trial of hormonal suppression for two cycles (8).

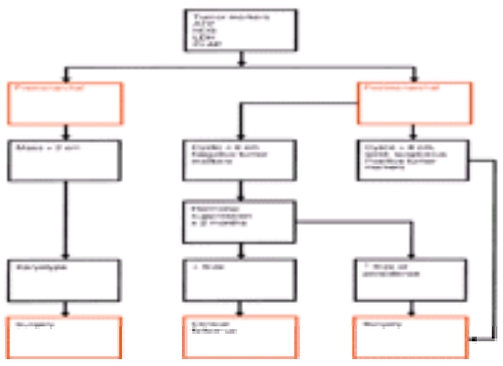

Figure 12.3 Evaluation of a pelvic mass in young female patients.

Dysgerminoma

The dysgerminoma is the most common malignant germ cell tumor, accounting for approximately 30% to 40% of all ovarian cancers of germ cell origin (2,6). The tumors represent only 1% to 3% of all ovarian cancers, but they represent as many as 5% to 10% of ovarian cancers in patients younger than 20 years of age. Seventy-five percent of dysgerminomas occur between the ages of 10 and 30 years, 5% occur before the age of 10 years, and they rarely occur after the age of 50 years (1,4). Because these malignancies occur in young women, 20% to 30% of ovarian malignancies associated with pregnancy are dysgerminomas.

Approximately 5% of dysgerminomas are discovered in patients with a female phenotype and abnormal gonads (1,7). This malignancy can be associated with patients who have pure gonadal dysgenesis (46XY, bilateral streak gonads), mixed gonadal dysgenesis (45X/46XY, unilateral streak gonad, contralateral testis), and the androgen insensitivity syndrome (46XY, testicular feminization). Therefore, in premenarchal patients with a pelvic mass, the karyotype should be determined (Fig. 12.4).

Figure 12.4 A 16-year-old girl with 46XY gonadal dysgenesis in whom a dysgerminoma developed on her second "streak" ovary, 4 years after having a dysgerminoma removed from her other ovary. Note the lack of breast development and pubic hair.

In most patients with gonadal dysgenesis, dysgerminomas arise in gonadoblastomas, which are benign ovarian tumors that are composed of germ cells and sex cord stroma. If gonadoblastomas are left *in situ*in patients with gonadal dysgenesis, more than 50% develop into ovarian malignancies (9).

Approximately 75% of dysgerminomas are stage I (i.e., confined to one or both ovaries) at diagnosis (1,3,10,11,12,13 and 14). Approximately 85% to 90% of stage I tumors are confined to one ovary; 10% to 15% are bilateral. In fact, dysgerminoma is the only germ cell malignancy that has this significant rate of bilaterality, other germ cell tumors rarely being bilateral.

In patients whose contralateral ovary has been preserved, disease can develop in 5% to 10% of the retained gonads over the next 2 years (1). This figure includes those not given additional therapy, as well as patients with gonadal dysgenesis.

In the 25% of patients who present with metastatic disease, the tumor most commonly spreads through the lymphatics. It can also spread hematogenously or by direct extension through the capsule of the ovary with exfoliation and dissemination of cells throughout the peritoneal surfaces. Metastases to the contralateral ovary may be present when there is no other evidence of spread. An uncommon site of metastatic disease is bone; when metastasis to this site occurs, the lesions are seen principally in the lower vertebrae. Metastases to the lungs, liver, and brain are seen most often in patients with long-standing or recurrent disease. Metastasis to the mediastinum and supraclavicular lymph nodes is usually a late manifestation of disease (10,11).

Treatment

The treatment of patients with early dysgerminoma is primarily surgical, including resection of the primary lesion and proper surgical staging. Chemotherapy and/or radiation is administered to patients with metastatic disease. Because the disease principally affects girls or young women, special consideration must be given to the preservation of fertility whenever possible. An algorithm for the management of ovarian dysgerminoma is presented in Fig. 12.5.

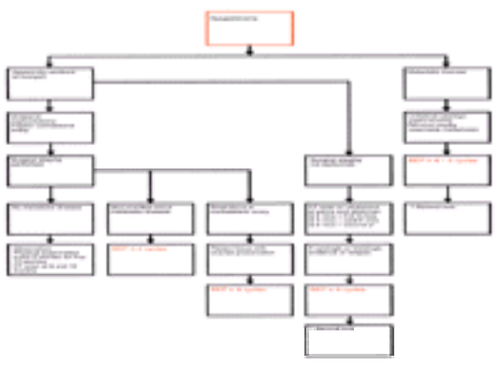

Figure 12.5 Management of dysgerminoma of the ovary. BEP, *bleomycin, etoposide*, and *cisplatin.*

Surgery

The minimum operation for ovarian dysgerminoma is a unilateral oophorectomy (12). **If there is a desire to preserve fertility, the contralateral ovary, fallopian tube, and uterus should be left *in situ*, even in the presence of metastatic disease, because of the sensitivity of the tumor to chemotherapy.** If fertility need not be preserved, it may be appropriate to perform a total abdominal hysterectomy and bilateral salpingo-oophorectomy in patients with advanced disease (14). In patients whose karyotype analysis reveals a Y chromosome, both ovaries should be removed, although the uterus may be left in situ for possible future embryo transfer. Although cytoreductive surgery is of unproven value, bulky disease that can be readily resected (e.g., an omental cake) should be removed at the initial operation.

In patients in whom the neoplasm appears on inspection to be confined to the ovary, a careful staging operation should be undertaken to determine the presence of any occult metastatic disease. All peritoneal surfaces should be inspected and palpated, and any suspicious lesions should be sampled for biopsy. Unilateral pelvic lymphadenectomy and at least careful palpation and biopsy of enlarged paraaortic nodes are particularly important parts of the staging. These tumors often metastasize to the paraaortic nodes around the renal vessels. Dysgerminoma is the only germ cell tumor that tends to be bilateral, and not all of the bilateral lesions have obvious ovarian enlargement. Therefore, excisional biopsy of any suspicious lesion on the contralateral ovary is necessary (12,13 and 14). If a small lesion is found on the contralateral ovary, it may be possible to resect it and preserve some normal ovary.

Radiation

Dysgerminomas are very sensitive to radiation therapy, and doses of 2,500 to 3,500 cGy may be curative, even for gross metastatic disease. Loss of fertility is a problem with radiation therapy, however, so radiation should rarely be used as first-line treatment (14).

Chemotherapy

Many patients with a dysgerminoma have a tumor that is apparently confined to one ovary and are referred after unilateral salpingo-oophorectomy without surgical staging. The options for such patients are repeat laparotomy for surgical staging, regular pelvic and abdominal surveillance with CT scans, or adjuvant chemotherapy. Because these are rapidly growing tumors, we prefer to perform regular CT or ultrasound surveillance. Tumor markers (LDH and b-hCG) should also be monitored in case occult mixed germ cell elements are present (Fig. 12.1).

There have been numerous reports of successful control of metastatic dysgerminomas with systemic chemotherapy, and this should now be regarded as the treatment of choice (14,15,16,17,18,19,20,21 and 22). **The obvious advantage is the preservation of fertility** (23).

The most frequently used chemotherapeutic regimens for germ cell tumors are BEP (*bleomycin, etoposide*, and *cisplatin*), VBP (*vinblastine, bleomycin*, and *cisplatin*), and VAC [*vincristine, actinomycin D*, and *cyclophosphamide (Cytoxan)*] (14,15,16,17,18 and 19) (Table 12.2).

Regimen and Drugs	*Dose and Schedule*[a]
BEP	
Bleomycin	15 units/m^2/week × 5; then on day 1 of course 4
Etoposide	100 mg/m^2/day × 5 days every 3 weeks
Cisplatin	20 mg/m^2/day × 5 days, or 100 mg/m^2/day × 1 day every 3 weeks
VBP	
Vinblastine	0.15 mg/kg on days 1 and 2 every 3 weeks
Bleomycin	15 units/m^2/week × 5; then on day 1 of course 4
Cisplatin	100 mg/m^2 on day 1 every 3 weeks
VAC	
Vincristine	1–1.5 mg/m^2 on day 1 every 4 weeks
Actinomycin D	0.5 mg/day × 5 days every 4 weeks
Cyclophosphamide	150 mg/m^2/day × 5 days every 4 weeks

[a]All doses given intravenously.

Table 12.2 Combination Chemotherapy for Germ Cell Tumors of the Ovary

The Gynecologic Oncology Group (GOG) studied three cycles of the EC regimen, consisting of *etoposide* (120 mg/m^2 intravenously on days 1, 2, and 3 every 4 weeks) and *carboplatin* (400 mg/m^2 intravenously on day 1 every 4 weeks) for patients with completely resected ovarian dysgerminoma, stages Ib, Ic, II, or III (22). The results showed a sustained disease-free remission rate of 100%.

For patients with advanced, incompletely resected germ cell tumors, the GOG studied *cisplatin*-based chemotherapy on two consecutive protocols (15,16). In the first study, patients received four cycles of *vinblastine* (12 mg/m^2 every 3 weeks), *bleomycin* (20 units/m^2 intravenously every week for 12 weeks), and *cisplatin*(20 mg/m^2/day intravenously for 5 days every 3 weeks). Patients with persistent or progressive disease at second-look laparotomy were treated with six cycles of VAC. In the second trial, patients received three cycles of BEP initially, followed by consolidation with VAC, which was later discontinued in patients with dysgerminomas (16). VAC does not appear to improve the outcome of the BEP regimen. A total of 20 evaluable patients with stage III and IV dysgerminoma were treated in these two protocols, and 19 are alive and free of disease after 6 to 68 months (median, 26 months). Fourteen of these patients had a second-look laparotomy, and all findings were negative. Another study at M. D. Anderson Hospital (17) used BEP in 14 patients with residual disease, and all patients were free of disease at long-term follow-up. **These results suggest that patients with advanced-stage, incompletely resected dysgerminoma have an excellent prognosis when treated with *cisplatin*-based combination chemotherapy. The best regimen is four cycles of BEP based on the data from testicular cancers** (24,25).

There appears to be no need to perform a second-look laparotomy in patients with dysgerminoma whose macroscopic disease has been

laparotomy, and all findings were negative. Another study at M. D. Anderson Hospital (17) used BEP in 14 patients with residual disease, and all patients were free of disease at long-term follow-up. **These results suggest that patients with advanced-stage, incompletely resected dysgerminoma have an excellent prognosis when treated with *cisplatin*-based combination chemotherapy. The best regimen is four cycles of BEP based on the data from testicular cancers** (24,25).

There appears to be no need to perform a second-look laparotomy in patients with dysgerminoma whose macroscopic disease has been completely resected at the primary operation (26,27 and 28). In patients with macroscopic residual disease at the start of chemotherapy, we prefer to perform a second-look operation because second-line therapy is available and the earlier persistent disease is identified, the better the prognosis should be.

Recurrent Disease

Approximately 75% of recurrences occur within the first year after initial treatment (1,2,3 and 4), the most common sites being the peritoneal cavity and the retroperitoneal lymph nodes. These patients should be treated with either radiation or chemotherapy, depending on their primary treatment. Patients with recurrent disease who have had no therapy other than surgery should be treated with chemotherapy. If prior chemotherapy with BEP has been given, POMB-ACE (*cisplatin, vincristine, methotrexate*, and *bleomycin;* and *actinomycin D, cyclophosphamide*, and *etoposide*) may be used (Table 12.3), and consideration should be given to the use of high-dose chemotherapy (e.g., with *carboplatin* and *etoposide*) and autologous bone marrow transplantation. Alternatively, radiation therapy is effective for this disease, with the major disadvantage being loss of fertility if pelvic and abdominal radiation is required.

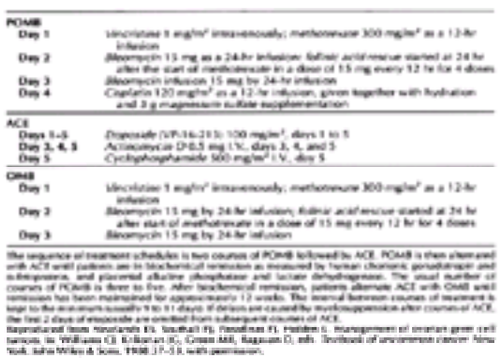

Table 12.3 POMB/ACE Chemotherapy for Germ Cell Tumors of the Ovary

Pregnancy

Because dysgerminomas tend to occur in young patients, they may coexist with pregnancy. When a stage IA cancer is found, the tumor can be removed intact and the pregnancy continued. In patients with more advanced disease, continuation of the pregnancy depends on gestational age. Chemotherapy can be given in the second and third trimesters in the same dosages as given for the nonpregnant patient without apparent detriment to the fetus (23).

Prognosis

In patients whose initial disease is stage IA (i.e., a unilateral encapsulated dysgerminoma), unilateral oophorectomy alone results in a 5-year disease-free survival rate of greater than 95% (13,14). The features that have been associated with a higher tendency to recurrence include lesions larger than 10 to 15 cm in diameter, age younger than 20 years, and a microscopic pattern that includes numerous mitoses, anaplasia, and a medullary pattern (1,6).

Although in the past surgery for advanced disease followed by pelvic and abdominal radiation resulted in a 5-year survival rate of 63% to 83%, cure rates of 90% to 100% for this same group of patients are now being reported with the use of VBP, BEP, or EC (*etoposide* and *carboplatin*) combination chemotherapy (14,15,16,17,18,19,20,21 and 22).

Immature Teratomas

Immature teratomas contain elements that resemble tissues derived from the embryo. Immature teratomatous elements may occur in combination with other germ cell tumors as mixed germ cell tumors. The pure immature teratoma accounts for fewer than 1% of all ovarian cancers, but it is the second most common germ cell malignancy. This lesion represents 10% to 20% of all ovarian malignancies seen in patients younger than 20 years of age, and 30% of the deaths from ovarian cancer in this age group (1). Approximately 50% of pure immature teratomas of the ovary occur between the ages of 10 and 20 years, and they rarely occur in postmenopausal women. Immature teratomas are classified according to a grading system (grades 1 to 3) that is based on the degree of differentiation and the quantity of immature tissue (29).

Malignant transformation of a mature teratoma is a rare event. Squamous cell carcinoma is the most frequent subtype of malignancy in this setting, but adenocarcinomas, primary melanomas, and carcinoids occur (see later) (21). The risk of malignant transformation is reported to be 0.5% to 2% of teratomas, usually in postmenopausal patients.

Diagnosis

The preoperative evaluation and differential diagnosis are the same as for patients with other germ cell tumors. Some of these lesions contain calcifications similar to those found in mature teratomas, and this can be detected by a radiograph of the abdomen or by ultrasonography. Rarely, they are associated with the production of steroid hormones and can be accompanied by sexual *pseudoprecosity* (4). Tumor markers are negative unless a mixed germ cell tumor is present.

Treatment

Surgery

In a premenopausal patient whose lesion appears confined to a single ovary, unilateral oophorectomy and surgical staging should be performed. In postmenopausal patients a total abdominal hysterectomy and bilateral salpingo-oophorectomy may be performed. Contralateral involvement is rare, and routine resection or wedge biopsy of the contralateral ovary is unnecessary (26). Any lesions on the peritoneal surfaces should be sampled and submitted for histologic evaluation. The most frequent site of dissemination is the peritoneum and, much less commonly, the retroperitoneal lymph nodes. Blood-borne metastases to organ parenchyma, such as the lungs, liver, or brain, are uncommon. When present, they are usually seen in patients with late or recurrent disease and most often in tumors that are poorly differentiated (i.e., grade 3) (4).

Chemotherapy

Patients with stage IA, grade 1 tumors have an excellent prognosis, and no adjuvant therapy is required. In patients whose tumors are stage IA, grades 2 or 3, adjuvant chemotherapy should be used (17,18,19,26,30,31,32,33,34,35,36,37 and 38). Chemotherapy is also indicated in patients who have ascites regardless of tumor grade.

The most frequently used combination chemotherapeutic regimen in the past has been VAC (32,33 and 34). However, in a GOG study, the relapse-free survival rate in patients with incompletely resected disease was only 75% (34).

The newer approach has been to incorporate *cisplatin* into the primary treatment of these tumors, and most of the experience has been with the VBP and BEP regimens. No direct comparison of these regimens with VAC has been reported, but the BEP combination can save some patients who have persistent or recurrent disease after VAC (38).

The GOG has been prospectively studying three courses of BEP therapy in patients with completely resected stage I, II, and III ovarian germ cell tumors (38). Overall, the toxicity has been acceptable, and 91 of 93 patients with nondysgerminomatous tumors treated are clinically free of disease. **Thus, the BEP regimen, which is used more extensively for testicular cancer, appears to be superior to the VAC regimen in the treatment of completely resected nondysgerminomatous germ cell tumors of the ovary.** Because some patients can progress rapidly, treatment should be initiated as soon as possible after surgery, preferably within 7 to 10 days.

The switch from VBP to BEP has been prompted by the experience in patients with testicular cancer, where the replacement of *vinblastine* with *etoposide* has been associated with a better therapeutic index (i.e., equivalent efficacy and lower morbidity), especially less neurologic and gastrointestinal toxicity. Furthermore, the use of *bleomycin* appears to be important in this group of patients. In a randomized study of three cycles of *etoposide* plus *cisplatin* with or without *bleomycin* (EP vs. BEP) in 166 patients with germ cell tumors of the testes, the BEP regimen had a relapse-free survival rate of 84% compared with 69% for the EP regimen (*p* 0.03) (24). In addition, *cisplatin* may be slightly better than *carboplatin* in the setting of metastatic germ cell tumors. One hundred ninety-two patients with germ cell tumors of the testes were entered into a study of four cycles of *etoposide* plus *cisplatin* (EP) versus four cycles of *etoposide* plus *carboplatin* (EC). There have been three relapses with the EP regimen versus seven with the EC regimen, although the overall survival of the two groups is identical thus far (25). **In view of these results, BEP is the preferred treatment regimen for patients with gross residual disease and has replaced the VAC regimen for patients with completely resected disease.**

Immature teratomas with malignant squamous elements appear to have a poorer prognosis than those tumors without these elements (21). The treatment in these patients is also the BEP regimen.

Radiation

Radiation therapy usually is not used in the primary treatment of patients with immature teratomas. Furthermore, there is no evidence that the combination of chemotherapy and radiation has a higher rate of disease control than chemotherapy alone. Radiation should be reserved for patients with localized persistent disease after chemotherapy (14,26).

Second-Look Laparotomy

The need for a second-look operation has been questioned (27,28). It seems not to be justified in patients who have received chemotherapy in an adjuvant setting (i.e., stage IA, grades 2 and 3) because chemotherapy in these patients is so effective. We continue to prefer second-look laparotomy in patients with macroscopic residual disease at the start of chemotherapy because there are no reliable tumor markers for this disease and such patients are at higher risk of failure.

If a second-look operation is performed, careful sampling of any peritoneal lesions should be performed and the retroperitoneal lymph nodes should be evaluated carefully. If only mature elements are found at the second look, chemotherapy should be discontinued. If persistent immature elements are documented, alternative chemotherapy should be employed. An enlarged contralateral ovary may contain a benign cyst or a mature cystic teratoma, which may be managed with an ovarian cystectomy (2,4).

Prognosis

The most important prognostic feature of the immature teratoma is the grade of the lesion (1,29). In addition, the stage of disease and the extent of tumor at the initiation of treatment also have an impact on the curability of the lesion. Patients whose tumors have been incompletely resected before treatment have a significantly lower probability of 5-year survival than those whose lesions have been completely resected (i.e., 94% vs. 50%) (4). Overall, the 5-year survival rate for patients with all stages of pure immature teratomas is 70% to 80%, and it is 90% to 95% for patients with surgical stage I lesions (26,29,30).

The degree or grade of immaturity generally predicts the metastatic potential and curability. The 5-year survival rates have been reported to be 82%, 62%, and 30% for patients with grades 1, 2, and 3, respectively (29). Occasionally, these tumors are associated with mature or low-grade glial elements that have implanted throughout the peritoneum, and such patients usually have a favorable long-term survival (4).

Endodermal Sinus Tumor

Endodermal sinus tumors have also been referred to as *yolk sac carcinomas* because they are derived from the primitive yolk sac (1). These lesions are the third most frequent malignant germ cell tumor of the ovary.

Patients with EST have a median age of 18 years (1,2 and 3,39,40). Approximately one third of the patients are premenarchal at the time of initial presentation. Abdominal and/or pelvic pain is the most frequent presenting symptom, occurring in approximately 75% of patients, whereas an asymptomatic pelvic mass is documented in 10% of patients (3).

Most EST secrete AFP, and rarely they may elaborate detectable a_1-antitrypsin. There is a good correlation between the extent of disease and the level of AFP, although discordance also has been observed. The serum level of these markers, particularly AFP, is useful in monitoring the patient's response to treatment (39,40,41,42,43,44 and 45).

Treatment

Surgery

The treatment of EST consists of surgical exploration, unilateral salpingo-oophorectomy, and a frozen section for diagnosis. The addition of a hysterectomy and contralateral salpingo-oophorectomy does not alter outcome (4,43). Any gross metastases should be removed if possible, but thorough surgical staging is not indicated because all patients need chemotherapy. At surgery, the tumors tend to be solid and large, ranging in size from 7 to 28 cm (median, 15 cm) in the GOG series (4,38). Bilaterality is not seen in these lesions, and the other ovary is involved with metastatic disease only when there are other metastases in the peritoneal cavity. Most patients have early-stage disease: 71% stage I, 6% stage II, and 23% stage III (45).

Chemotherapy

All patients with EST are treated with either adjuvant or therapeutic chemotherapy. Before the routine use of combination chemotherapy for this disease, the 2-year survival rate was only approximately 25%. After the introduction of the VAC regimen, this rate improved to 60% to 70%, indicating the chemosensitivity of most of these tumors (33,34). Furthermore, with conservative surgery and adjuvant chemotherapy, fertility can be preserved as with other germ cell tumors.

The VBP regimen is more effective in the treatment of EST, particularly in the treatment of measurable or incompletely resected tumors (38). In the GOG series, only approximately 20% of patients with residual metastatic disease responded completely to the VAC regimen, whereas approximately 60% of those treated with VBP had a complete response (18). In addition, this regimen may save some patients in whom VAC therapy has failed.

Workers at the Charing Cross Hospital in London have developed the POMB-ACE regimen for high-risk germ cell tumors of any histologic type (46) (Table 12.3). This protocol introduces seven drugs into the initial management, which is intended to minimize the chances for development of drug resistance. This is particularly relevant in patients with massive metastatic disease, and we use the POMB-ACE regimen as primary therapy for such cases, as well as in patients with liver or brain metastases. The POMB schedule is only moderately myelosuppressive, so the intervals between each course can be kept to a maximum of 14 days (usually 9 to 11 days), thereby minimizing the time for tumor regrowth between courses. When *bleomycin* is given by a 48-hour infusion, pulmonary toxicity is reduced. With a maximum of 9 years of follow-up, the Charing Cross group has seen no long-term side effects in patients treated with POMB-ACE. Children have developed normally, menstruation has been physiologic, and several have completed normal pregnancies.

Therefore, ***cisplatin*-containing combination chemotherapy, preferably BEP or POMB-ACE, should be used as primary chemotherapy for EST.** The optimal number of treatment cycles has not been established. The GOG protocols have used three to four treatment cycles given every 4 weeks (38,46). Our policy has been to give three cycles for patients with stage I and completely resected disease and two further cycles after negative tumor marker status for patients with macroscopic residual disease before chemotherapy.

Second-Look Laparotomy

The value of a second-look operation has yet to be established in patients with EST. It appears that it is reasonable to omit the operation in patients with pure low-stage lesions and in patients whose AFP values return to normal and remain normal for the balance of their treatment (44,45). There have been reported cases in which the AFP has returned to normal in spite of persistent measurable disease; some of these cases have been mixed germ cell tumors (45). In patients whose AFP titers do not return to normal, persistent disease can be assumed and alternative chemotherapy (e.g., POMB-ACE) offered.

Embryonal Carcinoma

Embryonal carcinoma of the ovary is an extremely rare tumor that is distinguished from a choriocarcinoma of the ovary by the absence of syncytiotrophoblastic and cytotrophoblastic cells. The patients are very young, their ages ranging between 4 and 28 years (median, 14 years) (47). Older patients have been reported (48). Embryonal carcinomas may secrete estrogens, with the patient exhibiting symptoms and signs of precocious pseudopuberty or irregular bleeding (1). The presentation is otherwise similar to that of EST. The primary lesions tend to be large, and approximately two thirds are confined to one ovary at the time of presentation. These lesions frequently secrete AFP and hCG, which are useful for following the response to subsequent therapy (44).

The treatment of embryonal carcinomas is the same as for EST (i.e., a unilateral oophorectomy followed by combination chemotherapy with BEP) (18,38). Radiation does not appear to be useful for primary treatment.

Choriocarcinoma of the Ovary

Pure nongestational choriocarcinoma of the ovary is an extremely rare tumor. Histologically, it has the same appearance as gestational choriocarcinoma metastatic to the ovaries (49). Most patients with this cancer are younger than 20 years of age. The presence of hCG can be useful in monitoring the patient's response to treatment. **In the presence of high hCG levels, isosexual precocity has been seen, occurring in approximately 50% of patients whose lesions appear before menarche (50).**

There are only a few limited reports on the use of chemotherapy for these nongestational choriocarcinomas, but complete responses have been reported to the MAC regimen (*methotrexate, actinomycin D*, and *cyclophosphamide*) used in a manner described for gestational trophoblastic disease (49) (see Chapter 15). Alternatively, the BEP regimen can be used. The prognosis for ovarian choriocarcinomas has been poor, with most patients having metastases to organ parenchyma at the time of initial diagnosis.

Polyembryoma

Polyembryoma of the ovary, another extremely rare tumor, is composed of “embryoid bodies.” This tumor replicates the structures of early embryonic differentiation (i.e., the three somatic layers: endoderm, mesoderm, and ectoderm) (1,6). The lesion tends to occur in very young, premenarchal girls with signs of pseudopuberty and elevated AFP and hCG titers. Anecdotally, the VAC chemotherapeutic regimen has been reported to be effective (33).

Mixed Germ Cell Tumors

Mixed germ cell malignancies of the ovary contain two or more elements of the lesions described previously. In one series (51), the most common component of a mixed malignancy was dysgerminoma, which occurred in 80%, followed by EST in 70%, immature teratoma in 53%, choriocarcinoma in 20%, and embryonal carcinoma in 16%. **The most frequent combination was a dysgerminoma and an EST. The mixed lesions may secrete either AFP, hCG, both, or neither, depending on the components.**

These lesions should be managed with combination chemotherapy, preferably BEP. The serum marker, if positive initially, may become negative during chemotherapy, but this may reflect regression only of a particular component of the mixed lesion. Therefore, in these patients a second-look laparotomy may be indicated to determine the precise response to therapy if macroscopic disease was present at initiation of chemotherapy.

The most important prognostic features are the size of the primary tumor and the relative amount of its most malignant component (51). In stage IA lesions smaller than 10 cm, the survival rate is 100%. Tumors composed of less than one third EST, choriocarcinoma, or grade 3 immature teratoma also have an excellent prognosis, but it is less favorable when these components comprise most of the mixed lesions.

Sex Cord–Stromal Tumors

Sex cord–stromal tumors of the ovary account for approximately 5% to 8% of all ovarian malignancies (1,2,3,4,52,53,54 and 55). This group of ovarian neoplasms is derived from the sex cords and the ovarian stroma or mesenchyme. The tumors usually are composed of various combinations of elements, including the “female” cells (i.e., granulosa and theca cells), and “male” cells (i.e., Sertoli and Leydig cells), as well as morphologically indifferent cells. A classification of this group of tumors is presented in Table 12.4.

1. *Granulosa-stromal cell tumors*
A. Granulosa cell tumor
B. Tumors in thecoma-fibroma group
(1) Thecoma
(2) Fibroma
(3) Unclassified
2. *Androblastomas; Sertoli-Leydig cell tumors*
A. Well differentiated
(1) Sertoli cell tumor
(2) Sertoli-Leydig cell tumor
(3) Leydig cell tumor; hilus cell tumor
B. Moderately differentiated
C. Poorly differentiated (sarcomatoid)
D. With heterologous elements
3. *Gynandroblastoma*
4. *Unclassified*

Modified and reprinted from Young RH, Scully RE. Ovarian sex cord-stromal tumors: recent progress. Int J Gynecol Pathol 1988;1:133, with permission.

Table 12.4 Sex Cord–Stromal Tumors

Granulosa–Stromal Cell Tumors

Granulosa–stromal cell tumors include granulosa cell tumors, thecomas, and fibromas. The granulosa cell tumor is a low-grade malignancy; rarely, thecomas and fibromas have morphologic features of malignancy and then may be referred to as *fibrosarcomas.*

Granulosa cell tumors, which secrete estrogen, are seen in women of all ages. They are found in prepubertal girls in 5% of cases; the remainder are distributed throughout the reproductive and postmenopausal years (55). They are bilateral in only 2% of patients.

Of the rare prepubertal lesions, 75% are associated with sexual pseudoprecocity because of estrogen secretion (55). In the reproductive age group, most patients have menstrual irregularities or secondary amenorrhea, and cystic hyperplasia of the endometrium is frequently present. In postmenopausal women, abnormal uterine bleeding is frequently the presenting symptom. Indeed, the estrogen secretion in these patients can be sufficient to stimulate the development of endometrial cancer. **Endometrial cancer occurs in association with granulosa cell tumors in at least 5% of cases, and 25% to 50% are associated with endometrial hyperplasia** (1,50,52,53,54 and 55). Rarely, granulosa cell tumors may produce androgens and cause virilization.

The other symptoms and signs of granulosa cell tumors are nonspecific and the same as most ovarian malignancies. Ascites is present in approximately 10% of cases, and rarely a pleural effusion is present (52,53,54 and 55). Granulosa tumors tend to be hemorrhagic: occasionally they rupture and produce a hemoperitoneum.

Granulosa cell tumors are usually stage I at diagnosis but may recur 5 to 30 years after initial diagnosis (54). The tumors may also spread hematogenously, and metastases can develop in the lungs, liver, and brain years after initial diagnosis. When they do recur, they can progress quite rapidly. Malignant thecomas are extremely rare, and their presentation, management, and outcome are similar to those of the granulosa cell tumors (52). **Inhibin is secreted by granulosa cell tumors and is a useful marker for the disease** (56,57 and 58).

Treatment

The treatment of granulosa cell tumors depends on the age of the patient and the extent of disease. For most patients, surgery alone is sufficient primary therapy, with radiation and chemotherapy reserved for the treatment of recurrent or metastatic disease (55,58).

Surgery

Because granulosa cell tumors are bilateral in only approximately 2% of patients, a unilateral salpingo-oophorectomy is appropriate therapy for stage IA tumors in children or in women of reproductive age (53). At the time of laparotomy, if a granulosa cell tumor is identified by frozen section, a staging operation is performed, including an assessment of the contralateral ovary. If the opposite ovary appears enlarged, it should be sampled for biopsy. In perimenopausal and postmenopausal women for whom ovarian preservation is not important, a hysterectomy and bilateral salpingo-oophorectomy should be performed. In premenopausal patients in whom the uterus is left *in situ*, a dilatation and curettage of the uterus should be performed because of the possibility of a coexistent adenocarcinoma of the endometrium (55).

Radiation

There is no evidence to support the use of adjuvant radiation therapy for granulosa cell tumors, although pelvic radiation may help to palliate isolated pelvic recurrences (55).

Chemotherapy

There is no evidence that adjuvant chemotherapy prevents recurrence of disease. Metastatic lesions and recurrences have been treated with a variety of different antineoplastic drugs. The most effective chemotherapeutic regimen appears to be BEP. In a GOG study (59), 37% (14 of 30) patients treated with BEP had a negative second-look laparotomy, and completely responding patients had a median time to progression of 24.4 months. The use of hormonal agents such as progestins or antiestrogens has been suggested, but there are no data available to suggest effectiveness (53).

Prognosis

Granulosa cell tumors have a prolonged natural history and a tendency toward late relapse, reflecting their low-grade biology. As such, 10-year survival rates of approximately 90% have been reported, with 20-year survival rates dropping to 75% (53,54 and 55). Most histologic types have the same prognosis, but the more poorly differentiated diffuse or sarcomatoid type tends to do worse (52).

The DNA ploidy of the tumors has been correlated with survival. Holland and colleagues (60) reported DNA aneuploidy in 13 of 37 patients (35%) with primary granulosa cell tumors. The presence of residual disease was found to be the most important predictor of progression-free survival, but DNA ploidy was an independent prognostic factor. **Patients with no residual disease and DNA diploid tumors had a 10-year progression-free survival rate of 96%.**

Sertoli-Leydig Tumors

Sertoli-Leydig tumors occur most frequently in the third and fourth decades, with 75% of the lesions seen in women younger than 40 years of age. These lesions are extremely rare and account for less than 0.2% of ovarian cancers (1). Sertoli-Leydig cell tumors are most frequently low-grade malignancies, although occasionally a poorly differentiated variety may behave more aggressively.

The tumors typically produce androgens, and clinical virilization is noted in 70% to 85% of patients (61). Signs of virilization include oligomenorrhea followed by amenorrhea, breast atrophy, acne, hirsutism, clitoromegaly, a deepening voice, and a receding hairline (Fig. 12.6). Measurement of plasma androgens may reveal elevated testosterone and androstenedione, with normal or slightly elevated dehydroepiandrosterone sulfate (1). Rarely, the Sertoli-Leydig tumor can be associated with manifestations of estrogenization (i.e., isosexual precocity, irregular or postmenopausal bleeding).

Figure 12.6 Temporal baldness in a young woman with Sertoli-Leydig cell tumor.

Treatment

Because these low-grade lesions are only rarely bilateral (<1%), the usual treatment is unilateral salpingo-oophorectomy and evaluation of the contralateral ovary in patients who are in their reproductive years (62). In older patients, hysterectomy and bilateral salpingo-oophorectomy are appropriate.

There are insufficient data to document the utility of radiation or chemotherapy in patients with persistent disease, but some responses in patients with measurable disease have been reported with pelvic radiation and the VAC chemotherapy regimen (4,62).

Prognosis

The 5-year survival rate is 70% to 90%, and recurrences thereafter are uncommon (4,62). Most deaths are associated with poorly differentiated lesions.

Uncommon Ovarian Cancers

There are several varieties of malignant ovarian tumors, which together comprise only 0.1% of ovarian malignancies. These lesions include lipoid (or lipid) cell tumors, primary ovarian sarcomas, and small cell ovarian carcinomas.

Lipoid Cell Tumors

Lipoid cell tumors are thought to arise in adrenal cortical rests that reside in the vicinity of the ovary. More than 100 cases have been reported, and bilaterality has been noted in only a few (1). Most are associated with virilization, and occasionally with obesity, hypertension, and glucose intolerance reflecting glucocorticoid secretion. Rare cases of estrogen secretion and isosexual precocity have been reported.

Most of these tumors have a benign or low-grade behavior, but approximately 20%, most of which are initially larger than 8 cm in diameter, produce metastatic lesions. Metastases are usually in the peritoneal cavity but occur rarely at distant sites. The primary treatment is surgical extirpation of the primary lesion. There are no data regarding radiation or chemotherapy for this disease.

Sarcomas

Malignant mixed mesodermal sarcomas of the ovary are extremely rare; only approximately 100 cases have been reported. Most lesions are heterologous, and 80% occur in postmenopausal women. The presentation is similar to that of most ovarian malignancies. These lesions are biologically aggressive, and most patients have evidence of metastases.

Such patients should be treated by cytoreductive surgery and postoperative platinum-containing combination chemotherapy (63,64). In patients in whom all macroscopic disease can be resected, we have observed disease-free survival of more than 3 years in two patients treated with six cycles of *cisplatin* and *epirubicin.*

Small Cell Carcinomas

This rare tumor occurs at an average age of 24 years (range, 2 to 46 years) (65). The tumors are all bilateral. Approximately two thirds of the tumors are accompanied by paraendocrine hypercalcemia. This tumor accounts for one half of all cases of hypercalcemia associated with ovarian tumors. Approximately 50% of the tumors have spread beyond the ovaries when they are diagnosed (65).

The management of these malignancies consists of surgery followed by platinum-based chemotherapy or radiation therapy. In addition to the primary treatment of the disease, control of the hypercalcemia may require aggressive hydration, loop diuretics, and the use of bisphosphonates or *calcitonin* (see Chapter 17). The prognosis tends to be poor, with most patients dying within 2 years of diagnosis in spite of treatment.

Metastatic Tumors

Approximately 5% to 6% of ovarian tumors are metastatic from other organs, most frequently from the female genital tract, the breast, or the gastrointestinal tract (66,67,68,69,70 and 71). The metastases may occur from direct extension of another pelvic neoplasm, by hematogenous spread, lymphatic spread, or transcelomic dissemination, with surface implantation of tumors that spread in the peritoneal cavity.

Gynecologic

Nonovarian cancers of the genital tract can spread by direct extension or they may metastasize to the ovaries. Tubal carcinoma involves the ovaries secondarily in 13% of cases (1), usually by direct extension. Under some circumstances, it is difficult to know whether the tumor originates in the tube or in the ovary when both are involved. Cervical cancer spreads to the ovary only in rare cases (<1%), and most of these are of an advanced clinical stage or are adenocarcinomas. Although adenocarcinoma of the endometrium can spread and implant directly onto the surface of the ovaries in as many as 5% of cases, two synchronous primary tumors probably occur with greater frequency. In these cases, an endometrioid carcinoma of the ovary is usually associated with the adenocarcinoma of the endometrium.

Nongynecologic

The frequency of metastatic breast carcinoma to the ovaries varies according to the method of determination, but the phenomenon is common. **In autopsy data of women who die of metastatic breast cancer, the ovaries are involved in 24% of cases, and 80% of the involvement is bilateral** (66,67,68 and 69). Similarly, when ovaries are removed to palliate advanced breast cancer, approximately 20% to 30% of the cases reveal ovarian involvement, 60% bilaterally. The involvement of ovaries in early-stage breast cancer appears to be considerably lower, but precise figures are not available. In almost all cases, either ovarian involvement is occult or a pelvic mass is discovered after other metastatic disease becomes apparent.

Krukenberg Tumor

The Krukenberg tumor, which can account for 30% to 40% of metastatic cancers to the ovaries, arises in the ovarian stroma and has characteristic mucin-filled signet ring cells (70). The primary tumor is most frequently in the stomach, but less commonly the colon, breast, or biliary tract. Rarely, the cervix or the bladder may be the primary site. Krukenberg tumors can account for approximately 2% of ovarian cancers at some institutions, and they are usually bilateral. The lesions are usually not discovered until the primary disease is advanced, and therefore most patients die of their disease within a year. In some cases, a primary tumor is never found.

Other Gastrointestinal

In other cases of metastasis from the gastrointestinal tract to the ovary, the tumor does not have the classic histologic appearance of a Krukenberg tumor; most of these are from the colon and, less commonly, the small intestine. In as many as 1% to 2% of women with intestinal carcinomas, metastases to the ovaries develop during the course of their disease (68). Before exploration for an adnexal tumor in a woman older than 40 years of age, a barium enema is indicated to exclude a primary gastrointestinal carcinoma with metastases to the ovaries, particularly if there are any gastrointestinal symptoms. Metastatic colon cancer can mimic a mucinous cystadenocarcinoma of the ovary histologically (67,68).

Melanoma

Rare cases of malignant melanoma metastatic to the ovaries have been reported (71). In these circumstances, the melanomas are usually widely disseminated. Removal would be warranted for palliation of abdominal and/or pelvic pain, bleeding, or torsion.

Carcinoid

Metastatic carcinoid tumors are rare, representing fewer than 2% of metastatic lesions to the ovaries (72). Conversely, only approximately 2% of primary carcinoids have evidence of ovarian metastasis, and only 40% of these patients have the carcinoid syndrome at the time of discovery of the metastatic carcinoid. However, in perimenopausal and postmenopausal women explored for an intestinal carcinoid, it is reasonable to remove the ovaries to prevent subsequent ovarian metastasis. Furthermore, the discovery of an ovarian carcinoid should prompt a careful search for a primary intestinal lesion.

Lymphoma and Leukemia

Lymphomas and leukemia can involve the ovary. When they do, the involvement is usually bilateral (73,74). Approximately 5% of patients with Hodgkin's disease have lymphomatous involvement of the ovaries, but this occurs typically with advanced-stage disease. **With Burkitt's lymphoma, ovarian involvement is very common. Other types of lymphoma involve the ovaries much less frequently, and leukemic infiltration of the ovaries is uncommon.** Sometimes the ovaries can be the only apparent site of involvement of the abdominal or pelvic viscera with a lymphoma, and if this circumstance is found, a careful surgical exploration may be necessary. An intraoperative consultation with a hematologist-oncologist should be obtained to determine the need for these procedures if frozen-section evaluation of a solid ovarian mass reveals a lymphoma. In general, most lymphomas no longer require extensive surgical staging, although enlarged lymph nodes should in general be biopsied. In some cases of Hodgkin's disease, a more extensive evaluation may be necessary. Treatment involves that of the lymphoma or leukemia in general. Removal of a large ovarian mass may improve patient comfort and facilitate a response to subsequent radiation or chemotherapy.

Fallopian Tube Cancer

Carcinoma of the fallopian tube accounts for 0.3% of all cancers of the female genital tract (2,75,76,77,78 and 79). In histologic features and behavior, fallopian tube carcinoma is similar to ovarian cancer; thus, the evaluation and treatment are also essentially the same. The fallopian tubes are frequently involved secondarily from other primary sites, most often the ovaries, endometrium, gastrointestinal tract, or breast. They may also be involved in primary peritoneal carcinomatosis. The criteria for distinguishing primary from metastatic tubal cancer are discussed in Chapter 6. Almost all cancers are of “epithelial” origin, most frequently of serous histologic type. Rarely, sarcomas have also been reported.

Clinical Features

Tubal cancers are seen most frequently in the fifth and sixth decades, with a mean age of 55 to 60 years (2,75). There are no known predisposing factors.

Symptoms and Signs

The classic triad of symptoms and signs associated with fallopian tube cancer is (a) a prominent watery vaginal discharge (i.e., hydrops tubae profluens); (b) pelvic pain; and (c) a pelvic mass. However, this triad is noted in fewer than 15% of patients (2).

Vaginal discharge or bleeding is the most common symptom reported by patients with tubal carcinoma, and is documented in more than 50% of patients (2,76). Lower abdominal or pelvic pressure and pain also are noted in many patients. However, the presentation may be rather vague and nonspecific. In perimenopausal and postmenopausal women with an unusual, unexplained, or persistent vaginal discharge, even in the absence of bleeding, the clinician should be concerned about the possibility of an occult tubal cancer. Fallopian tube cancer is often found incidentally in asymptomatic women at the time of abdominal hysterectomy and bilateral salpingo-oophorectomy.

On examination, a pelvic mass is present in approximately 60% of patients, and ascites may be present if advanced disease exists. Patients with tubal carcinoma have a negative dilatation and curettage (3,78), although abnormal or adenocarcinomatous cells may be seen in cytologic specimens obtained from the cervix in 10% of patients.

Spread Pattern

Tubal cancers spread in much the same manner as epithelial ovarian malignancies, principally by the transcelomic exfoliation of cells that implant throughout the peritoneal cavity. In approximately 80% of the patients with advanced disease, metastases are confined to the peritoneal cavity at the time of diagnosis (77).

The fallopian tube is richly permeated with lymphatic channels, and spread to the paraaortic and pelvic lymph nodes is common. Metastases to the paraaortic lymph nodes have been documented in at least 33% of the patients with all stages of disease (79).

Staging

Fallopian tube cancer is staged according to the International Federation of Gynecology and Obstetrics (FIGO) (74). **The staging is based on the surgical findings at laparotomy** (Table 12.5). According to this system, approximately 37% of patients have stage I disease, 20% have stage II, 31% have stage III, and 10% have stage IV (75). A somewhat lower incidence of advanced disease is seen in these patients than in patients with epithelial ovarian carcinomas, presumably because of the earlier occurrence of symptoms, particularly vaginal bleeding or unusual vaginal discharge.

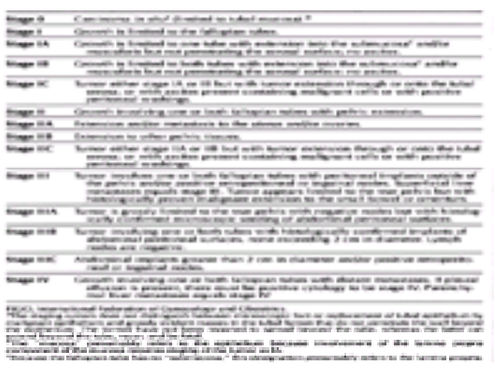

Table 12.5 Modified FIGO Fallopian Tube Staging

Treatment

The treatment of this disease is identical to that of epithelial ovarian cancer (2,75,78,80). Exploratory laparotomy is necessary to remove the primary tumor, to stage the disease, and to resect metastases. After surgery, the most frequently used treatment is platinum combination chemotherapy, although radiation is also used in selected cases with no residual disease.

Surgery

Patients with tubal carcinoma should undergo total abdominal hysterectomy and bilateral salpingo-oophorectomy (2). **If there is no evidence of gross tumor spread, a staging operation is performed.** The retroperitoneal lymph nodes should be adequately evaluated, and peritoneal cytologic studies and biopsies should be performed, along with an infracolic omentectomy.

In patients with metastatic disease, an effort should be made to remove as much tumor bulk as possible. The role of cytoreductive surgery in this disease is unclear, but extrapolation from the experience with epithelial ovarian cancer indicates that significant benefit might be expected, particularly if all macroscopic disease can be resected.

Chemotherapy

The most active single agents appear to be alkylating agents and *cisplatin*. Experience with *cisplatin* given in combination with *cyclophosphamide* (PC) or *doxorubicin* and *cyclophosphamide* (PAC) indicates that complete responses can be obtained (2,80). It appears justifiable, therefore, to use the same protocols that are used for epithelial ovarian cancer in patients with epithelial tubal malignancies. **We recommend *carboplatin* and *paclitaxel (Taxol)* in these patients.**

Data on well staged lesions are scarce. Therefore, it is unclear whether patients with disease confined to the fallopian tube (i.e., a stage IA, grade 1 or 2 carcinoma) benefit from adjuvant therapy.

Radiation

Whereas most patients with tubal cancers have been treated with radiation in the past, the role of radiation in the management of the disease remains unclear, because patients have not been treated in any consistent manner and the small numbers treated preclude any meaningful conclusions (78). Pelvic radiation alone was once popular, but this approach seems inappropriate when the pattern of spread of this disease to the upper abdomen is considered (76). Intraperitoneal ^{32}P has also been used, but these data are limited. More recently, whole-abdomen radiation with a pelvic boost has been used in patients with no evidence of gross disease in the abdomen (i.e., completely resected disease or microscopic metastases only). As with epithelial ovarian cancer, there may be a role in properly selected patients.

Prognosis

The overall 5-year survival rate for patients with epithelial tubal carcinomas is 56% (75). This number is higher than for patients with ovarian cancer and reflects the somewhat higher proportion of patients with early-stage disease. The outlook is clearly related to the stage of disease. The reported 5-year survival rate for patients with stage I disease is 84%. The 5-year survival rate for patients with stage II disease is 52%, and 36% for patients with stage III disease (75).

Tubal Sarcomas

Tubal sarcomas, particularly malignant mixed mesodermal tumors, have been described but are rare. They occur mainly in the sixth decade and are typically advanced at the time of diagnosis. If all gross disease can be resected, *cisplatin*-based combination chemotherapy should be tried. However, the survival rate is poor, and most patients die of their disease within 2 years (62).

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13 Vulvar Cancer

Neville F. Hacker

Vulvar cancer is uncommon, representing approximately 4% of malignancies of the female genital tract. Squamous cell carcinomas account for approximately 90% of the cases, whereas melanomas, adenocarcinomas, basal cell carcinomas, and sarcomas are much less common. **The incidence of *in situ* vulvar cancer has more than doubled over the past two decades, whereas the rate of invasive squamous cell carcinoma has remained stable** (1).

In the early part of the 20th century, patients commonly presented with advanced disease, and surgical techniques were poorly developed; thus, the 5-year survival rate for vulvar cancer was 20% to 25% (2,3). Basset (4), in France, was the first to suggest an *en bloc* dissection of the vulva, groin, and iliac lymph nodes, although he performed the operation only on cadavers. Taussig (5), in the United States, and Way (6), in Great Britain, pioneered the radical *en bloc* dissection for vulvar cancer and reported 5-year survival rates of 60% to 70%. Postoperative morbidity was high after these procedures, with wound breakdown, infection, and prolonged hospitalization the norm. For patients with disease involving the anus, rectum, or proximal urethra, pelvic exenteration was often combined with radical vulvectomy.

Since approximately 1980, a number of significant advances have been made in the management of vulvar cancer. These changes include:

1. Individualization of treatment for all patients with invasive disease (7,8)
2. Vulvar conservation for patients with unifocal tumors, and an otherwise normal vulva (7,8,9,10 and 11)
3. Omission of the groin dissection for patients with T_1 tumors and no more than 1 mm of stromal invasion (7,8)
4. Elimination of routine pelvic lymphadenectomy (12,13,14,15 and 16)
5. The use of separate groin incisions for the groin dissection to improve wound healing (17,18)
6. Omission of the contralateral groin dissection in patients with lateral T_1 lesions and negative ipsilateral nodes (8,19)
7. The use of preoperative radiation therapy to obviate the need for exenteration in patients with advanced disease (20,21)
8. The use of postoperative radiation to decrease the incidence of groin recurrence in patients with multiple positive groin nodes (16)

This paradigm shift in the management philosophy of vulvar cancer was well exemplified in retrospective reviews of the experience at the University of Miami (22) and the Mayo Clinic (23). Both centers reported a trend toward a more conservative approach and both reported decreased postoperative morbidity, without compromised survival.

Etiology

No specific etiologic factor has been identified for vulvar cancer, and the relationship of the invasive disease to vulvar dystrophy and to vulvar intraepithelial neoplasia (VIN) is controversial. Chronic pruritus is usually an important antecedent phenomenon in patients with invasive vulvar cancer (24). **VIN has traditionally been considered to have a low malignant potential,** with progression to invasive disease most likely in the elderly or immunosuppressed (25). **This concept has been challenged** by Jones et al. (26), who reported progression to malignant disease in 7 of 8 untreated patients within 8 years, whereas only 4 of 105 (3.8%) treated patients eventually developed vulvar cancer 7 to 18 years later. Vulvar cancer has been reported to be more common in patients who are obese, hypertensive, diabetic, or nulliparous (27,28), but a case–control study of vulvar cancer was unable to confirm any of these as risk factors (29).

A second primary malignancy, usually invasive or preinvasive cervical cancer, has been reported in up to 22% of cases (19,30). Using data on 2,685 patients with invasive vulvar cancer from the National Cancer Institute's Surveillance Epidemiology and End Results program (SEER), Sturgeon et al. (31)reported an increased risk of a subsequent cancer of 1.3. **Most of the second cancers were smoking related** (i.e., cancers of the lung, buccal cavity, pharynx, nasal cavity, and larynx) or related to infection with human papillomavirus (HPV; e.g., cervix, vagina, and anus).

The common association between cervical, vaginal, and vulvar cancer suggests a common pathogen, and the case–control study by Brinton et al. (29) found a significantly increased risk in association with multiple sexual partners, a history of genital warts, and smoking. HPV DNA has been reported in 20% to 60% of patients with invasive vulvar cancer (32). Hording et al. (33) reported HPV subtypes 16 or 33 in only 2 of 51 (4%) invasive keratinizing carcinomas, whereas one or the other was demonstrated in 12 of 17 (71%) invasive warty carcinomas and 10 of 10 (100%) invasive basaloid carcinomas. The HPV-positive group has been characterized by a younger mean age, greater tobacco use, and the presence of VIN in association with the invasive component (33,34,35 and 36).

These studies suggest two different etiologic types of vulvar cancer. **One type is seen mainly in younger patients, is related to HPV infection and smoking, and is commonly associated with VIN. The more common type is seen mainly in elderly patients, is unrelated to smoking or HPV infection, and concurrent VIN is uncommon, but there is a high incidence of dystrophic lesions, including lichen sclerosus, adjacent to the tumor.**

Other diseases known to be associated with vulvar cancer include syphilis and nonluetic granulomatous venereal disease, particularly lymphogranuloma venereum and granuloma inguinale *(Donovanosis).* **In approximately 5% of patients with vulvar cancer, a serologic test for syphilis is positive;** these patients develop the disease at an earlier age and have more poorly differentiated lesions(27,28). Antecedent chronic granulomatous disease has been reported in 66% of black patients with vulvar cancer in Jamaica (37), but such diseases are not seen commonly in Western countries.

Noninvasive Disease

Nonneoplastic Epithelial Disorders

In the past, a number of terms have been used to denote disorders of epithelial growth and differentiation that produce a variety of nonspecific macroscopic vulvar changes. These terms included *leukoplakia, lichen sclerosus et atrophicus, primary atrophy, sclerotic dermatosis, atrophic and hyperplastic vulvitis*, and *kraurosis vulvae* (38).

In 1966, Jeffcoate (39) suggested that these terms did not refer to separate disease entities because their macroscopic and microscopic appearances were variable and interchangeable. He assigned the generic term *chronic vulvar dystrophy* to the entire group of lesions.

Several classifications of vulvar diseases have been subsequently proposed, and this has been confusing for clinicians and pathologists alike. The most recent recommendation from the International Society for the Study of Vulvar Disease (ISSVD) is that the old "dystrophy" terminology should be replaced by a new classification under the pathologic heading *Nonneoplastic epithelial disorders of skin and mucosa.* The classification is shown in Table 13.1. Diagnosis in all cases requires biopsy of suspicious lesions, which are best detected by careful inspection of the vulva in a bright light, aided if necessary by a magnifying glass (40).

Nonneoplastic epithelial disorders of skin and mucosa
Lichen sclerosus (as before)
Squamous hyperplasia, not otherwise specified (formerly "hyperplastic dystrophy without atypia")
Other dermatoses
Mixed nonneoplastic and neoplastic epithelial disorders
Intraepithelial neoplasia
Squamous intraepithelial neoplasia (formerly "dystrophies with atypia")
VIN 1
VIN 2
VIN 3 (severe dysplasia or carcinoma *in situ*)
Nonsquamous intraepithelial neoplasia
Paget's disease
Tumors of melanocytes, noninvasive
Invasive tumors

VIN, Vulvar intraepithelial neoplasia.
From Committee on Terminology, International Society for the Study of Vulvar Disease. New nomenclature for vulvar disease. Int J Gynecol Pathol 1986;5:1-11, with permission.

Table 13.1 Classification of Vulvar Diseases

The malignant potential of these nonneoplastic epithelial disorders is low, particularly now that the lesions with atypia are classified as VIN. However, patients with lichen sclerosus and concomitant hyperplasia may be at particular risk. Rodke and colleagues (41) reported the development of vulvar carcinoma in 3 of 18 such cases (17%), postulating that the areas of hyperplasia were superimposed on a background of lichen sclerosus because of chronic irritation and trauma.

Vulvar Intraepithelial Neoplasia

As with the vulvar dystrophies, there has been confusion in the past over the nomenclature for VIN. Four major terms were used: *erythroplasia of Queyrat, Bowen's disease, carcinoma in situ simplex*, and *Paget's disease.* In 1976, the ISSVD decreed that the first three lesions were merely gross variants of the same disease process and that all should be included under the umbrella term *squamous cell carcinoma in situ* (stage 0) (38). In 1986, they recommended the term *VIN*, with carcinoma *in situ* of the vulva being VIN 3 (Table 13.1).

The term *bowenoid papulosis* has been used by some dermatologists to refer to cases of VIN associated with multiple papule formations (42). Use of the terms *bowenoid papulosis* or *bowenoid dysplasia* is not recommended by the ISSVD for either clinical or pathologic use. Treatment of VIN is discussed in Chapter 8.

Paget's Disease of the Vulva

Extramammary Paget's disease of the vulva *(adenocarcinoma in situ)* was first described in 1901 (43), 27 years after the description by Sir James Paget of the mammary lesion that now bears his name. Unlike its counterpart in the breast, which is invariably associated with an underlying ductal carcinoma, **only approximately 10% to 12% of patients have invasive vulvar Paget's disease, and 4% to 8% have an underlying adenocarcinoma** (44). **When the anal mucosa is involved, there is usually an underlying rectal adenocarcinoma** (44,45 and 46).

Clinical Features The disease predominantly affects postmenopausal white women, and the presenting symptoms are usually pruritus and vulvar soreness. **The lesion has an eczematoid appearance macroscopically and usually begins on the hair-bearing portions of the vulva.** It may extend to involve the mons pubis, thighs, and buttocks. Extension to involve the mucosa of the rectum, vagina, or urinary tract also has been described (45). The more extensive lesions are usually raised and velvety in appearance. Persistent weeping, which may necessitate the constant protection of a napkin, is a distressing feature of extensive Paget's disease.

Treatment **Unlike squamous cell carcinoma *in situ*, where the histologic extent of disease usually correlates closely with the macroscopic lesion, Paget's disease usually extends well beyond the gross lesion** (47). This results in positive surgical margins and frequent local recurrence unless a wide local excision is performed. It is desirable to check the surgical margins with frozen sections to ensure complete removal of the disease (46). **Underlying adenocarcinomas are usually clinically apparent, but this is not invariable. In addition, Paget's cells may invade the underlying dermis, and therefore the underlying dermis should be removed for adequate histologic evaluation.** For this reason, laser therapy is unsatisfactory for primary Paget's disease. If an underlying invasive carcinoma is present, it should be treated in the same manner as a squamous vulvar cancer. This usually requires radical vulvectomy and at least an ipsilateral inguinofemoral lymphadenectomy.

The disease is characterized by local recurrences over many years (48,49). **Recurrent lesions are almost always *in situ*,** although there has been at least one case report of an underlying adenocarcinoma in recurrent Paget's disease (45). Investigators at the Norwegian Radium Hospital have recently demonstrated that nondiploid tumors have an increased risk of recurrence regardless of surgical radicality (50). In general, it is reasonable to treat recurrent lesions with surgical excision or laser therapy.

Invasive Vulvar Cancer

Squamous Cell Carcinoma

Squamous cell carcinoma of the vulva is predominantly a disease of postmenopausal women, with a mean age at diagnosis of approximately 65 years.

Clinical Features

Most patients present with a vulvar lump or mass, although there is often a long history of pruritus, usually associated with a vulvar dystrophy. Less common presenting symptoms include vulvar bleeding, discharge, or dysuria. Occasionally a large metastatic mass in the groin may be the initial presenting symptom, although this is much less common than in the past because women are now more likely to present with earlier-stage disease.

On physical examination, the lesion is usually raised and may be fleshy, ulcerated, leukoplakic, or warty in appearance. **There is an increasing incidence of warty carcinoma of the vulva, and such lesions account for approximately 20% of all cases** (51). These warty carcinomas may occur at any age after adolescence and are multifocal in approximately one third of the cases (51). They are often initially diagnosed as condylomata acuminata.

Most squamous carcinomas of the vulva occur on the labia majora, but the labia minora, clitoris, and perineum also may be primary sites. Approximately 10% of the cases are too extensive to determine a site of origin, and approximately 5% of the cases are multifocal.

As part of the clinical assessment, the groin lymph nodes should be evaluated carefully and a complete pelvic examination performed. A Papanicolaou smear should be taken from the cervix, and **colposcopy of the cervix and vagina should be performed because of the common association with other squamous intraepithelial neoplasms of the lower genital tract.**

Diagnosis

Diagnosis requires a wedge biopsy specimen, which usually can be taken in the office with the patient under local anesthesia. The biopsy specimen should include some surrounding skin and some underlying dermis and connective tissue so that the pathologist can adequately evaluate the depth and nature of the stromal invasion. It is preferable to leave the primary lesion *in situ*, if possible, to allow the treating surgeon to fashion adequate surgical margins.

Physician delay is a common problem in the diagnosis of vulvar cancer, particularly if the lesion has a warty appearance. Although isolated condylomata do not require histologic confirmation for diagnosis, **any confluent warty lesion should be adequately biopsied before medical or ablative therapy is initiated.**

Routes of Spread

Vulvar cancer spreads by the following routes:

1. **Direct extension,** to involve adjacent structures such as the vagina, urethra, and anus
2. **Lymphatic embolization** to regional lymph nodes
3. **Hematogenous spread** to distant sites, including the lungs, liver, and bone

Lymphatic metastases may occur early in the disease. Initially, spread is usually to the inguinal lymph nodes, which are located between Camper's fascia and the fascia lata (9). From these superficial groin nodes, the disease spreads to the femoral nodes, which are located medial to the femoral vein (Fig. 13.1). *Cloquet's node*, situated beneath the inguinal ligament, is the most cephalad of the femoral node group. **Metastases to the femoral nodes without involvement of the inguinal nodes have been reported**(52,53,54 and 55).

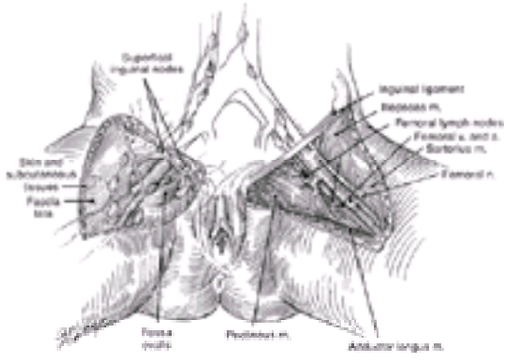

Figure 13.1 Inguinal-femoral lymph nodes.(Reproduced from Hacker NF. Vulvar cancer. In: Hacker NF, Moore JG, eds. *Essentials of obstetrics and gynecology*,3rd ed. Philadelphia: WB Saunders, 1998:675, with permission.)

From the inguinofemoral nodes, the cancer spreads to the pelvic nodes, particularly the external iliac group. **Although direct lymphatic pathways from the clitoris and Bartholin gland to the pelvic nodes have been described, these channels seem to be of minimal clinical significance** (12,56, 57).

Since 1970, the overall incidence of lymph node metastases is reported to be approximately 30% (Table 13.2). This incidence is much lower than the 61% reported by Way (6) in 1960 and reflects the trend toward earlier diagnosis and smaller lesions. The incidence of nodal metastases is related to lesion size, stage of disease, and depth of invasion. The incidence in relation to lesion size is as follows: 1 cm or less, 5%; 1 to 2 cm, 16%; 2 to 4 cm, 33%; greater than 4 cm, 53% (64). The incidence in relation to clinical stage of disease is shown in Table 13.3, and that in relation to depth of invasion is shown in Table 13.4.

Author	*No. of Cases*	*Positive Nodes*	*Percent*
Rutledge et al., 1970 (58)	110	40	36.4
Creen et al., 1978 (59)	142	54	38.0
Krupp and Bohm, 1978 (60)	195	40	20.5
Benedet et al., 1979 (61)	120	34	28.3
Curry et al., 1980 (12)	191	57	29.8
Iversen et al., 1980 (62)	268	86	32.1
Hacker et al., 1983 (13)	113	31	27.4
Podratz et al., 1983 (63)	175	59	33.7
Monaghan and Hammond, 1984 (14)	134	37	27.6
Total	1448	438	30.2

Table 13.2 Incidence of Lymph Node Metastases in Operable Vulvar Cancer

Stage	*No. of Cases*	*Positive Nodes*	*Percent*
I	140	15	10.7
II	145	38	26.2
III	137	88	64.2
IV	18	16	88.9

Data compiled from Creen, 1978 (59); Iversen et al., 1980 (62); and Hacker et al., 1983 (13).

Table 13.3 Incidence of Lymph Node Metastases in Relation to Clinical Stage of Disease

Depth of Invasion	*No.*	*Positive Nodes*	*Nodes*
<1 mm	163	0	0
1.1–2 mm	145	11	7.6
2.1–3 mm	131	11	8.4
3.1–5 mm	101	27	26.7
>5 mm	38	13	34.2
Total	578	62	10.7

Data compiled from Parker et al., 1975 (53); Magrina et al., 1979 (65); Iversen et al., 1981 (7); Wilkinson et al., 1982 (66); Hoffman et al., 1983 (67); Hacker et al., 1984 (13); Boice et al., 1984 (68); Ross and Ehrmann, 1987 (69); Rowley et al., 1988 (70); Shiraki et al., 1989 (71).

Table 13.4 Nodal Status in T_1 Squamous Cell Carcinoma of the Vulva Versus Depth of Stromal Invasion

Table 13.4 Nodal Status in T_1 Squamous Cell Carcinoma of the Vulva Versus Depth of Stromal Invasion

Metastases to pelvic nodes are uncommon, the overall reported frequency being approximately 9% (72). Pelvic nodal metastases are rare in the absence of clinically suspicious (N_2) groin nodes (13) and three or more positive groin nodes (12,13,62). **Approximately 20% of patients with positive groin nodes have positive pelvic nodes** (72).

Hematogenous spread usually occurs late in the course of vulvar cancer and is rare in the absence of lymph node metastases. Hematogenous spread is uncommon in patients with one or two positive groin nodes, but is more common in patients with three or more positive nodes (13).

Staging

A clinical staging system based on the TNM classification was adopted by the International Federation of Gynecology and Obstetrics (FIGO) in 1969 (Table 13.5). The staging was based on a clinical evaluation of the primary tumor and regional lymph nodes and a limited search for distant metastases.

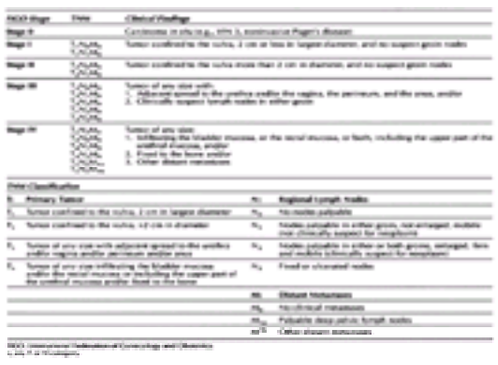

Table 13.5 Clinical Staging of Carcinoma of the Vulva

Clinical evaluation of the groin lymph nodes is inaccurate in approximately 25% to 30% of the cases (6,14,73). Microscopic metastases may be present in nodes that are not clinically suspicious, and suspicious nodes may be enlarged because of inflammation only. **Compared with surgical staging of vulvar cancer, the percentage of error in clinical staging increases from 18% for stage I disease to 44% for stage IV disease**(74).

These factors led the Cancer Committee of FIGO to introduce a surgical staging for vulvar cancer in 1988. Various modifications have been made, with a subdivision of stage I in 1994. The current FIGO staging is shown in Table 13.6. Most available data are still based on the 1969 FIGO staging, which is appropriate because the new staging system requires further modification. There are two major problems with the staging system as currently proposed. First, patients with negative lymph nodes have a very good prognosis, regardless of the size of the primary tumor (13,74), so the survival rate for both stages I and II should be better than 80%. Second, survival depends on the number of positive lymph nodes (12,13,63,74). Therefore, stage III represents a very heterogeneous group of patients, ranging from those with negative nodes and involvement of the distal urethra or vagina, who should have an excellent prognosis, to those with multiple positive groin nodes, who have a very poor prognosis.

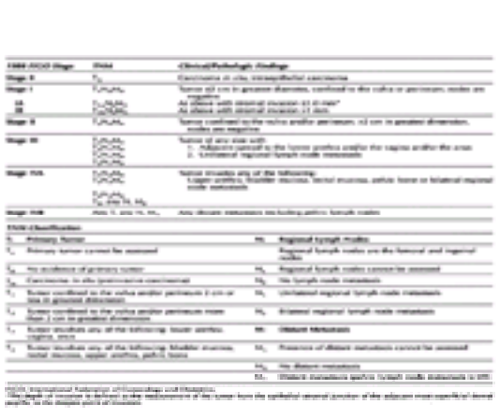

Table 13.6 FIGO Staging for Vulvar Cancer (1994)

Treatment

After the pioneering work of Taussig (5) in the United States and Way (3,6) in Great Britain, ***en bloc*** **radical vulvectomy and bilateral dissection of the groin and pelvic nodes became the standard treatment for most patients with operable vulvar cancer.** If the disease involved the anus, rectovaginal septum, or proximal urethra, some type of pelvic exenteration was combined with this dissection.

Although the survival rate improved markedly with this aggressive surgical approach, **several factors have led to modifications of this "standard" treatment plan during the past 20 years.** These factors may be summarized as follows:

1. **The disease is occurring in younger women, who are presenting with smaller tumors.** Up to 50% of patients in many centers have T_1 lesions. Jones et al. (75) retrospectively reviewed two cohorts of women with squamous carcinoma of the vulva in New Zealand. Only 1 of 56 patients (1.8%) seen between 1965 and 1974 was younger than 50 years, whereas 12 of 57 women (21%) seen between 1990 and 1994 were in the younger age group ($p = 0.001$). The younger women had significantly more basaloid or warty VIN associated with invasive carcinoma ($p = 0.001$), and cigarette smoking and multiple lower genital tract neoplasia were also more commonly seen ($p = 0.001$).
2. **There has been concern about the postoperative morbidity and associated long-term hospitalization common with the *en bloc* radical dissection.**
3. **There has been an increasing awareness of the psychosexual consequences of radical vulvectomy.**

Modern management of vulvar cancer requires an experienced, multidisciplinary team approach, which is available only in tertiary referral centers. The shortcomings of treatment in nonreferral units were highlighted in two community-based European studies.

In the British study, investigators retrospectively reviewed the records of 411 patients with squamous cell carcinoma who had been notified to the Central Intelligence Unit of the West Midlands during two 3-year periods; 1980 to 1982 and 1986 to 1988 (76). The women were treated at 35 different hospitals, 16 of which averaged one case or less per year.

Fifteen different operations were used, the most common of which were simple vulvectomy (35%) and radical vulvectomy with bilateral inguinal lymphadenectomy (34%). Hemivulvectomy was performed in only five patients (1.2%). Management of the lymph nodes was equally inappropriate. Only 190 of the 411 patients (46%) had a lymphadenectomy performed, and a unilateral dissection was performed in only 9 patients (2.1%).

Survival data for all FIGO stages compared unfavorably with the Gynecologic Oncology Group (GOG) data from tertiary units in the United States (74): 78% versus 98% for stage I disease; 53% versus 85% for stage II; 27% versus 74% for stage III; and 13% versus 31% for stage IV. Omission of lymphadenectomy was the single most important prognostic factor, but treatment in a hospital with less than 20 cases in total was a poor prognostic factor in univariate analysis.

A similar experience was reported from The Netherlands (77). As in the British study, older patients tended not to be referred to gynecologic oncology units, and 80% of patients in the community hospitals had omission of groin node dissection.

Management of Early Vulvar Cancer (T_1 N_0 or N_1)

The modern approach to the management of patients with T_1 carcinoma of the vulva should be individualized (7,8). There is no "standard" operation applicable to every patient, and emphasis is on performing the most conservative operation consistent with cure of the disease.

In considering the appropriate operation, it is necessary to determine independently the appropriate management of:

1. **The primary lesion**
2. **The groin lymph nodes**

Before any surgery, all patients should have colposcopy of the cervix, vagina, and vulva because preinvasive (and rarely invasive) lesions may be present at other sites along the lower genital tract.

Management of the Primary Lesion **The two factors to take into account in determining the management of the primary tumor are:**

1. **The condition of the remainder of the vulva**
2. **The patient's age**

Although radical vulvectomy has been regarded as the standard treatment for the primary vulvar lesion, this operation is associated with significant disturbances of sexual function and body image. DiSaia et al. (9) regarded psychosexual disturbance as the major long-term morbidity associated with the treatment of vulvar cancer. Andersen and Hacker (78) reported that sexual arousal was reduced to the 8th percentile and body image to the 4th percentile in women who had undergone vulvectomy compared with healthy adult women.

Since the early 1980s, several investigators have advocated a radical local excision rather than a radical vulvectomy for the primary lesion in patients with T_1 tumors (7,8,9,10 and 11, 72). Traditionally, vulvar cancer has been considered to be a "diffuse disease involving the entire vulva" (28). Anything less than radical vulvectomy has been considered inadequate local treatment that is likely to result in local recurrence. In addition, there has been concern that without an *en bloc* resection, intervening tissue left between the primary tumor and the regional lymph nodes may contain microscopic tumor foci in draining lymphatics. However, squamous carcinomas spread by embolization, not permeation (79), and experience with a separate incision technique for node dissection has confirmed that metastases rarely occur in the skin bridge in patients without clinically suspicious (N_2) nodes in the groin (18).

Regardless of whether a radical vulvectomy or a radical local excision is performed, the surgical margins adjacent to the tumor are the same, and an analysis of the available literature indicates that the incidence of local invasive recurrence after radical local excision is not higher than that after radical vulvectomy (Table 13.7). This suggests that in the presence of an otherwise normal-appearing vulva, radical local excision is a safe surgical option regardless of the depth of invasion. Local recurrences do occur, but reflect the biologic behavior of the disease, not the inadequacies of the surgical resection. Many occur quite remotely from the primarylesion, and should probably be regarded as second primary lesions.

	No.	Recurrence[a]	Dead of Disease
Radical local excision	165	12 (7.2%)	1 (0.6%)
Radical vulvectomy	365	23 (6.3%)	2 (0.5%)

[a] $p = 0.85$.

Data compiled from Parker et al., 1975 (53); DiSaia et al., 1979 (9); Iversen et al., 1981 (7); Wilkinson et al., 1982 (66); Chu et al., 1982 (82); Hacker et al., 1984 (8); Boice et al., 1984 (68); Ross and Ehrmann, 1987 (69); Rowley et al., 1988 (70); Berman et al., 1985 (83); Struijk et al., 1988 (71).

Only in papers 7, 8, and 66 are all patients with T_1 lesions included. In the other papers, some type of selection was made (e.g., only tumors with ≤5 mm of invasion, only unilocal lesions, only tumors ≤3 cm in diameter). Length of follow-up ranged from >12 months (71) to >43 months (68).

Table 13.7 Incidence of Local Invasive Recurrence after Radical Local Excision and Radical Vulvectomy for T_1 Squamous Cell Carcinoma of the Vulva

Table 13.7 Incidence of Local Invasive Recurrence after Radical Local Excision and Radical Vulvectomy for T_1 Squamous Cell Carcinoma of the Vulva

A review of 135 patients from the University of California, Los Angeles (UCLA) with all stages of disease revealed that a 1-cm tumor-free surgical margin on the vulva resulted in a very high rate of local control (82). Neither clinical tumor size nor the presence of coexisting benign vulvar disease correlated with local invasive recurrence.

When vulvar cancer arises in the presence of VIN or some nonneoplastic epithelial disorder, treatment is influenced by the patient's age. Elderly patients who have often had many years of chronic itching are not usually disturbed by the prospect of a radical vulvectomy. In younger women, it is desirable to conserve as much of the vulva as possible; thus, radical local excision should be performed for the invasive disease and the associated disease should be treated in the most appropriate manner. For example, topical steroids may be required for squamous hyperplasia, whereas VIN may require superficial local excision and primary closure.

Radical local excision is most appropriate for lesions on the lateral or posterior aspects of the vulva (Fig. 13.2), where preservation of the clitoris is feasible. For anterior lesions that involve the clitoris or are close to it, any type of surgical excision has psychosexual consequences, particularly in younger patients. In addition, marked edema of the posterior vulva may occur. In young patients with periclitoral lesions, consideration should be given to treating the primary lesion with a small field of radiation therapy. Small vulvar lesions respond very well to approximately 5,000 cGy external radiation, and biopsy can be performed after therapy to confirm the absence of any residual disease.

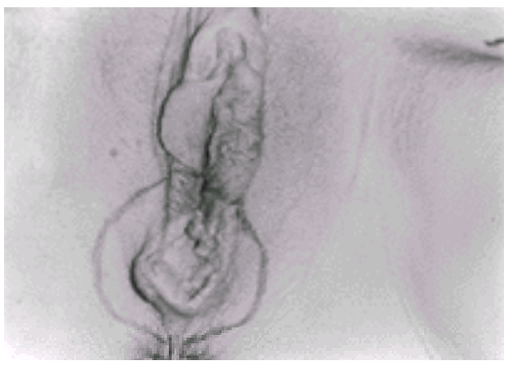

Figure 13.2 Small (T_1) vulvar carcinoma at the posterior fourchette.

Technique for Radical Local Excision Radical local excision implies a wide and deep excision of the primary tumor. The surgical margins should be at least 1 cm. The incision should be carried down to the inferior fascia of the urogenital diaphragm, which is coplanar with the fascia lata and the fascia over the pubic symphysis. The surgical defect is closed in two layers. For perineal lesions, proximity to the anus may preclude adequate surgical margins, and consideration should be given to preoperative or postoperative radiation in such cases. For periurethral lesions, the distal half of urethra may be resected without loss of continence. Figure 13.3 shows the satisfactory cosmetic result achieved in the treatment of the lesion shown in Fig. 13.2.

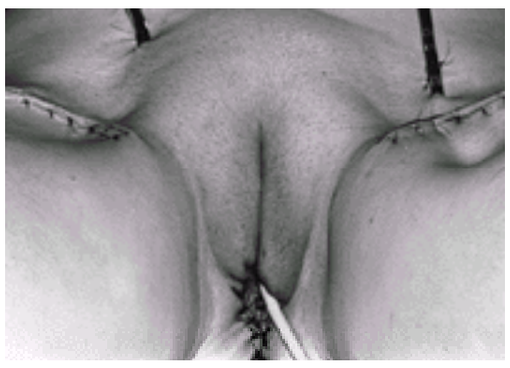

Figure 13.3 Satisfactory cosmetic result after radical local excision and bilateral groin dissection (for the small posterior vulvar carcinoma shown in Fig. 13.2).

Management of the Groin Lymph Nodes Groin dissection is associated with postoperative wound infection and breakdown and chronic leg edema. Although the incidence of wound breakdown is reduced significantly when separate incisions are used for the groin dissection (18), chronic leg edema remains a major problem.

On the basis of some early reports on clinical stage I vulvar cancer, the groin dissection was omitted in many patients with less than 5 mm of stromal invasion (53,83). However, with an increasing number of reports in the literature, two facts became apparent:

1. **The only patients without risk of lymph node metastases were those whose tumor invaded the stroma to a depth no greater than 1 mm** (Table 13.4).
2. **Patients in whom recurrent disease developed in an undissected groin had a very high mortality rate** (Table 13.8).

Author	Recurrence	Dead of Disease
Rutledge et al., 1970 (58)	4	3
Magrina et al., 1979 (65)	4	3
Hoffman et al., 1983 (67)	4	4
Hacker et al., 1584 (8)	3	3
Monaghan and Hammond, 1984 (14)	4	4
Lingard et al., 1992 (84)	7	7
Total	26	24 (92%)

Table 13.8 Death from Recurrence in an Undissected Groin

Appropriate groin dissection is the single most important factor in decreasing the mortality for early vulvar cancer. All patients with more than 1 mm of stromal invasion require inguinofemoral lymphadenectomy. A wedge biopsy specimen of the primary tumor should be obtained, and the depth of invasion should be determined. If it is less than 1 mm on the wedge biopsy specimen, the entire lesion should be locally excised and analyzed histologically to determine the depth of invasion. If there is still no invasive focus deeper than 1 mm, groin dissection may be omitted. Although an occasional patient with less than 1 mm of stromal invasion has had documented groin node metastases(85,86), the incidence is so low that it is of no practical significance.

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If groin dissection is indicated in patients with early vulvar cancer, it should be a thorough inguinofemoral lymphadenectomy. The GOG reported six groin recurrences among 121 patients with T_1 N_0 or N_1 tumors after a superficial (inguinal) dissection, even though the inguinal nodes were reported as negative (87). Whether all these recurrences were in the femoral nodes is unclear, but this larger, multiinstitutional study does indicate that modification of the groin dissection increases groin recurrences and, therefore, mortality.

From the accumulated experience now available in the literature, it is clear that **it is not necessary to perform a bilateral groin dissection if the primary lesion is unilateral** (Table 13.9), **although lesions involving the anterior labia minora should have bilateral dissection** because of the more frequent contralateral lymph flow from this region (89).

Author	Unilateral Lesions	Contalateral Nodes Positive	Percentage
Wharton et al., 1974 (83)	25	0	0
Parker et al., 1975 (53)	41	0	0
Magrina et al., 1979 (65)	77	2	2.6
Iversen et al., 1981 (7)	112	0	0
Buscema et al., 1981 (68)	38	0	0
Hoffman et al., 1983 (67)*	70	0	0
Hacker et al., 1984 (8)	60	0	0
Stuyk et al., 1989 (71)	53	0	0
Total	476	2	0.4

*Information not contained in reference but obtained from personal communication.

Table 13.9 Incidence of Positive Contralateral Nodes in Patients with Lateral T_1 Squamous Cell Vulvar Carcinomas and Negative Ipsilateral Nodes

Lymphatic Mapping In an attempt to decrease the morbidity associated with inguinofemoral lymphadenectomy, efforts have been made to identify one or more sentinel nodes in the groin. This concept was initially introduced for the management of melanomas by Morton et al. (90), **the hypothesis being that if the sentinel node is negative, all other nodes will be negative, so the patient can be spared the morbidity of full groin dissection.**

The sentinel node (or nodes) is identified by a combination of intradermal isosulfan blue dye and intradermal radioactive ^{99m}Tc-labeled sulfur colloid injected around the primary vulvar lesion, after which the node is isolated in the groin by dissection and gamma counting.

Preliminary results suggest a low false-negative rate for sentinel node identification when using the combined approach of blue dye and lymphoscintigraphy, but only a few reports are available, and the technique should be considered experimental (91, 92 and 93). However, if larger patient accrual confirms the preliminary result, significant modification of the groin dissection may be appropriate in the future.

Measurement of Depth of Invasion The Nomenclature Committee of the International Society of Gynecological Pathologists has recommended that depth of invasion should be measured from the most superficial dermal papilla adjacent to the tumor to the deepest focus of invasion. This method was originally proposed by Wilkinson et al. (67). Tumor thickness is also commonly measured (66,94), and Fu and Reagan (95) estimated that the average difference between tumor thickness and depth of invasion as determined by the Wilkinson method was 0.3 mm.

Technique for Groin Dissection A linear incision is made along the medial four-fifths of a line drawn between the anterior superior iliac spine and the pubic tubercle. Anatomic studies have demonstrated that there are no lymph nodes adjacent to the anterior superior iliac spine (96) (Fig. 13.4). The incision is carried through the subcutaneous tissues to the superficial fascia. The latter is incised and grasped with artery forceps to place it on traction, and the fatty tissue between it and the fascia lata is removed over the femoral triangle (Fig.13.5). The dissection is carried 2 cm above the inguinal ligament to include all the inguinal nodes. The saphenous vein is tied off at the apex of the femoral triangle and at its point of entry into the femoral vein. **To avoid skin necrosis, all subcutaneous tissue above the superficial fascia must be preserved.**

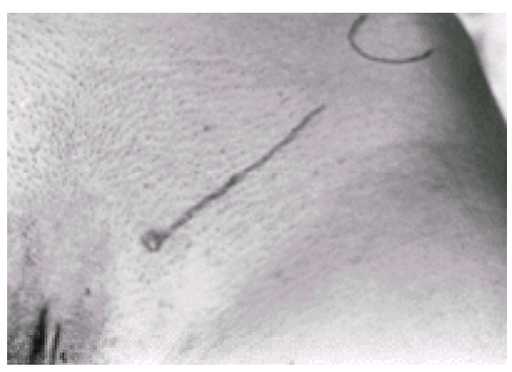

Figure 13.4 Skin incision for groin dissection through a separate incision. The incision is made along the medial four fifths of a line drawn between the anterior superior iliac spine and the pubic tubercle.

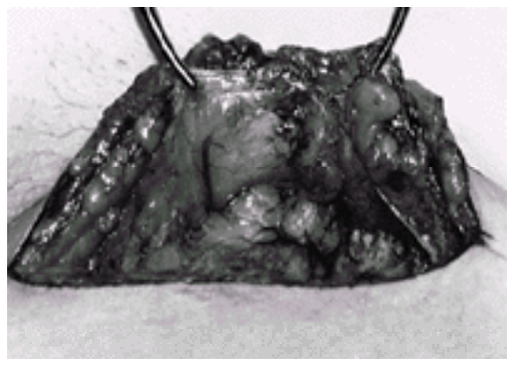

Figure 13.5 Camper's fascia kept on traction with forceps while the underlying node-bearing fatty tissue is dissected out of the femoral triangle. Note the preservation of the subcutaneous tissue above the superficial fascia. This ensures that skin necrosis will not occur.

The fatty tissue containing the femoral lymph nodes is removed from within the fossa ovalis. **There are only one to three femoral lymph nodes, and they are always situated medial to the femoral vein in the opening of the fossa ovalis** (97). Hence, there is no need to remove the fascia lata lateral to the femoral vessels and no need to perform a sartorius muscle transposition. Cloquet's node is not consistently present but should be checked for by retraction of the inguinal ligament cephalad over the femoral canal. At the conclusion of the

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Management of a Patient with Positive Groin Nodes No additional treatment is recommended if one microscopically positive groin node is found. The prognosis for this group of patients is excellent (13), and only careful observation is required. Even if a unilateral groin dissection has been performed for a lateral lesion, there seems to be no indication for dissection of the other groin because contralateral lymph node involvement is likely only if there are multiple ipsilateral inguinal node metastases (16,98).

Management of two or more positive groin nodes, which is unusual in patients with T_1 vulvar cancer, is discussed later.

Management of Patients with T_2 and Early T_3 Tumors and N_0 or N_1 Nodes

In general, the management of patients with T_2 and early T_3 tumors consists of radical vulvectomy and bilateral inguinofemoral lymphadenectomy. If the disease involves the distal urethra or vagina, partial resection of these organs is required. Alternatively, it may be preferable to give preoperative radiation therapy to allow a less radical resection.

Two basic surgical approaches can be used:

1. **The *en bloc* approach** through a trapezoid or butterfly incision (73,99) (Fig. 13.6)

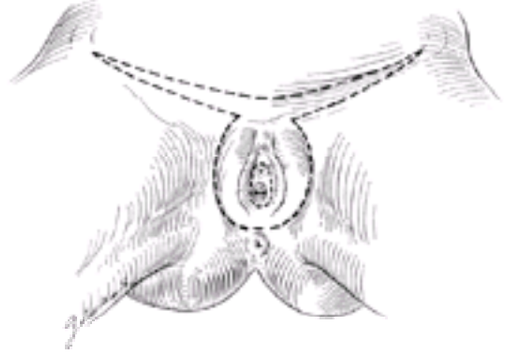

Figure 13.6 Incision used for *en bloc* radical vulvectomy and bilateral groin dissection.

2. **The separate incision approach,**involving three separate incisions, one for the radical vulvectomy and one for each groin dissection (17,18) (Fig. 13.3)

***Technique for En Bloc* Radical Vulvectomy and Groin Dissection** The operation is usually performed with the patient in the low lithotomy position, and groin and vulvar dissections can proceed simultaneously with two teams of surgeons if appropriate. The skin incision has been significantly modified from the original Stanley Way technique to allow primary skin closure. The groin dissection is accomplished initially, with the abdominal incision carried down to the aponeurosis of the external oblique muscle, approximately 2 cm above the inguinal ligament. A skin flap is raised over the femoral triangle, with preservation of the subcutaneous fat above the superficial (Camper's) fascia. The technique for groin dissection has been described earlier.

The vulvar incision is carried posteriorly along each labiocrural fold, or within a 1-cm margin of the primary lesion. The technique for vulvectomy is described in the next section.

Technique for Radical Vulvectomy If the radical vulvectomy is performed through a separate incision, the lateral incision is basically elliptical. Each lateral incision should commence on the mons pubis anteriorly and extend through the fat and superficial fascia to the fascia over the pubic symphysis. It is then easy to develop bluntly the plane immediately above the pubic symphysis and fascia lata. The skin incision is extended posteriorly along the labiocrural folds to the perianal area and carried down to the fascia lata. The medial incision is usually placed around the introitus, just anterior to the external urethral meatus. However, either incision may need to be modified to clear the primary tumor with surgical margins of at least 1 cm. If necessary, the distal half of the urethra may be resected without compromising continence. **If the tumor is close to the urethra or the vagina, dissection around the tumors is facilitated by transection of the vulva, thereby improving exposure of the involved area.**

The specimen includes the bulbocavernosus muscles and the vestibular bulb. Because of the vascularity, it is desirable to perform most of the dissection by diathermy after the initial skin incision. In addition, the vessels supplying the clitoris should be clamped and tied, as should the internal pudendal vessels posterolaterally.

Closure of Large Defects It is usually possible to close the vulvar defect without tension. However, if a more extensive dissection has been required because of a large primary lesion, a number of options are available to repair the defect. These include the following:

1. **An area may be left open to granulate,**which it usually does over a period of 6 to 8 weeks (100). This is particularly useful around the urethra, where sutures can cause urethral deviation and misdirection of the urinary stream.
2. **Full-thickness skin flaps may be devised** (101,102). An example is the rhomboid flap, which is best suited for covering large defects of the posterior vulva (103).
3. **Unilateral or bilateral gracilis myocutaneous grafts** may be developed. These are most useful when an extensive area from the mons pubis to the perianal area has been resected. Because the graft brings a new blood supply to the area, it is particularly applicable if the vulva is poorly vascularized from prior surgical resection or radiation(104).
4. **If extensive defects exist in the groin and vulva, the tensor fascia lata myocutaneous graft is applicable** (105).

The technique for these grafts is discussed in Chapter 19.

Vulvar Conservation for T_2 and Early T_3 Tumors The indications for vulvar conservation have been extended by some surgeons to selected patients with T_2 and early T_3 tumors. Although the reported experience is limited (10,11,106), a study from UCLA suggests that the local recurrence rate for patients with conservatively treated stage II tumors is identical to that for patients with stage I tumors (107) as long as surgical margins of at least 1 cm are obtained. Burke et al. (10) at the M. D. Anderson Hospital reported radical local excision for 15 T_2 tumors, the diameters of which ranged from 20 to 65 mm. With a mean follow-up of 36 months, no patient had local invasive recurrence. The tumor-free margin should be the same regardless of whether a radical vulvectomy or a radical local excision is performed, so it would seem to be both feasible and desirable to extend the indications for vulvar conservation, particularly in younger patients.

Management of the Pelvic Lymph Nodes In the past, pelvic lymphadenectomy was considered to be part of the routine surgery for invasive vulvar cancer. However, the incidence of pelvic node metastases is less than 10%, so a more selective approach is justified.

Most authors (19,58,73) suggest that pelvic lymphadenectomy should be reserved for patients with positive groin nodes. In a review of the UCLA data, Hacker et al.(13) reported that **pelvic nodal metastases did not occur unless the patient had**

1. **Clinically suspicious (N_2) groin nodes, or**
2. **Three or more positive unilateral groin nodes**

All positive pelvic nodes were located on the same side as the multiple positive groin nodes. A similar experience has been reported from the M. D. Anderson Hospital (12), the Mayo Clinic (63), and the University of Michigan (15).

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In 1977, the GOG initiated a prospective trial in which patients with positive groin nodes were randomized to either ipsilateral pelvic node dissection or bilateral pelvic plus groin irradiation (16). Radiation therapy consisted of 4,500 to 5,000 cGy to the midplane of the pelvis at a rate of 180 to 200 cGy/day. The survival rate for the radiation group (68% at 2 years) was significantly better than that for the pelvic lymphadenectomy group (54% at 2 years; $p = 0.03$). The survival advantage was limited to patients with clinically evident groin nodes or more than one positive groin node. Groin recurrence occurred in 3 of 59 patients (5.1%) treated with radiation, compared with 13 of 55 (23.6%) treated with lymphadenectomy ($p = 0.02$). Four patients who received radiation had a pelvic recurrence, compared with one who had lymphadenectomy. **These data highlight the value of prophylactic groin irradiation in preventing groin recurrence in patients with multiple positive groin nodes.**

In the 1990s, several investigators have demonstrated that the morphology of the positive groin nodes is also of prognostic significance, allowing further discrimination among patients with positive nodes. Origoni et al. (108)demonstrated that for patients with positive lymph nodes, there was a significant difference in survival depending on the size of the involved nodes and the presence or absence of extracapsular spread. **Patients whose involved nodes were less than 5 mm in diameter had a 5-year survival rate of 90.9%, compared with 41.6% for nodes 5 to 15 mm in diameter and 20.6% for nodes larger than 15 mm diameter** ($p = 0.001$). Similarly, if nodal involvement remained intracapsular, the 5-year survival rate was 85.7%, compared with 25% if there was extracapsular spread ($p = 0.001$). Similar results were obtained by the group at Gateshead, who reported that in a multivariate analysis, the only significant variables were FIGO stage (III, IVA, or IVB) and the presence or absence of extracapsular spread (109). Van der Velden et al. (110) demonstrated that **even for patients with one positive node, the presence of extracapsular spread decreased the survival rate from 88% (14 of 16 patients) to 44% (7 of 16 patients).**

From the foregoing observations, our recommendations for the management of patients with positive groin nodes are as follows:

1. **Patients with one or two micrometastases (£5 mm diameter) should be observed.**
2. **Patients with three or more micrometastases, one macrometastasis (³10 mm diameter), or any evidence of extracapsular spread should receive bilateral groin and pelvic radiation.**

Postoperative Management In spite of the age and general medical condition of most patients with vulvar cancer, the surgery is usually remarkably well tolerated. However, a postoperative mortality rate of approximately 2% can be expected, usually as a result of pulmonary embolism or myocardial infarction. Patients should be able to commence a low-residue diet on the first postoperative day. **Bed rest is advisable for 3 to 5 days to allow immobilization of the wounds to foster healing.** Pneumatic calf compression and subcutaneous heparin should be used to help prevent deep venous thrombosis, and active, non–weight-bearing leg movements are to be encouraged. Frequent wound dressings and perineal swabs are given. Suction drainage of each groin is continued for approximately 10 days to help decrease the incidence of groin seromas. A Foley catheter is left in the bladder until the patient is ambulatory. When the patient is fully mobilized, Sitz baths or whirlpool therapy are helpful, followed by drying of the perineum with a hair dryer.

Early Postoperative Complications The major immediate morbidity is related to **groin wound infection, necrosis, and breakdown,** and this has been reported in up to 85% of patients having an *en bloc* operation(63). With the separate incision approach, the incidence of wound breakdown can be reduced to approximately 44%, with major breakdown occurring in approximately 14% of patients (18). With debridement and wound dressings, the area granulates and reepithelializes over the next few weeks and may be managed with home nursing. Whirlpool therapy is effective for areas of extensive breakdown.

Other early postoperative complications include **urinary tract infection, seromas in the femoral triangle, deep venous thrombosis, pulmonary embolism, myocardial infarction, hemorrhage, and, rarely, osteitis pubis.** Seromas occur in approximately 30% of cases and seem to have become more common since introduction of the practice of leaving the fascia lata over the muscles in the floor of the femoral triangle. Significant seromas are usually best managed by making a linear incision approximately 1 cm long to allow adequate drainage. Drainage must be maintained until the skin flaps seal to the underlying tissues. Early mobilization seems to increase the incidence of seromas.

Late Complications The major late complication is **chronic leg edema,** which has been reported in up to 69% of patients (63). **Recurrent lymphangitis** or cellulitis of the leg occurs in approximately 10% of patients and usually responds to *erythromycin* tablets. **Urinary stress incontinence,** with or without **genital prolapse,** occurs in approximately 10% of patients and may require corrective surgery. **Introital stenosis** can lead to dyspareunia and may require a vertical relaxing incision, which is sutured transversely. An uncommon late complication is **femoral hernia,** which can usually be prevented during surgery by closure of the femoral canal with a suture from the inguinal ligament to Cooper's ligament. **Pubic osteomyelitis** and **rectovaginal or rectoperineal fistulas** are rare late complications.

Advanced Disease

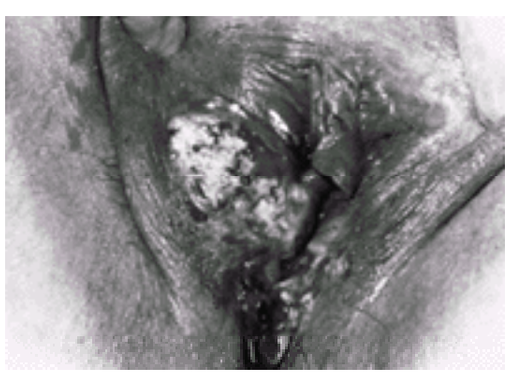
Vulvar cancer may be considered to be advanced on the basis of a large T_3 or a T_4 primary tumor or the presence of bulky, positive groin nodes. As with early vulvar cancer, management needs to be individualized.

Management of Patients with a Large T_3 or a T_4 Primary Tumor When the primary disease involves the anus, rectum, rectovaginal septum, or proximal urethra, **adequate surgical clearance of the primary tumor is possible only by pelvic exenteration combined with radical vulvectomy and bilateral groin dissection.** Such radical surgery is often inappropriate for these elderly patients, and even in suitable surgical candidates, psychological morbidity is high (78,111). In addition, the operative mortality rate is approximately 10%, and the postoperative physical morbidity is significant. Nevertheless, a 5-year survival rate of approximately 50% can be expected with this approach (112,113,114 and 115). Surgery alone is rarely curative for patients with fixed or ulcerated (N_3) groin nodes.

Radiation therapy traditionally has been considered to have a limited role in the management of patients with vulvar cancer. In the orthovoltage era, local tissue tolerance was poor and vulvar necrosis was common, but, with megavoltage therapy, tolerance has improved significantly.

Boronow (20) **was the first to suggest a combined radiosurgical approach as an alternative to pelvic exenteration for patients with advanced vulvar cancer.** In his initial report, he recommended intracavitary radium, with or without external irradiation, to eliminate the internal genital disease, and subsequent surgery, usually radical vulvectomy and bilateral groin dissection, to treat the external genital disease.

In 1984, Hacker et al. (21) reported the use of preoperative teletherapy in patients with advanced vulvar cancer; brachytherapy was reserved for patients with persistent disease that would otherwise necessitate exenteration (Fig.13.7, Fig 13.8). Rather than performing radical vulvectomy for all patients, only the tumor bed was resected, on the assumption that any microscopic foci originally present in the vulva would have been sterilized by the radiation. In specimens from one half of the patients, there was no residual disease. Long-term morbidity was low with the predominant use of teletherapy, and no patient developed a fistula. Two patients whose primary tumor was fixed to bone were long-term survivors (21).



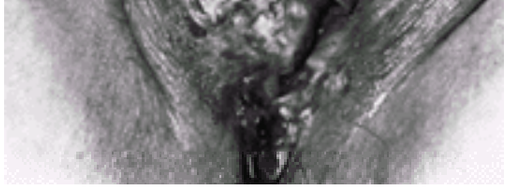


Figure 13.7 Advanced squamous cell carcinoma of the vulva involving the anal canal. A primary surgical approach would have necessitated radical vulvectomy, anoproctectomy, and permanent colostomy.

Figure 13.8 Advanced vulvar cancer shown in Figure 13.7 after 50.4 cGy of external-beam radiation therapy. Resection of the tumor bed showed microscopic residual disease. The radiation therapy prevented the need for a permanent stoma.

In 1987, Boronow et al. (116) updated their experience with preoperative radiation for locally advanced vulvovaginal cancer, reporting 37 primary cases and 11 cases of recurrent disease. The 5-year survival rate for the primary cases was 75.6%, whereas the recurrent cases had a 5-year survival rate of 62.6%. Seventeen of 40 vulvectomy specimens (42.5%) contained no residual disease. Eight patients (16.7%) had a local recurrence, and five patients (10.4%) developed a fistula.

As the experience of these investigators has evolved, their approach has been refined. They now recommend external-beam therapy for all cases, with more selective use of brachytherapy. The radicality of the surgery has also been significantly modified. A more limited vulvar resection is now advocated, and bulky N_2 and N_3 nodes are resected without full groin dissection to avoid the leg edema associated with groin dissection and radiation.

In 1989, Thomas et al. (117) reported on the use of radiation with concurrent infusional *5-fluorouracil (5-FU)*, with or without *mitomycin C*, for 33 patients with vulvar cancer. Median follow-up was 16 months. Of nine patients who received primary chemoradiation, six had an initial complete response in the vulva, but three of the six subsequently had a local recurrence.

Several subsequent studies have reported on the use of chemoradiation followed by wide excision of the tumor bed. Italian investigators reported 31 patients with locoregionally advanced vulvar cancer who were treated with a combination of *mitomycin C* and *5-FU* in combination with radiation to the vulva, groins, and pelvis. A total of 54 Gy was given, with a 2-week break after 36 Gy. The pathologic complete response rate was 36% in the vulva and 55% in the groins. The 5-year survival rate was 55% for patients treated for primary lesions and 57% for those with recurrent disease (118). A second similar Italian study of 58 patients reported a pathologic complete response rate of 31% in both the vulva and the groin (119).

The pathologic complete response rate in the vulva with these radiation doses is not greater than that seen with radiation alone, but the local acute toxicity is much greater with the addition of chemotherapy, invariably necessitating at least a 1-week break in therapy.

Cunningham et al. (120) used radiation therapy in combination with *cisplatin* (50 mg/m^2 on day 1) and 5-FU (1,000 mg/m^2/24 hours × 96 hours) during the first and last weeks of therapy. Radiation doses to the vulva and groins ranged from 50 to 65 Gy. Nine of 14 patients (64%) had a complete clinical response, and surgical excision of the primary site was not performed in these 9 patients. Only one recurrence was noted with a mean follow-up of 36 months (range, 7 to 81 months).

Leiserowitz et al. (121) omitted groin dissection after preoperatic chemoradiation with *5-FU*, with or without *cisplatin*, in 23 patients. No patient failed in the groins, but with a median radiation dose to the groins of only 36 Gy, it is difficult to believe that these results could be duplicated.

Our preference for patients with no clinically or radiologically suspicious groin nodes is to perform primary inguinofemoral lymphadenectomy through separate groin incisions. If there are negative nodes, or up to two micrometastases (£5 mm), the groins can be eliminated from the radiation fields.

With the experience now accrued, preoperative radiation, with or without concurrent chemotherapy, should be regarded as the treatment of first choice for patients with advanced vulvar cancer who would otherwise require some type of pelvic exenteration.

Management of Patients with Bulky Positive Groin Nodes In the past, such patients would have undergone a pelvic lymphadenectomy after full groin dissection. The GOG study showed the advantage of postoperative pelvic and groin irradiation in decreasing the incidence of groin recurrence and improving survival for patients with bulky, positive groin nodes (16). However, the incidence of pelvic recurrence was higher in the group receiving pelvic radiation, possibly because of the inability of external-beam therapy to sterilize bulky positive pelvic nodes. In addition, our experience is that full groin dissection combined with groin irradiation often produces quite severe leg edema.

In view of these considerations, our current approach to patients with N_2 or N_3 groin nodes is as follows:

1. **A preoperative computed tomographic (CT) scan of the pelvis is obtained** to determine whether there are any enlarged pelvic nodes.
2. **All enlarged groin nodes are removed through a separate incision approach and sent for frozen-section diagnosis.** If metastatic disease is confirmed, full lymphadenectomy is not carried out.
3. **Any enlarged pelvic nodes seen on CT scan are removed** by an extraperitoneal approach.
4. **Full pelvic and groin irradiation is given as soon as the groin incisions are healed, which is usually approximately 2 weeks.**
5. **If the frozen section reveals no metastatic disease in the removed nodes, full groin dissection is performed.**

An algorithm for the management of patients with advanced vulvar cancer is shown in Fig. 13.9.

Figure 13.9 Algorithm for the management of patients with locally advanced vulvar cancer.

Figure 13.9 Algorithm for the management of patients with locally advanced vulvar cancer.

Role of Radiation

Radiation therapy, with or without the addition of concurrent chemotherapy, is playing an increasingly important role in the management of patients with vulvar cancer. The indications for radiation therapy in patients with this disease are still evolving. At present, radiation seems to be clearly indicated in the following situations:

1. **Before surgery, in patients with advanced disease** who would otherwise require pelvic exenteration
2. **After surgery, to treat the pelvic lymph nodes and groins** in patients with more than two micrometastases, one macrometastasis, or extracapsular spread

Possible roles for radiation therapy include the following:

1. **After surgery, to help prevent local recurrence** and improve survival **in patients with involved or close surgical margins** (<5 mm) (122, 123 and 124)
2. **As primary therapy for patients with small primary tumors, particularly clitoral or periclitoral lesions** in young and middle-aged women, in whom surgical resection would have significant psychological consequences

Groin irradiation has been proposed as an alternative to groin dissection in patients with N_0 lymph nodes. The GOG reported the results of a phase III trial in which patients with T_1, T_2, or T_3 tumors and N_0 or N_1 groin nodes were randomized between surgical resection (and postoperative irradiation for patients with positive groin nodes) and primary groin irradiation (125). Patients with N_1 nodes were allowed fine-needle aspiration cytologic analysis of the nodes and exclusion from the trial if findings were positive. The study was closed prematurely because 5 of 26 patients in the groin irradiation arm of the study had recurrences in the groin. Of 23 patients undergoing groin dissection, 5 showed groin node metastases, but no groin recurrences occurred after postoperative irradiation. The dose of radiation was 5,000 cGy given in daily 200-cGy fractions to a depth of 3 cm below the anterior skin surface.

Subsequently, Koh et al. (126) reviewed pretreatment CT scans of 50 patients with gynecologic cancer to determine the distance of each femoral vessel beneath the overlying skin surface. Femoral vessel depths in these patients ranged from 2.0 to 18.5cm, with an average depth of 6.1 cm.

It is apparent that many patients in the GOG study would have been underdosed because CT scanning was not used to define the target. However, surprisingly large positive nodes, not likely to be controlled by tolerable radiation doses, may be clinically inapparent in the groin, so standard inguinofemoral lymphadenectomy should still represent the standard of care for medically fit patients.

Recurrent Vulvar Cancer

Recurrence of vulvar cancer correlates most closely with the number of positive groin nodes (13). **Patients with fewer than three positive nodes, particularly if the nodes are only microscopically involved, have a low incidence of recurrence at any site, whereas patients with three or more positive nodes have a high incidence of local, regional, and systemic recurrences** (13,16).

Local vulvar recurrences are most likely in patients with primary lesions larger than 4 cm in diameter (122) and **are usually amenable to further surgical excision,** often with a gracilis myocutaneous graft to cover the defect. If this is the only site of recurrence, most patients can be salvaged (18,127).

Radiation therapy, particularly a combination of external-beam therapy plus interstitial needles, has also been used to treat vulvar recurrences. Hoffman et al. (128) reported on ten patients treated in this manner, and nine were still alive with a mean follow-up of 28 months. However, six of the ten had severe radionecrosis at a median of 8.5 months after radiation, and the authors concluded that although this treatment was highly effective, it was also highly morbid.

Regional and distant recurrences are difficult to manage (122). Radiation therapy may be used with surgery for groin recurrence, whereas chemotherapeutic agents that have activity against squamous carcinomas may be offered for distant metastases. The most active agents are *cisplatin, methotrexate, cyclophosphamide (Cytoxan), bleomycin*, and *mitomycin C*, but response rates are low and the duration of response is usually disappointing. Long-term survival is very uncommon with regional or distant recurrence (122).

Prognosis

With appropriate management, the prognosis for vulvar cancer is generally good, the overall 5-year survival rate in operable cases being approximately 70%. Survival correlates with the FIGO clinical stage of disease (Table 13.10) and also with lymph node status. **Patients with negative lymph nodes have a 5-year survival rate of approximately 90%** (Table 13.11), **but this falls to approximately 50% for patients with positive nodes** (Table 13.12).

Clinical FIGO Stage	No.	Dead of Disease	Corrected 5-Year Survival (%)
I	376	36	90.4
II	310	71	77.1
III	238	116	51.3
IV	111	91	18.0
Total	1,035	314	69.7

FIGO, International Federation of Gynecology and Obstetrics.
Data compiled from Rutledge et al., 1970 (58), Boutselis, 1972 (129), Morley, 1976 (73), Lagasse et al., 1977 (130), Benedet et al., 1979 (61), Hacker et al., 1983 (13), Cavanagh et al., 1986 (131).

Table 13.10 Five-Year Survival Rate Versus Stage for Patients Treated with Curative Intent

Author	No.	Dead of Disease	5-Year Survival (%)
Rutledge et al., 1970 (58)	53	0	100.0
Morley, 1976 (73)	118	9	92.4
Green, 1978 (59)	63	3	95.2
Hacker et al., 1983 (13)	82	5	93.9
Podratz et al., 1983 (63)	115	12	90.0
Monaghan and Hammond, 1984 (14)	95	9	90.5
Cavanagh et al., 1986 (131)	96	16	83.3
Total	622	54	91.3

Table 13.11 Five-Year Survival Rate for Patients with Negative Lymph Nodes

Author	No.	Dead of Disease	5-Year Survival (%)
Rutledge et al., 1970 (58)	28	15	46.4
Morley, 1976 (73)	62	38	38.7
Green, 1978 (59)	46	18	60.9
Benedet et al., 1979 (61)	34	16	52.9
Curry et al., 1980 (12)	52	30	42.3
Hacker et al., 1983 (13)	31	10	67.7
Cavanagh et al., 1986 (131)	58	36	37.9
Total	311	163	47.6

Table 13.12 Five-Year Survival Rate for Patients with Positive Lymph Nodes Treated with Curative Intent

The GOG staged 588 patients with vulvar cancer by the new criteria and reported 5-year survival rates of 98%, 85%, 74%, and 31% for stages I, II, III, and IV, respectively(74).

The number of positive groin nodes is the single most important prognostic variable (13,15,16,63). Patients with one microscopically positive node have a good prognosis, regardless of the stage of disease (13,15), but patients with three or more positive nodes have a poor prognosis. Because the number of positive nodes correlates with the clinical status of the groin nodes (13), survival also correlates significantly with this variable. In the GOG study, patients with N_0 or N_1 nodes had a 2-year survival rate of 78%, compared with 52% for patients with N_2 nodes and 33% for patients with N_3 nodes ($p = 0.01$) (16). Extracapsular spread is a poor prognostic factor (108, 109 and 110). **The survival rate for patients with positive pelvic nodes is approximately 11% (72).**

Workers at the Norwegian Radium Hospital evaluated DNA ploidy for its prognostic significance in 118 squamous cell carcinomas of the vulva (132). The 5-year crude survival rate was 62% for the diploid and 23% for the aneuploid tumors ($p < 0.001$). Aneuploid tumors without lymph node metastases had a 5-year cancer-related survival rate of 44%, compared with 58% for the diploid tumors with lymph node metastases. In a multivariate Cox regression analysis, the most important independent prognostic parameters were:

1. Lymph node involvement (p <0.0001)
2. Tumor ploidy ($p = 0.0001$), and
3. Tumor size ($p = 0.0039$)

Melanoma

Vulvar melanomas are rare, although they are the second most common vulvar malignancy. Most arise *de novo* (133), but they may arise from a preexisting junctional nevus. **They occur predominantly in postmenopausal white women, most commonly on the labia minora or the clitoris** (Fig. 13.10). The incidence of cutaneous melanomas worldwide is increasing significantly.

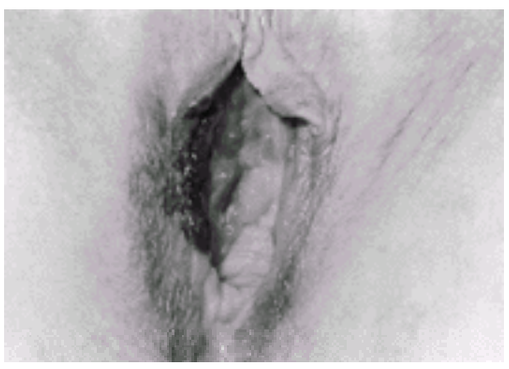


Figure 13.10 Melanoma of the vulva involving the right labium minus.

Most patients with a vulvar melanoma have no symptoms except for the presence of a pigmented lesion that may be enlarging. Some patients have itching or bleeding, and a few present with a groin mass. Amelanotic varieties occasionally occur. **Any pigmented lesion on the vulva should be excised or sampled for biopsy, unless it is known to have been present and unchanged for some years.**

There are three basic histologic types. The most common is the **superficial spreading melanoma,** which tends to remain relatively superficial early in its development. The **lentigo maligna melanoma** is a flat freckle, which may become quite extensive but also tends to remain superficial. The most aggressive lesion is the **nodular melanoma,** which is a raised lesion that penetrates deeply and may metastasize widely.

Staging

The FIGO staging used for squamous lesions is not applicable for melanomas because these lesions are usually much smaller and the prognosis is related to the depth of penetration rather than to the diameter of the lesion (134,135 and 136). The leveling system established by Clark et al. (137) for cutaneous melanomas is less readily applicable to vulvar lesions because of the different skin morphology. Chung et al. (134) proposed a modified system that retained Clark's definitions for levels I and V but arbitrarily defined levels II, III, and IV, using measurements in millimeters. Breslow (138) measured the thickest portion of the melanoma from the surface of intact epithelium to the deepest point of invasion. A comparison of these systems is shown in Table 13.13.

	Clark's Levels (137)	Chung et al. (134)	Breslow (138)
I	Intraepithelial	Intraepithelial	<0.76 mm
II	Into papillary dermis	≤1 mm from granular layer	0.76–1.50 mm
III	Filling dermal papillae	1.1–2 mm from granular layer	1.51–2.25 mm
IV	Into reticular dermis	>2 mm from granular layer	2.26–3.0 mm
V	Into subcutaneous fat	Into subcutaneous fat	>3 mm

Table 13.13 Microstaging Of Vulvar Melanomas

Treatment

With better understanding of the prognostic significance of the microstage, some individualization of treatment has developed. **Lesions with less than 1 mm of invasion may be treated with radical local excision alone** (134,135). Traditionally, for more invasive lesions, *en bloc* resection of the primary tumor and regional groin nodes has been performed. In line with trends toward more conservative surgery for cutaneous melanomas (139,140), **there is a trend toward more conservative resection for vulvar melanomas** (141, 142 and 143). Although it would be impossible ever to conduct a randomized study of radical vulvectomy versus radical local excision for melanoma of the vulva, there is no evidence to show that the biologic behavior of vulvar melanomas differs from that of other primary cutaneous melanomas(144).

Davidson et al. (142) reported on 32 patients with vulvar melanoma who underwent local excision (n = 14), simple vulvectomy (n = 7), or radical resection (n = 11). No group had a superior survival, although the overall survival rate at 5 years was only 25%. Trimble et al. (143) reported on 59 patients who underwent radical vulvectomy and 19 who underwent more conservative resections. Survival was not improved by the more radical approach, and they recommended radical local excision for the primary tumor, with groin dissection for tumors thicker than 1 mm.

The advisability of groin node dissection has been controversial, but **the Intergroup Surgical Melanoma Program has conducted a prospective, multiinstitutional, randomized trial of elective lymph node dissection versus observation for intermediate thickness cutaneous melanomas** (1 to 4 mm) (145). There were 740 patients entered into the trial, and **elective lymph node dissection resulted in a significantly better 5-year survival rate for** the 522 **patients 60 years of age or younger** (88% vs. 81%; $p = 0.04$), the 335 **patients with tumors 1 to 2 mm thick** (96% vs. 86%; $p = 0.02$), the 403 **patients without tumor ulceration** (95% vs. 84%; $p = 0.01$), and the 284 **patients with tumors 1 to 2 mm thick and no ulceration** (97% vs. 87%; $p = 0.005$).

Pelvic node metastases do not occur in the absence of groin node metastases (146, 147 and 148). In addition, the prognosis for patients with positive pelvic nodes is so poor that there appears to be no value in performing pelvic lymphadenectomy for this disease.

As melanomas commonly involve the clitoris and labia minora, the vaginourethral margin of resection is a common site of failure, and care should be taken to obtain an adequate “inner” resection margin (146). Podratz et al.(136) demonstrated a 10-year survival rate of 61% for lateral lesions, compared with 37% for medial lesions ($p = 0.027$).

Interferon alfa-2b (IFN-a-2b) **is the first agent to show significant value as an adjuvant in a randomized, controlled trial** (149). The Eastern Cooperative Oncology Group entered 287 patients onto an adjuvant trial of IFN-a-2b after surgery for deep primary (>4 mm) or regionally metastatic melanoma. With a median follow-up of 6.9 years, there was a significant prolongation of relapse-free and overall survival for the group receiving interferon. The proportion of patients who remained disease free also improved from 26% to 37%.

Chemotherapy for vulvar melanoma is disappointing. Estrogen receptors have been demonstrated in human melanomas (150), and occasional responses to *tamoxifen* have been reported (151,152).

Prognosis

The behavior of melanomas can be quite unpredictable, but the overall prognosis is poor. **The mean 5-year survival rate for reported cases of vulvar melanoma ranges from 21.7%** (133) **to 54%** (136). Patients with lesions invading to 1 mm or less have an excellent prognosis, but as depth of invasion increases, prognosis worsens. Chung et al. (134) reported a corrected 5-year survival rate of 100% for patients with level II lesions, 40% for level III or IV lesions, and 20% for level V lesions. Tumor volume has been reported to correlate with prognosis, with patients whose lesion has a volume under 100 mm^3 having an excellent prognosis (148). DNA ploidy and angioinvasion have been shown to be independent prognostic factors for disease-free survival(153).

Bartholin Gland Carcinoma

Primary carcinoma of the Bartholin gland accounts for approximately 5% of vulvar malignancies. Because of its rarity, individual experience with the tumor is limited and recommendations for management must be based on literature reviews(56,154).

The bilateral Bartholin glands are greater vestibular glands situated posterolaterally in the vulva. Their main duct is lined with stratified squamous epithelium, which changes to transitional epithelium as the terminal ducts are reached. Because tumors may arise from the gland or the duct, a variety of histologic types may occur, including adenocarcinomas, squamous carcinomas, and, rarely, transitional cell, adenosquamous, and adenoid cystic carcinomas.

Classification of a vulvar tumor as a Bartholin gland carcinoma has typically required that it fulfill **Honan's criteria,** which are:

1. **The tumor is in the correct anatomic position**
2. **The tumor is located deep in the labium majus**
3. **The overlying skin is intact**
4. **There is some recognizable normal gland present**

Strict adherence to these criteria results in underdiagnosis of some cases. Large tumors may ulcerate through the overlying skin and obliterate the residual normal gland. Although transition between normal and malignant tissue is the best criterion, some cases are diagnosed on the basis of their histologic characteristics and anatomic location.

A history of preceding inflammation of the Bartholin gland may be obtained in approximately 10% of patients, and malignancies may be mistaken for benign cysts or abscesses. Hence, **delay of diagnosis is common, particularly in premenopausal patients.** The differential diagnosis of any pararectovaginal neoplasm should include cloacogenic carcinoma and secondary neoplasm (154).

The **adenoid cystic variety** accounts for approximately 10% of Bartholin gland carcinomas. It is **a slow-growing tumor with a marked propensity for perineural and local invasion.** The perineural infiltration is quite characteristic and may account for the pruritus and burning sensation that many patients experience long before a palpable mass is evident (155).

Treatment

Traditionally, treatment has been by radical vulvectomy, with bilateral groin and pelvic node dissection (156). However, there seems to be no indication for dissection of the pelvic nodes in the absence of positive groin nodes, and Copeland et al.(154) at the M. D. Anderson Hospital have reported good results with hemivulvectomy or radical local excision for the primary tumor. Because these lesions are deep in the vulva, extensive dissection is required in the ischiorectal fossa, and, even then, surgical margins are often close. **Postoperative radiation to the vulva decreased the likelihood of local recurrence** in Copeland and colleagues' series from 27% (6 of 22) to 7% (1 of 14). If the ipsilateral groin nodes are positive, bilateral groin and pelvic radiation may decrease regional recurrence. If the tumor is fixed to the inferior pubic ramus or involves adjacent structures, such as the anal sphincter or rectum, preoperative radiation is preferable to avoid exenterative surgery and permanent colostomy.

Radical local excision is also the treatment of choice for the primary lesion with adenoid cystic carcinomas, and adjuvant radiation is recommended for positive margins or perineural invasion.

Prognosis

Because of the deep location of the gland, cases tend to be more advanced than squamous carcinomas at the time of diagnosis, but stage for stage, the prognosis is similar.

Adenoid cystic tumors are less likely to metastasize to lymph nodes and carry a somewhat better prognosis. Late recurrences may occur in the lungs, liver, or bone, so 10- and 15-year survival rates are more appropriate when evaluating therapy (157). The slowly progressive nature of these tumors is reflected in the disparity between progression-free interval and survival curves (158).

Other Adenocarcinomas

Adenocarcinomas of the vulva usually arise in a Bartholin gland or occur in association with Paget's disease. They **may rarely arise from the skin appendages, paraurethral glands, minor vestibular glands, aberrant breast tissue, endometriosis, or a misplaced cloacal remnant** (95).

A particularly aggressive type is the *adenosquamous carcinoma.* This tumor has a number of synonyms, including cylindroma, pseudoglandular squamous cell carcinoma, and adenoacanthoma of the sweat gland of Lever. **The tumor has a propensity for perineural invasion, early lymph node metastasis, and local recurrence.** Underwood et al. (159) reported a crude 5-year survival rate of 5.6% (1 of 18) for adenosquamous carcinoma of the vulva, compared with 62.3% (48 of 77)for patients with squamous cell carcinoma. Treatment should be by radical vulvectomy and bilateral groin dissection, and postoperative radiation may be appropriate.

Basal Cell Carcinoma

Basal cell carcinomas represent approximately 2% of vulvar cancers. As with other basal cell carcinomas, vulvar lesions commonly appear as a “rodent ulcer” with rolled edges, although nodules and macules are other morphologic varieties. Most lesions are smaller than 2 cm in diameter and are usually situated on the anterior labia majora. Giant lesions occasionally occur(160). Basal cell carcinomas usually affect postmenopausal white women, with a mean age of 74 years in a report from Vancouver (161). **They are locally aggressive and radical local excision usually is adequate treatment.** Metastasis to regional lymph nodes has been reported but is rare (162,163 and 164). The local recurrence rate is approximately 20% (165).

Approximately 3% to 5% of basal cell carcinomas contain a malignant squamous component, the so-called **basosquamous carcinoma. These lesions are more aggressive and should be treated as squamous carcinomas** (164). **Another subtype of basal cell carcinoma is the adenoid basal cell carcinoma,** which must be differentiated from the more aggressive adenoid cystic carcinoma arising in a Bartholin gland or the skin (164).

Verrucous Carcinoma

Verrucous carcinoma is a variant of squamous cell carcinoma and has distinctive clinical and pathologic characteristics (166). Although most commonly found in the oral cavity, verrucous lesions may be found on any moist membrane composed of squamous epithelium (167).

Grossly, the tumors have a cauliflower-like appearance, and the diameter of reported lesions ranges from 1 to 15 cm (168). **Microscopically, they contain multiple papillary fronds that lack the central connective tissue core that characterizes condylomata acuminata.**The gross and microscopic features of a verrucous carcinoma are very similar to those of the *giant condyloma of Buschke-Loewenstein*, and they probably represent the same disease entity (95). Adequate biopsy from the base of the lesion is required to differentiate a verrucous carcinoma from a benign condyloma acuminatum or a squamous cell carcinoma with a verrucous growth pattern.

Clinically, verrucous carcinomas usually occur in postmenopausal women, and they are slowly growing but locally destructive lesions. Even bone may be invaded. Metastasis to regional lymph nodes is rare but has been reported (169). **Radical local excision is the basic treatment,** although if there are palpably suspicious groin nodes, these should be evaluated with fine-needle aspiration cytologic testing or excisional biopsy. Usually, enlarged nodes are due to inflammatory hypertrophy (170). If the nodes contain metastases, radical vulvectomy and bilateral inguinofemoral lymphadenectomy are indicated.

Radiation therapy is contraindicated because it may induce anaplastic transformation with subsequent regional and distant metastasis (171). Japaze et al. (170) reported a corrected 5-year survival rate of 94% for 17 patients treated with surgery alone, compared with 42% for 7 patients treated with surgery and radiation. If there is a recurrence, further surgical excision is the treatment of choice. This may occasionally necessitate some type of exenteration.

Vulvar Sarcomas

Sarcomas represent 1% to 2% of vulvar malignancies and comprise a heterogenous group of tumors. **Leiomyosarcomas** are the most common, and other histologic types include **fibrosarcomas, neurofibrosarcomas, liposarcomas, rhabdomyosarcomas, angiosarcomas, epithelioid sarcomas, and malignant schwannomas** (95). The primary treatment is wide surgical excision. Adjuvant radiation may be helpful for high-grade tumors and locally recurrent low-grade lesions (172). The overall survival rate is approximately 70%.

Leiomyosarcomas usually appear as enlarging, often painful masses, usually in the labium majus. In a review of 32 smooth muscle tumors of the vulva, Tavassoli and Norris (173)reported that recurrence was associated with three main determinants: diameter greater than 5 cm, infiltrating margins, and five or more mitotic figures per 10 high-power fields. Neoplasms with these three features should be regarded as sarcomas. The absence of one, or even all, of these features does not guarantee that recurrence will not occur (173). **Lymphatic metastases are uncommon, and radical local excision is the usual treatment.**

Epithelioid sarcomas characteristically develop in the soft tissues of the extremities of young adults but may rarely occur on the vulva. Ulbright et al.(174) described two cases and reviewed three other reports. They concluded that these tumors may mimic a Bartholin cyst, thus leading to inadequate initial treatment. They also suggested that vulvar epithelioid sarcomas behave more aggressively than their extragenital counterparts, with four of the five patients dying of metastatic disease. They suggested that **early recognition and wide excision should improve the prognosis.**

Rhabdomyosarcomas are the most common soft tissue sarcomas in childhood, and 20% involve the pelvis or genitourinary tract (175). Dramatic gains have been made in the treatment of these tumors since the late 1970s. Previously, **radical pelvic surgery was the standard approach, but results were poor. More recently, a multimodality approach has evolved and survival rates have improved significantly, with a corresponding decrease in morbidity.**

Hays et al. (176) reported the experience of the Intergroup Rhabdomyosarcoma Study I and II (1972 to 1984) with primary tumors of the female genital tract. Nine patients 1 to 19 years of age had primary vulvar tumors, and these were often regarded as a form of Bartholin gland infection before biopsy. They were all managed with chemotherapy *[vincristine, dactinomycin* ± *cyclophosphamide* ± *doxorubicin(Adriamycin)]*, with or without radiation therapy. Wide local excision of the tumor, with or without inguinofemoral lymphadenectomy, was carried out before or after the chemotherapy. Seven of the nine patients were free of disease 4 years or more from diagnosis, one patient was free of disease when lost to follow-up at 5 years, and one patient was alive with disease.

Rare Vulvar Malignancies

Other than the tumors mentioned previously, a number of malignancies more commonly seen in other areas of the body may rarely present as isolated vulvar tumors. These are described in the following sections.

Lymphomas

The genital tract may be involved primarily by malignant lymphomas, but involvement more commonly is a manifestation of systemic disease. In the lower genital tract, the cervix is most commonly involved, followed by the vulva and the vagina (95). Most patients are in their third to sixth decade of life, and approximately three fourths of the cases involve diffuse large cell or histiocytic non-Hodgkin's lymphomas. The remainder are nodular or Burkitt's lymphomas (177). **Treatment is by surgical excision followed by chemotherapy and/or radiation,** and the overall 5-year survival rate is approximately 70% (177).

Endodermal Sinus Tumor

There have been four case reports of endodermal sinus tumor of the vulva, and three of the four patients died of distant metastases (95,178). All patients were in their third decade of life, but none was treated with modern chemotherapy.

Merkel Cell Carcinoma

Merkel cell carcinomas are **primary small cell carcinomas of the skin** that resemble oat cell carcinomas of the lung. They metastasize widely and have a very poor prognosis (179,180). They should be **locally excised and treated with *cisplatin*-based chemotherapy.**

Dermatofibrosarcoma Protuberans

This is a rare, low-grade cutaneous malignancy of the dermal connective tissue that occasionally involves the vulva. It has a marked tendency for local recurrence but a low risk of systemic spread (181,182). **Radical local excision should be sufficient treatment.**

Malignant Schwannoma

Five cases of malignant schwannoma in the vulvar region have been reported. The patients ranged in age from 25 to 45 years. Four of the five were free of tumor from 1 to 9 years after radical surgery, and the fifth patient died of multiple pulmonary metastases (95).

Secondary Vulvar Tumors

Eight percent of vulvar tumors are metastatic (95). The most common primary site is the cervix, followed by the endometrium, kidney, and urethra. Most patients in whom vulvar metastases develop have advanced primary tumors at presentation, and in approximately one fourth of the patients, the primary lesion and the vulvar metastasis are diagnosed simultaneously (183).

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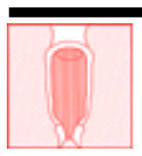

14 Vaginal Cancer

Neville F. Hacker

Primary cancer of the vagina constitutes 1% to 2% of malignant neoplasms of the female genital tract. It represents one of the most challenging therapeutic problems in gynecologic oncology, and until the late 1930s, the disease was in general considered to be incurable. In spite of the opportunity for early diagnosis with routine vaginal examinations and Papanicolaou (Pap) smears, the disease has spread beyond the vagina by the time most patients are seen. However, **with improved techniques for radiation therapy, cure rates of even advanced cases should now be comparable with those for cervical cancer** (1,2).

Fu and Reagan (3) reported that **84% of carcinomas involving the vagina were secondary, usually from the cervix (32%), endometrium (18%), colon and rectum (9%), ovary (6%), or vulva (6%).** Of 164 squamous cell carcinomas, 44 (27%) were primary and 120 (73%) were secondary. Among the latter, 95 (79%) originated from the cervix, 17 (14%) from the vulva, and 8 (7%) from the cervix and the vulva (3). This is partly related to the International Federation of Gynecology and Obstetrics (FIGO) classification and staging of malignant tumors of the female pelvis. The staging requires that a tumor that has extended to the portio and reached the area of the external os should be regarded as a carcinoma of the cervix, whereas a tumor that involves the vulva and vagina should be classified as a vulvar carcinoma. **Endometrial carcinomas and choriocarcinomas commonly metastasize to the vagina, whereas tumors from the bladder or rectum may invade the vagina directly.**

Primary Vaginal Tumors

The histologic types of primary vaginal tumor are shown in Table 14.1 (4,5,6,7,8,9,10,11,12 and 13). Squamous cell carcinomas are the most common, although adenocarcinomas, melanomas, and sarcomas are also seen. Sarcomas occasionally follow radiation therapy for cervical cancer.

Histologic Types	*Number*	*Percentage*
Squamous cell	627	83.4
Adenocarcinoma	70	9.3
Sarcoma	20	2.6
Melanoma	20	2.6
Undifferentiated	8	1.0
Small cell	5	0.7
Lymphoma	2	0.3
Carcinoid	1	0.1
Total	**753**	**100.0**

Data compiled from Perez et al., 1974 (4); Pride and Buchler, 1977 (5); Bull and Berman, 1982 (6); Houghton and Iversen, 1982 (7); Benedet et al., 1983 (8); Peters et al., 1985 (9); Rubin et al., 1988 (10); Suzuki et al., 1988 (11); Eddy et al., 1991 (12); Ali et al., 1994 (13).

Table 14.1 Primary Vaginal Cancer: Reported Incidence of Histologic Types

Squamous Cell Carcinoma

Squamous cell carcinoma is the most common vaginal cancer. The mean age of the patients is approximately 60 years, although the disease occasionally is seen in the third and fourth decades of life (2,4,7,10). Perez et al. (4) reported that 76% of patients were older than 50 years.

Etiology

The cause of squamous cell carcinoma of the vagina is unknown, although interest has focused on the association between human papillomavirus infection and multifocal carcinoma of the lower female genital tract (14). **Vaginal intraepithelial neoplasia (VAIN) has been the subject of increasing attention as a precursor of vaginal cancer** (15), **although the true malignant potential of VAIN is not known.** Benedet and Saunders (16) reviewed 136 cases of carcinoma *in situ* of the vagina seen over a 30-year period. Four cases (3%) progressed to invasive vaginal cancer in spite of various methods of treatment. Lenehan et al. (15) reported invasive vaginal cancer after treatment for VAIN in 3 of 59 patients (5%). Chronic local irritation from long-term use of a pessary may be of significance (3) (Fig. 14.1), although pessaries are used less commonly in modern gynecology.

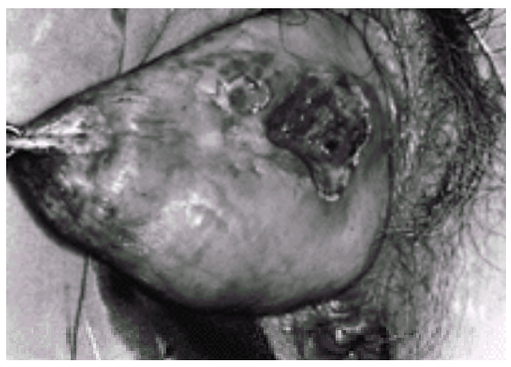

Figure 14.1 Squamous cell carcinoma of the vagina in a patient with a procidentia. The cancer was apparently related to long-term pessary use.

Up to 30% of patients with primary vaginal carcinoma have a history of *in situ* or invasive cervical cancer treated at least 5 years earlier (8,9 and 10). In a report from the University of South Carolina, a past history of invasive cervical cancer was present in 20% of the cases and of cervical intraepithelial neoplasia (CIN) in 7% (12). The median interval between the diagnosis of cervical cancer and the diagnosis of vaginal cancer was 14 years, with a range of 5 years, 8 months to 28 years. Sixteen percent of the patients had a history of prior pelvic irradiation.

There are three possible mechanisms for the occurrence of vaginal cancer after cervical neoplasia:

1. **Occult residual disease**
2. **New primary disease arising in an "at-risk" lower genital tract**
3. **Radiation carcinogenicity**

In the first instance, extension of intraepithelial neoplasia from the cervix to the upper vagina is not appreciated and an adequate vaginal cuff is not taken because vaginal colposcopy was not performed before surgical management of the cervical tumor. Surgical margins of the upper vaginal resection usually show carcinoma in situ, and these persistent foci eventually progress to invasive disease. In the second instance, vaginal colposcopy is negative and the surgical margins of resection are free of disease. In such circumstances, **any new vaginal carcinoma developing at least 5 years after the cervical cancer should be considered a new primary lesion.** Prior pelvic radiation therapy has been considered a possible cause of vaginal carcinoma (5), and this may be particularly important in young patients who live long enough to develop a second neoplasm in the irradiated vagina (17).

Screening

For screening to be cost effective, the incidence of the disease must be sufficient to justify the cost of screening. In the United States, the age-adjusted incidence of vaginal cancer is 0.6 per 100,000, making routine screening of all patients inappropriate (18). However, **women with a history of cervical intraepithelial or invasive neoplasia are at increased risk and should be followed carefully with Pap smears.**

Up to 59% of patients with vaginal cancer have had a prior hysterectomy (6), and some authors have suggested that all patients who have had a hysterectomy should be followed routinely with Pap smears (19,20). When vaginal cancer occurs in patients who have had a hysterectomy because of benign disease, it is usually more advanced at presentation (19), presumably because these patients have not been under gynecologic surveillance. However, **when age and prior cervical disease are controlled for, there is no increased risk of vaginal cancer in women who have had a hysterectomy for benign disease** (21).

Symptoms and Signs

Most patients with vaginal cancer present with painless vaginal bleeding and discharge. The bleeding is usually postmenopausal but may be postcoital. Because the bladder neck is close to the vagina, bladder pain and frequency of micturition occur earlier than with cervical cancer. Posterior tumors may produce tenesmus. Approximately 5% of patients present with pelvic pain because of extension of disease beyond the vagina, and approximately 5% to 10% of patients have no symptoms, the disease being detected on routine pelvic examination and Pap smear.

Most lesions are situated in the upper one third of the vagina, usually on the posterior wall. Macroscopically, the lesions are usually exophytic (fungating, polypoid), but they may be endophytic. Surface ulceration usually occurs late in the course of the disease.

Diagnosis

The diagnosis of carcinoma of the vagina is often missed on first examination, particularly if the lesion is small and situated in the lower two thirds of the vagina, where it may be covered by the blades of the speculum. Frick et al. (22) reported that at least 10 of 52 cases (19%) in their series were missed on initial examination. Definitive diagnosis is usually made by biopsy of a gross lesion, which can often be performed in the office without anesthesia. Particularly in elderly patients or in those with some degree of vaginal stenosis, examination while the patient is under anesthesia may be desirable to allow adequate biopsy and clinical staging. The latter may require cystoscopy or proctoscopy, depending on the location of the tumor.

In patients with an abnormal Pap smear result and no gross abnormality, careful vaginal colposcopy and the liberal use of Lugol's iodine to stain the vagina are necessary. This is performed in the office initially, but needs to be repeated with the patient under regional or general anesthesia to allow excision of colposcopically abnormal lesions. **For definitive diagnosis of early vaginal carcinoma, it may be necessary to resect the entire vaginal vault and submit it for careful histologic evaluation because the lesion may be partially buried by closure of the vaginal vault at the time of hysterectomy.** Inadvertent cystotomy may occur occasionally, and this requires immediate repair.

Hoffman et al. (23) at the University of South Florida reported on 32 patients who underwent upper vaginectomy for VAIN 3. Occult invasive carcinoma was found in nine patients (28%). In five cases, the depth of invasion was less than 2 mm, but in four cases invasion ranged from 3.5 mm to full-thickness involvement.

Staging

The FIGO staging for vaginal carcinoma is shown in Table 14.2. The staging is clinical and is based on the findings at general physical and pelvic examination, cystoscopy, proctoscopy, chest, and possible skeletal radiographs, if the latter are indicated because of bone pain.

Stage 0	Carcinoma *in situ*; intraepithelial neoplasia grade 3
Stage I	The carcinoma is limited to the vaginal wall
Stage II	The carcinoma has involved the subvaginal tissue but has not extended to the pelvic wall
Stage III	The carcinoma has extended to the pelvic wall
Stage IV	The carcinoma has extended beyond the true pelvis or has involved the mucosa of the bladder or rectum; bullous edema as such does not permit a case to be allotted to stage IV
IVA	Tumor invades bladder and/or rectal mucosa and/or direct extension beyond the true pelvis
IVB	Spread to distant organs

FIGO, International Federation of Obstetrics and Gynecology

Table 14.2 Carcinoma of the Vagina: FIGO Nomenclature

Because it is difficult to determine accurately any spread into subvaginal tissues, particularly from anterior or posterior lesions, differences in observations are common. This is reflected in the wide range of stage distributions reported and the wide range of survival within a given stage. The distribution by FIGO stage from 11 series is shown in Table 14.3 (1,2,6,7,8,9 and 10,12,13,24,25). Fewer than one third of patients present with disease confined to the vagina.

Stage	Number	Percentage
I	358	26.0
II	511	37.2
III	331	24.1
IV	175	12.7
Total	**1,375**	**100.0**

Data compiled from Ball and Berman, 1982 (6), Houghton and Iversen, 1982 (7), Benedet et al., 1983 (8), Peters et al., 1985 (9), Rubin et al., 1985 (10), Kucera et al., 1985 (24), Eddy et al., 1990 (12), Kirkbridge et al., 1995 (2), Stock et al., 1995 (25), Chyle et al., 1996 (1), Ali et al., 1996 (13).

Table 14.3 Primary Vaginal Carcinoma: Distribution by Stage of Disease

Surgical staging for vaginal cancer has been used less commonly than for cervical cancer, but in selected premenopausal patients, a pretreatment laparotomy may allow better definition of the extent of disease, excision of any grossly enlarged lymph nodes, and placement of an ovary up into the paracolic gutter beyond the radiation field.

Peters et al. (26) suggested criteria for microinvasive carcinoma of the vagina: focal invasion associated with VAIN 3, no lymph-vascular invasion, free margins on partial or total vaginectomy, and a maximum depth of invasion of less than 2.5 mm, measured from the overlying surface. However, Eddy et al. (27) reported six patients who met these criteria and were treated by either partial or total vaginectomy. In one of the six, a bladder recurrence developed at 35 months.

Patterns of Spread

Vaginal cancer spreads by the following routes:

1. **Direct extension** to the pelvic soft tissues, pelvic bones, and adjacent organs (bladder and rectum).
2. **Lymphatic dissemination** to the pelvic and later the paraaortic lymph nodes. Lesions in the lower one third of the vagina metastasize directly to the inguinofemoral lymph nodes, with the pelvic nodes being involved secondarily.
3. **Hematogenous dissemination** to distant organs, including lungs, liver, and bone. Hematogenous dissemination is a late phenomenon in vaginal cancer, and the disease usually remains confined to the pelvis for most of its course.

There is little information available on the incidence of lymph node metastases in vaginal cancer because most patients are treated with radiation therapy. Rubin et al. (10) reported that 16 of 38 patients (42.1%) with all stages of disease had lymphangiographic abnormalities, but many of these abnormalities were not confirmed histologically. Al-Kurdi and Monaghan (28) performed lymph node dissections on 35 patients and reported positive pelvic nodes in 10 patients (28.6%). Positive inguinal nodes were present in 6 of 19 patients (31.6%), with disease involving the lower vagina. Stock et al. (25) reported positive pelvic nodes in 10 of 29 patients (34.5%) with all stages of disease who underwent bilateral pelvic lymphadenectomy as part of their therapy or staging. Positive paraaortic nodes were present in one of eight patients (12.5%) undergoing paraaortic dissection.

Preoperative Evaluation

Apart from the standard staging investigations, a computed tomographic (CT) scan of the pelvis and abdomen is useful for evaluation of the status of the primary tumor, liver, pelvic and paraaortic lymph nodes, and ureters.

Treatment

There is no consensus as to the proper management of primary vaginal cancer; this is related in part to the rarity of the disease. Most gynecologic oncology centers in the United States see only two to five new cases per year, and even in some European centers, where referral of oncology cases tends to be more centralized, only approximately one new case per month can be expected (24). **Therapy must be individualized and varies depending on the stage of disease and the site of vaginal involvement, further limiting individual experience.**

Anatomic factors and psychological considerations place significant constraints on treatment planning. The proximity of the vagina to the rectum, bladder, and urethra limits the dose of radiation that can be delivered and restricts the surgical margins that can be attained unless an exenterative procedure is performed. **For most patients, maintenance of a functional vagina is an important factor in the planning of therapy.**

Surgery

Surgery has a limited role in the management of patients with vaginal cancer because of the radicality required to achieve clear surgical margins, but in selected cases, satisfactory results can be achieved (6,25,28). Surgery may be useful in the following circumstances:

1. **In patients with stage I disease involving the upper posterior vagina.** If the uterus is still *in situ*, these patients require radical hysterectomy, partial vaginectomy, and bilateral pelvic lymphadenectomy. If the patient has had a hysterectomy, radical upper vaginectomy and pelvic lymphadenectomy can be performed after development of the paravesicular and pararectal spaces and dissection of each ureter out to its point of entry into the bladder.
2. **In young patients who require radiation therapy.** Pretreatment laparotomy in such patients may allow ovarian transposition, surgical staging, and resection of any enlarged lymph nodes.
3. **In patients with stage IVA disease, particularly if a rectovaginal or vesicovaginal fistula is present.** Primary pelvic exenteration is a suitable treatment option for such patients, provided they are medically fit. Eddy et al. (27) reported a 5-year disease-free survival in three of six patients with stage IVA disease treated with preoperative radiation followed by anterior or total pelvic exenteration. In sexually active patients, vaginal reconstruction should be performed simultaneously.
4. **In patients with a central recurrence after radiation therapy.** Surgical resection, which usually necessitates pelvic exenteration, is the only option for this group of patients.

Radiation Therapy

Radiation therapy is the treatment of choice for all patients except those listed previously and comprises an integration of teletherapy and intracavitary/ interstitial therapy (1,2,4,24). Selected stage I and II lesions can be treated adequately with intracavitary radiation alone (1,2,29). For larger lesions, treatment is usually started with approximately 5,000 cGy external irradiation to shrink the primary tumor and treat the pelvic lymph nodes. Intracavitary treatment follows. **There is improved local control with total tumor doses of at least 7,000 cGy** (1,30). If the uterus is intact and the lesion involves the upper vagina, an intrauterine tandem and ovoids can be used. If the uterus has been previously removed, a Bloedorn type of applicator or vaginal cylinder may be used. If the lesion is more deeply invasive (thicker than 0.5 cm), interstitial irradiation, alone or in conjunction with the intracavitary therapy, improves the dose distribution. Extended-field radiation has rarely been used for patients with vaginal cancer, but if positive paraaortic nodes are documented after either surgical staging or CT scanning and fine-needle aspiration cytologic evaluation, this treatment should be given. **If the lower one third of the vagina is involved, the groin nodes should be treated or dissected.**

There is limited reported experience with chemoradiation for vaginal cancer (2). However, in view of the problem with control of the central tumor, the concurrent use of *5-fluorouracil (5-FU)* and/or *cisplatin* with radiation therapy, as is being done for cervical carcinomas, seems appropriate. The small number of cases makes it virtually impossible to ever conduct a randomized, prospective study.

Complications of Therapy

Major complications of therapy are usually reported in 10% to 15% of patients treated for primary vaginal cancer, whether the treatment is by surgery or radiation. **The close proximity of the rectum, bladder, and urethra predisposes these structures to injury, and radiation cystitis, rectovaginal or vesicovaginal fistulas, and rectal strictures or ulceration may occur.** Radiation necrosis of the vagina occasionally occurs, and radiation-induced fibrosis and subsequent vaginal stenosis are a constant concern. Workers at the M. D. Anderson Hospital reported serious complications in 39 of 311 patients (13%), but estimated an actuarial incidence of 19% at 20 years (1).

Patients who are sexually active must be encouraged to continue regular intercourse, but those who are not sexually active or for whom intercourse is temporarily too painful should be encouraged to use topical estrogen and a vaginal dilator every second night. There is inadequate documentation of the adequacy of vaginal function after either surgery or radiation therapy.

Prognosis

The reported overall 5-year survival rate for vaginal cancer is approximately 44%, which is at least 15% poorer than that for carcinoma of the cervix or vulva and reflects the difficulties involved in treating this disease, and the late stage at presentation (2,7,8,10,12,24,31) (Table 14.4). Even for patients with stage I disease, the 5-year survival rate in combined series is only approximately 70%.

Stage	No.	5-Year Survival	Percentage
I	212	147	69.3
II	274	132	48.2
III	245	80	32.7
IV	132	24	18.2
Total	863	383	44.4

Data compiled from Price et al., 1979 (31), Houghton and Iversen, 1982 (7), Benedet et al., 1983 (8), Rubin et al., 1985 (12), Kucera et al., 1988 (24), Eddy et al., 1991 (13), Kirkbridge et al., 1995 (2).

Table 14.4 Primary Vaginal Carcinoma: 5-Year Survival Rates

Better results have been reported in two series from the M. D. Anderson Hospital in Houston and the Princess Margaret Hospital in Toronto. In a report of 301 cases of primary vaginal squamous or adenocarcinoma from the M. D. Anderson Hospital, Chyle et al. (1) reported actuarial survival rates at 5, 10, 15, 20, and 25 years of 60%, 49%, 38%, 29%, and 23% respectively. The major determinants of local control for squamous lesions were tumor bulk (specified by size in centimeters, or by FIGO stage), tumor site (upper lesions doing better), and tumor circumferential location (lesions involving the posterior wall faring worse). Similarly, Kirkbridge et al. (2) from Toronto reported on 138 patients with invasive vaginal carcinoma. The 5-year cause-specific survival rates by stage were 77% for stages I/II and 56% for stages III/IV. In a multivariate analysis, only tumor size and stage of disease were significant variables.

Most recurrences are in the pelvis, so improved radiation therapy, which may include chemoradiation and/or increasing experience with interstitial techniques, may improve the results. Chyle et al. (1) reported that salvage after first relapse was uncommon, with a 5-year survival rate of only 12%.

Because of the rarity of the disease, these patients should be referred centrally to a limited number of tertiary referral units so that increasing experience can be gained in their management.

Adenocarcinoma

Approximately 9% of primary vaginal carcinomas are adenocarcinomas, and they affect a younger population of women, regardless of whether exposure to *diethylstilbestrol (DES) in utero has* occurred (32). Adenocarcinomas may arise in areas of vaginal adenosis, particularly in patients exposed to *DES in utero*, but they probably also arise in wolffian rest elements, periurethral glands (22), and foci of endometriosis. Secondary tumors from such sites as the colon, endometrium, or ovary should be considered when vaginal adenocarcinoma is diagnosed.

Diethylstilbestrol Exposure *In Utero*

In 1970, Herbst and Scully (33) initially reported on seven women 15 to 22 years of age with clear cell adenocarcinoma of the vagina, seen over a 4-year period. Subsequently, Herbst et al. (34) reported an association with maternal *DES* ingestion during pregnancy in six of these seven cases. A Registry for Research on Hormonal Transplacental Carcinogenesis was established by Herbst and Scully in 1971 to investigate the clinical, pathologic, and epidemiologic aspects of clear cell adenocarcinoma of the vagina and cervix occurring in women born after 1940 (i.e., during the years when DES was used to maintain high-risk pregnancies). Such high-risk situations included diabetic and twin pregnancies in women with a history of spontaneous abortion. The use of *DES* for pregnant patients was discontinued in the United States in 1971.

More than 500 cases of clear cell carcinoma of the vagina or cervix have been reported to the Registry, although **only approximately two thirds of the completely investigated cases have a history of prenatal exposure to *DES*.** In all instances, the mother was treated in the first half of the pregnancy (35). An additional 10% of the mothers received some unknown medication, but in 25% of the cases there was no indication of maternal hormone ingestion.

These cancers become most frequent after the age of 14 years, and the peak age at diagnosis is 19 years. The oldest reported DES-exposed patient with vaginal clear cell carcinoma was 33 years of age. **The estimated risk of clear cell adenocarcinoma in an exposed offspring is 1:1,000 or less. Approximately 70% of vaginal adenocarcinomas are stage I at diagnosis.**

Although *DES* exposure in utero rarely leads to vaginal adenocarcinoma, vaginal adenosis occurs in approximately 45% of such patients, and approximately 25% of exposed women have structural changes to the cervix and vagina. Such changes include a transverse vaginal septum, a cervical collar, a cockscomb (a raised ridge, usually on the anterior cervix), or cervical hypoplasia. The occurrence of these abnormalities is related to the dosage of medication given and the time of first exposure, the risk being insignificant if administration is begun after the 22nd week.

Two types of cells have been described in vaginal adenosis and cervical ectropion: the mucinous cell, which resembles the endocervical epithelium, and the tuboendometrial cell. Robboy et al. (36) reported foci of atypical tuboendometrial epithelium in 16 of 20 (80%) cases of clear cell adenocarcinoma of the cervix or vagina. The foci were almost immediately adjacent to the tumor, and they suggested that atypical vaginal adenosis and atypical cervical ectropion of the tuboendometrial type may be precursors of clear cell adenocarcinoma. In 1980, Sandberg and Christian (37) reported the appearance of cervicovaginal clear cell adenocarcinoma in only one of a genetically identical (monozygotic) pair of twins, simultaneously exposed to *DES in utero*. Benign teratologic changes were present in both twins. This discordance suggests that factors other than embryonic exposure to *DES* may be operative in tumorigenesis.

Areas of vaginal adenosis and cervical ectropion are progressively covered with metaplastic squamous epithelium as the individual matures, and areas of adenosis may disappear completely and be replaced by normally glycogenated squamous epithelium. Structural abnormalities (e.g., cervical hoods) also tend to disappear progressively (38). During the process of squamous metaplasia, colposcopic examination reveals mosaicism and punctation, changes commonly associated with squamous dysplasia (39). Women exposed *in utero* to *DES* may have twice the incidence of CIN and VAIN of unexposed women, although the reason for this increased risk is not clear (40).

In addition to benign changes in the lower genital tract, a number of other abnormalities in the upper genital tract have been reported in DES-exposed female offspring. Kaufman et al. (41) reported abnormalities of the hysterosalpingogram in 185 of 267 (69%) exposed women. The most common abnormality was a T-shaped uterus, with or without a small cavity; less common abnormalities included constriction rings, uterine filling defects, synechia, diverticula, and uterus unicornis or bicornis. These abnormalities translate into an impaired reproductive experience for DES-exposed offspring, with an increased incidence of primary infertility, ectopic pregnancy, spontaneous abortion, and premature delivery (42).

It is recommended that a young woman exposed to *DES in utero* should be initially seen when she begins to menstruate, or at approximately 14 years of age. The most important aspects of the examination are careful inspection and palpation of the entire vagina and cervix, and cytologic sampling by direct scraping of the vagina and cervix. Colposcopy is not essential if clinical and cytologic evaluations are negative, but staining with half-strength Lugol's iodine delineates areas of adenosis.

Treatment

In general, these tumors may be treated in a way similar to that for squamous carcinomas, except that in these young patients every effort should be made to preserve vaginal and ovarian function. **For early-stage tumors, particularly those involving the upper vagina, radical hysterectomy, pelvic lymphadenectomy, vaginectomy, and replacement of the vagina with a split-thickness skin graft have been successful in a high percentage of cases.** A combination of wide local excision, retroperitoneal lymphadenectomy, and local irradiation can be effective therapy for stage I tumors (43). Local surgical excision alone for small primary tumors is associated with a higher incidence of local and regional recurrence. Approximately 16% of patients with stage I disease have positive pelvic nodes (44). If radiation alone is used, a pretreatment staging laparotomy to allow pelvic lymphadenectomy and ovarian transposition facilitates an optimal functional outcome.

Prognosis

The overall 5-year survival rate for Registry patients with clear cell carcinoma of the vagina, regardless of the mode of therapy, is 78%. **The survival rate correlates well with stage of disease: 87% for patients with stage I disease, 76% for patients with stage II, and 30% for those with stage III** (33). Survival for non-clear cell adenocarcinomas is significantly worse than for squamous cancers (1).

Verrucous Carcinoma

Verrucous carcinomas of the vagina are rare, but their clinical and pathologic features are similar to those of their vulvar counterparts (45). **They are large, warty tumors that are locally aggressive but have a minimal tendency to metastasize. Wide surgical excision of the tumor is the treatment of choice.** Crowther et al. (46), in a literature review, reported a successful outcome in four of five patients with small lesions treated by wide excision. Similarly, for larger lesions, exenteration or vaginectomy was successful in seven of seven patients, but there were three postoperative deaths. Regional lymphadenectomy is not required, provided there is no suspicious lymphadenopathy. **Radiation therapy has been implicated in the rapid transformation of such lesions to a more malignant tumor** (47). Crowther et al. (46) reported recurrence in all four patients treated with primary radiation therapy.

Vaginal Melanoma

Malignant melanomas of the vagina are rare, with only approximately 200 reported cases (48). They presumably arise from melanocytes that are present in the vagina in 3% of normal women (49). The average age of the patients is 58 years, but vaginal melanomas have been reported from the third to the ninth decades of life (50). **Almost all cases occur in white women** (51).

Clinically, most patients are seen with vaginal bleeding, a vaginal mass, or vaginal discharge. **The lesions most commonly arise in the distal part of the vagina, particularly on the anterior wall** (51,52). They may be nonpigmented and are frequently ulcerated, making them easily confused with squamous carcinomas. Most are deeply invasive. Expressing the lesion in terms of Chung's level of invasion [as defined for vulvar melanomas (53)], Chung et al. (52) reported that 13 of 15 vaginal melanomas were at level IV. Approximately 60% of the cases exhibit spread of melanocytic cells into the adjacent epithelium, and in approximately 30% of the cases the lateral spread is extensive (52).

Radical surgery has been the mainstay of treatment, and this has often involved anterior, posterior, or total pelvic exenteration, depending on the location of the lesion. Small upper vaginal lesions may be treated with radical hysterectomy, subtotal vaginectomy, and pelvic lymphadenectomy; small distal vaginal lesions may be amenable to partial vaginectomy, total or partial vulvectomy, and bilateral inguinofemoral lymphadenectomy. If vaginal mucosa is left, frozen sections should be obtained to exclude lateral superficial spread because the most common site of initial recurrence is the vagina (49,52). More conservative operations (e.g., wide local excision) have also been used, and both Reid et al. (51) and Buchanan et al. (48) reported that there was no significant benefit in terms of survival or disease-free interval for radical versus conservative surgery. **Radiation therapy, particularly a combination of external and interstitial radiation, may be effective in selected patients. High-dose fractions (>400 cGy) may yield better response rates than conventional or low-dose fractions** (54). Chemotherapy [e.g., with *methyl-CCNU (semustine)* or *dacarbazine*] is disappointing.

The overall prognosis for patients with vaginal melanoma is poor because most patients have deeply penetrating lesions at the time of diagnosis. Buchanan et al. (48) reviewed the literature and reported that only 18 of 197 patients (9.1%) survived for 5 years or longer. Six of the 18 patients were treated with radical operative procedures, 4 with radiation, 6 with wide local excision, and 1 with radiation plus wide excision. In one patient, the mode of therapy was unknown. Both reviews by Reid et al. (51) and Buchanan (48) noted that size of the lesion was the best prognostic factor. Among thirteen 5-year survivors who had their tumor size noted, 11 (84.6%) had lesions less than 3 cm in maximal diameter. Among ten 5-year survivors who had depth of invasion noted, only 2 (20%) had invasion of greater than 2 mm (48).

Adjuvant therapy with *interferon alfa-2b* has been shown to improve relapse-free and overall survival in patients with high-risk cutaneous melanomas (55), but there are as yet no data on this treatment for vaginal melanomas.

Once a recurrence is noted, prognosis is extremely poor, with a mean survival time of 8.5 months.

Vaginal Sarcomas

Vaginal sarcomas, such as **fibrosarcomas** and **leiomyosarcomas,** are rare tumors. They are usually bulky lesions and occur most commonly in the upper vagina. Tavassoli and Norris (56) reported 60 smooth muscle tumors of the vagina, only 5 of which recurred. All recurrences were seen in tumors more than 3 cm in diameter with moderate to marked cytologic atypia and more than five mitoses per 10 high-power fields.

Surgical excision is the mainstay of treatment. If the lesion is well differentiated and the surgical margins are not involved, as is likely with tumors of low malignant potential, the likelihood of cure is good. For frankly malignant lesions, lymphatic and hematogenous dissemination is common. Adjuvant pelvic radiation is indicated for such tumors (57).

Embryonal Rhabdomyosarcoma

Embryonal rhabdomyosarcoma is a malignant tumor of the rhabdomyoblasts characterized by two structural variants, a solid form and a multicystic grape-like form referred to as *sarcoma botryoides*. Sarcoma botryoides is a highly malignant tumor. **In the female genital tract, sarcoma botryoides is usually found in the vagina during infancy and early childhood, in the cervix during the reproductive years, and in the corpus uteri during the postmenopausal period.** Hilgers et al. (58) reported a peak incidence of vaginal sarcoma botryoides at approximately 3 years of age, and these lesions may rarely be present at birth.

The term *botryoides* comes from the Greek word *botrys*, which means “grapes,” and, grossly, the tumor usually appears as a polyploid mass extruding from the vagina and resembling a bunch of grapes. Microscopically, the characteristic feature is the presence of cross-striated rhabdomyoblasts (strap cells).

In the past, exenterative surgery was usually performed for these tumors, but survival was poor. More recently, conservative surgery has been used in conjunction with preoperative or postoperative chemotherapy and radiation, with significantly improved survival (59,60). The usual chemotherapy has consisted of *vincristine, actinomycin D*, and *cyclophosphamide* (VAC). If the tumor is small and can be resected with organ preservation, surgery should be the initial treatment. If the lesion is bulky, preoperative chemotherapy or radiation should be given (61). Permanent local control with drugs alone occurs in fewer than 15% of cases (62).

Endodermal Sinus Tumor (Yolk Sac Tumor)

These rare germ cell tumors are occasionally found in extragonadal sites such as the vagina. Leverger et al. (63) reported 11 such cases from the Institut Gustave-Roussy. The average age of the patients was 10 months, and the presenting symptom was vaginal bleeding. Diagnosis was made by examination and biopsy with the patient under anesthesia. All children had high serum a -fetoprotein levels. Since 1977, six of eight children have been cured, with an average follow-up of 3 years. Treatment consisted of primary chemotherapy to reduce the tumor volume, followed by either partial colpectomy, radiation therapy, or both.

Carcinoma of the Urethra

Primary carcinoma of the female urethra is a rare malignancy, accounting for fewer than 0.1% of all female genital malignancies (64). The disease has been reported from the third to the ninth decades of life, with a median age of approximately 65 years. The most common presenting symptoms are urethral bleeding, hematuria, dysuria, urinary obstruction, urinary frequency, and a mass at the introitus. Uncommon presenting symptoms include urinary incontinence, perineal pain, and dyspareunia.

Most tumors involve the anterior or distal urethra and may be confused with a urethral caruncle or mucosal prolapse. Histologically, these distal lesions are usually squamous cell carcinomas. Tumors involving the posterior or proximal urethra are usually adenocarcinomas or transitional cell carcinomas. The relative frequency of the various histologic variants is shown in Table 14.5 (64,65,66,67 and 68). Urethral carcinomas occasionally arise in a urethral diverticulum (67).

Type	No.	Percentage
Squamous cell	120	53.3
Adenocarcinoma	48	21.3
Transitional cell	43	19.1
Undifferentiated	8	3.5
Melanoma	4	1.7
Sarcoma	1	0.5
Unknown	1	0.5
Total	225	100.0

Data compiled from Bracken et al., 1976 (65); Benson et al., 1982 (67); Weghaupt et al., 1984 (64); Prempeed et al., 1984 (66); Grigsby, 1998 (68).

Table 14.5 Histology of Urethral Carcinomas

There is no FIGO staging for the disease, and several staging classifications have been suggested (66,69,70). The TNM staging system is shown in Table 14.6. **Distal tumors spread to the lymph nodes of the groin, whereas proximal tumors spread to pelvic nodes, and treatment planning should take this into consideration.** Bladder neck involvement is a common cause of local recurrence, and examination under anesthesia, endoscopic evaluation, and biopsy of the bladder neck should be undertaken as part of the pretreatment work-up.

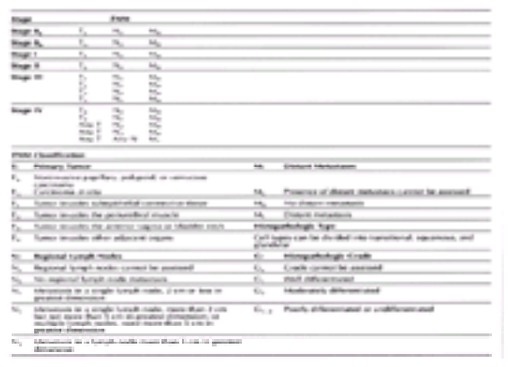

Table 14.6 TNM Staging for Urethral Cancer

The treatment of urethral cancer must be individualized (64). **Radiation therapy is considered to be the treatment of choice, although, when used for urethral cancer, it may cause complications such as urinary stricture, fistula, or total incontinence.** Surgery is used in conjunction with radiation for more advanced lesions (66). Interstitial radiation may be satisfactory for early lesions, but for more advanced lesions, preoperative external pelvic radiation followed by anterior exenteration and, if necessary, vulvectomy should be performed (65). For medically inoperable patients, high-dose–rate brachytherapy may be delivered with a remote afterloader, using a shielded vaginal applicator and modified urethral catheter (71). **For lesions involving the distal half of the urethra, bilateral inguinofemoral lymphadenectomy should be performed for all but the most superficial lesions.** The distal half of the urethra can be excised without loss of urinary continence.

The main cause of treatment failure is local recurrence. **In an attempt to improve local control in advanced cases, two approaches have been suggested: chemoradiation and ultraradical surgery.** Klein et al. (72) from Memorial Sloan-Kettering reported on five women who were treated with preoperative radiation followed by anterior exenteration combined with resection of the inferior pubic rami. Two died with distant metastases, and one died of surgical complications at 1 month. Only one patient treated with chemoradiation has been reported (73). However, in view of the experience with other primary sites, this would seem to be an acceptable initial approach for locally advanced cases.

Bracken et al. (65) from the M. D. Anderson Hospital reported an overall 5-year survival rate of only 32% for 81 cases of carcinoma of the female urethra (65). Grigsby (68), from the Mallinckrodt Institute of Radiology in St. Louis, reported a 5-year survival rate of 42% for 44 cases. Stage distribution was as follows: T_1 in 8, T_2 in 5, T_3 in 22, and T_4 in 9. Treatment was with surgery in 7 cases, radiation therapy in 25 cases, and combined surgery and radiation therapy in 12. The severe complication rate was 29% for treatment with surgery, 24% for radiation therapy, and 8% for combined therapy. **The most important clinical factors affecting prognosis were tumor size and histologic type—none of 13 women with adenocarcinomas was alive at 5 years, and only 1 of 10 women with tumors greater than 4 cm diameter was a 5-year survivor.**

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15 Gestational Trophoblastic Neoplasia

Ross S. Berkowitz and Donald P. Goldstein

Gestational trophoblastic neoplasia (GTN) is among the rare human malignancies that can be cured even in the presence of widespread metastases (1,2 and 3). GTN includes a spectrum of interrelated tumors, including hydatidiform mole, invasive mole, placental-site trophoblastic tumor, and choriocarcinoma, that have varying propensities for local invasion and metastasis. Although persistent GTN most commonly ensues after a molar pregnancy, it may follow any gestational event, including therapeutic or spontaneous abortion and ectopic or term pregnancy. Dramatic advances have been made in the diagnosis, treatment, and follow-up of patients with GTN since the introduction of chemotherapy in 1956.

Hydatidiform Mole

Complete Versus Partial Hydatidiform Mole

Hydatidiform moles may be categorized as either complete or partial moles on the basis of gross morphology, histopathology, and karyotype (Table 15.1).

	Complete Mole	*Partial Mole*
Fetal or embryonic tissue	Absent	Present
Hydatidiform swelling of chorionic villi	Diffuse	Focal
Trophoblastic hyperplasia	Diffuse	Focal
Scalloping of chorionic villi	Absent	Present
Trophoblastic stromal inclusions	Absent	Present
Karyotype	46XX; 46XY	69XXY; 69XXY

Reproduced from Berkowitz RS, Goldstein DP. The management of molar pregnancy and gestational trophoblastic tumors. In: Knapp RC, Berkowitz RS, eds. Gynecologic oncology. New York: MacMillan, 1992:425, with permission.

Table 15.1 Features of Complete and Partial Hydatidiform Moles

Complete Hydatidiform Mole

Pathology Complete moles lack identifiable embryonic or fetal tissues, and the chorionic villi exhibit generalized hydatidiform swelling and diffuse trophoblastic hyperplasia.

Chromosomes **Cytogenetic studies have demonstrated that complete hydatidiform moles usually have a 46XX karyotype, and the molar chromosomes are entirely of paternal origin** (4). Complete moles appear to arise from an ovum that has been fertilized by a haploid sperm, which then duplicates its own chromosomes, and the ovum nucleus may be either absent or inactivated (5). Although most complete moles have a 46XX chromosomal pattern, approximately 10% have a 46XY karyotype (6). Chromosomes in a 46XY complete mole also appear to be entirely of paternal origin, but in this circumstance, an apparently empty egg is fertilized by two sperm.

Partial Hydatidiform Mole

Pathology Partial hydatidiform moles are characterized by the following pathologic features (7):

1. Chorionic villi of varying size with focal hydatidiform swelling and cavitation
2. Marked villous scalloping
3. Focal trophoblastic hyperplasia with or without atypia
4. Prominent stromal trophoblastic inclusions
5. Identifiable embryonic or fetal tissues

Chromosomes Partial moles usually have a triploid karyotype (69 chromosomes), with the extra haploid set of chromosomes derived from the father (8). When a fetus is present in conjunction with a partial mole, it usually exhibits the stigmata of triploidy, including growth retardation and multiple congenital malformations.

Clinical Features

The presenting symptoms and signs of patients with complete and partial molar pregnancy are presented in Table 15.2 (9,10).

Sign	Complete Mole[a] N = 307 (%)	Partial Mole[b] N = 81 (%)
Vaginal bleeding	97	73
Excessive uterine size	51	4
Prominent ovarian theca lutein cysts	50	0
Toxemia	27	3
Hyperemesis	26	0
Hyperthyroidism	7	0
Trophoblastic emboli	2	0

Adapted from [a]Berkowitz RS, Goldstein DP. Pathogenesis of gestational trophoblastic neoplasms. Pathobiol Annu 1981;11:291, and [b]Berkowitz RS, Goldstein DP, Bernstein MR. Natural history of partial molar pregnancy. Obstet Gynecol 1985;66(5):677–681.

Table 15.2 Presenting Symptoms and Signs in Patients with Complete and Partial Molar Pregnancy

Complete Hydatidiform Mole

Vaginal Bleeding Vaginal bleeding is the most common presenting symptom in patients with complete molar pregnancy and occurs in 97% of cases. Molar tissues may separate from the decidua and disrupt maternal vessels, and large volumes of retained blood may distend the endometrial cavity. As intrauterine clots undergo oxidation and liquefaction, “prune juice”-like fluid may leak into the vagina. Because vaginal bleeding may be considerable and prolonged, half of these patients present with anemia (hemoglobin <10 g/100 mL) (11).

Excessive Uterine Size Excessive uterine enlargement relative to gestational age is one of the classic signs of a complete mole, although it is present in only approximately half of the patients. The endometrial cavity may be expanded by both chorionic tissue and retained blood. Excessive uterine size is usually associated with markedly elevated levels of human chorionic gonadotropin (hCG), because uterine enlargement results in part from exuberant trophoblastic growth (11).

Toxemia Preeclampsia is observed in approximately 27% of patients with a complete hydatidiform mole. Although preeclampsia is often associated with hypertension, proteinuria, and hyperreflexia, eclamptic convulsions rarely occur. Toxemia develops almost exclusively in patients with excessive uterine size and markedly elevated hCG levels. The diagnosis of hydatidiform mole should be considered whenever preeclampsia develops early in pregnancy.

Hyperemesis Gravidarum Hyperemesis requiring antiemetic and/or intravenous replacement therapy occurs in one fourth of the patients with a complete mole, particularly those with excessive uterine size and markedly elevated hCG levels. Severe electrolyte disturbances may develop occasionally and require treatment with parenteral fluids.

Hyperthyroidism Clinically evident hyperthyroidism is observed in approximately 7% of patients with a complete molar gestation. These patients may present with tachycardia, warm skin, and tremor, and the diagnosis can be confirmed by detection of elevated serum levels of free thyroxine (T_4) and triiodothyronine (T_3).

Laboratory evidence of hyperthyroidism is commonly detected in asymptomatic patients with hydatidiform moles. Galton et al. (12) reported 11 patients whose thyroid function test values were elevated before molar evacuation, and the thyroid function test values rapidly returned to normal in all patients after evacuation.

If hyperthyroidism is suspected, it is important to administer b-adrenergic blocking agents before the induction of anesthesia for molar evacuation because anesthesia or surgery may precipitate a thyroid storm. The latter may be manifested by hyperthermia, delirium, convulsions, atrial fibrillation, high-output heart failure or cardiovascular collapse. Administration of b-adrenergic blocking agents prevents or rapidly reverses many of the metabolic and cardiovascular complications of a thyroid storm.

Some investigators have suggested that hCG is the thyroid stimulator in patients with a hydatidiform mole because positive correlations between serum hCG and total T_4 or T_3 concentrations have sometimes been observed. However, Amir et al. (13) measured thyroid function in 47 patients with a complete mole and reported no correlation between serum hCG levels and the serum free T_4 index or free T_3 index. Thus, the identity of a thyrotropic factor in hydatidiform mole has not been clearly delineated. Although some investigators have speculated about a separate chorionic thyrotropin, this substance has not yet been isolated.

Trophoblastic Embolization **Respiratory distress develops in approximately 2% of patients with a complete mole. These patients may have chest pain, dyspnea, tachypnea, and tachycardia and may experience severe respiratory distress after molar evacuation.** Auscultation of the chest usually reveals diffuse rales, and the chest radiograph may demonstrate bilateral pulmonary infiltrates. The signs and symptoms of respiratory distress usually resolve within 72 hours with cardiopulmonary support. Respiratory insufficiency may result not only from trophoblastic embolization but from the cardiopulmonary complications of thyroid storm, toxemia, and massive fluid replacement.

Theca Lutein Ovarian Cysts **Prominent theca lutein ovarian cysts (>6 cm in diameter) develop in approximately half the patients with a complete mole** (11). These cysts contain amber-colored or serosanguineous fluid and are usually bilateral and multilocular. Their formation may be related to increased serum levels of hCG and prolactin (14). Ovarian enlargement occurs almost exclusively in patients with markedly elevated hCG values. Because the uterus may also be excessively enlarged, theca lutein cysts may be difficult to palpate on physical examination; however, ultrasonography can accurately document their presence and size. After molar evacuation, theca lutein cysts normally regress spontaneously within 2 to 4 months.

Prominent theca lutein cysts frequently cause symptoms of marked pelvic pressure, and they may be decompressed by laparoscopic or transabdominal aspiration to relieve such symptoms. If acute pelvic pain develops, laparoscopy should be performed to assess possible cystic torsion or rupture, and laparoscopic manipulation may successfully manage incomplete ovarian torsion or cystic rupture (15).

Although in the 1960s, 1970s and early 1980s, complete moles were usually diagnosed in the second trimester, in more recent years the diagnosis has commonly been made in the first trimester (16). Because of this, the diagnosis of complete mole is now often made before the classic clinical signs and symptoms develop. With earlier diagnosis, excessive uterine size, hyperemesis, anemia, and preeclampsia were observed at presentation in only 28%, 8%, 5%, and 1% of our patients, respectively (16). Between 1988 and 1993, none of our 74 patients with complete mole had respiratory distress or hyperthyroidism. However, patients continue to present with vaginal bleeding and markedly elevated hCG levels.

Partial Hydatidiform Mole

Patients with a partial hydatidiform mole usually do not have the clinical features characteristic of complete molar pregnancy. **In general, these patients present with the signs and symptoms of incomplete or missed abortion, and the diagnosis of partial mole may be made only after histologic review of the curettings** (17).

The main presenting sign among 81 patients with a partial mole seen at the New England Trophoblastic Disease Center (NETDC) was vaginal bleeding, which occurred in 59 patients (72.8%). There was absence of a fetal heart beat in 12 patients (14.8%) (9). Excessive uterine enlargement and preeclampsia were present in only three (3.7%) and two (2.5%) patients, respectively. No patient presented with theca lutein ovarian cysts, hyperemesis, or hyperthyroidism. The presenting clinical diagnosis was incomplete or missed abortion in 74 patients (91.4%) and hydatidiform mole in only 5 patients (6.2%). Preevacuation hCG levels were measured in 30 patients and were greater than 100,000 mIU/mL in

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Natural History

Complete Hydatidiform Mole

Complete moles are well recognized to have a potential for local invasion and distant spread. **After molar evacuation, local uterine invasion occurs in 15% of patients and metastases in 4%** (10).

A review of 858 patients with complete hydatidiform mole (10) revealed that two fifths of the patients had the following signs of marked trophoblastic proliferation at the time of presentation:

1. Human chorionic gonadotropin level greater than 100,000 mIU/mL
2. Excessive uterine enlargement
3. Theca lutein cysts larger than 6 cm in diameter

Patients with any of these signs are at high risk for postmolar persistent tumor. The sequelae of 858 patients with low- and high-risk complete hydatidiform moles are shown in Table 15.3. After molar evacuation, local uterine invasion occurred in 31%, and metastases developed in 8.8% of the 352 high-risk patients. For the 506 low-risk patients, local invasion was found in only 3.4% and metastases developed in 0.6%.

Outcome	No. of Patients (%)	
	Low Risk	High Risk
Normal involution	486/506 (96.0)	212/352 (60.2)
Persistent GTN		
Nonmetastatic	17/506 (3.4)	109/352 (31.0)
Metastatic	3/506 (0.6)	31/352 (8.8)
Totals	**506/858 (59.0)**	**352/858 (41.0)**

GTN, gestational trophoblastic neoplasia.
All patients managed by evacuation without prophylactic chemotherapy.
Reproduced from Goldstein DP, Berkowitz RS, Bernstein MR: Management of molar pregnancy. *J Reprod Med* 1981;26:208, with permission.

Table 15.3 Sequelae of Low- and High-Risk Complete Hydatidiform Moles

Patients older than 40 years of age are also at increased risk of postmolar GTN. Tow (18) reported that persistent GTN developed in 37% of such women.

Partial Hydatidiform Mole

Approximately 2% to 4% of patients with a partial mole have persistent postmolar tumor and require chemotherapy to achieve remission (19). Those patients in whom persistent disease develops have no distinguishing clinical or pathologic characteristics.

Diagnosis

Ultrasonography is a reliable and sensitive technique for the diagnosis of complete molar pregnancy. Because the chorionic villi exhibit diffuse hydatidiform swelling, complete moles produce a characteristic vesicular sonographic pattern, usually referred to as a “snowstorm” pattern.

Ultrasonography may also contribute to the diagnosis of partial molar pregnancy by demonstrating focal cystic spaces in the placental tissues and an increase in the transverse diameter of the gestational sac (20).

Treatment

After molar pregnancy is diagnosed, the patient should be evaluated carefully for the presence of associated medical complications, including preeclampsia, hyperthyroidism, electrolyte imbalance, and anemia. After the patient has been stabilized, a decision must be made concerning the most appropriate method of evacuation.

Hysterectomy

If the patient desires surgical sterilization, a hysterectomy may be performed with the mole *in situ.* The ovaries may be preserved at the time of surgery, even though theca lutein cysts are present. Prominent ovarian cysts may be decompressed by aspiration. Although hysterectomy eliminates the risks associated with local invasion, it does not prevent distant spread.

Suction Curettage

Suction curettage is the preferred method of evacuation, regardless of uterine size, in patients who desire to preserve fertility. It involves the following steps:

1. **Oxytocin infusion**—this is begun in the operating room before the induction of anesthesia.
2. **Cervical dilatation**—as the cervix is being dilated, the surgeon frequently encounters increased uterine bleeding. Retained blood in the endometrial cavity may be expelled during cervical dilatation. However, active uterine bleeding should not deter the prompt completion of cervical dilatation.
3. **Suction curettage**—within a few minutes of commencing suction curettage, the uterus may decrease dramatically in size and the bleeding is usually well controlled. If the uterus is more than 14 weeks in size, one hand may be placed on top of the fundus and the uterus massaged to stimulate uterine contraction and reduce the risk of perforation.
4. **Sharp curettage**—when suction evacuation is thought to be complete, sharp curettage is performed to remove any residual molar tissue.

The specimens obtained on suction and sharp curettage should be submitted separately for pathologic review.

Prophylactic Chemotherapy

The use of prophylactic chemotherapy at the time of molar evacuation is controversial (21). The debate concerns the wisdom of exposing all patients to potentially toxic treatment when only approximately 20% are at risk for development of persistent GTN.

In a study of 247 patients with complete molar pregnancy who received a single course of *actinomycin D (Act-D)* prophylactically at the time of evacuation, local uterine invasion subsequently developed in only 10 patients (4%), and in no case did metastases occur (Table 15.4).

	No. of Patients (%)	
Outcome	Act-D	No Act-D
Normal involution	237 (96.0)	668 (81.4)
Persistent GTN		
Nonmetastatic	10 (4.0)	126 (14.6)
Metastatic	0 (0)	34 (4.2)
Totals	247 (100)	858 (100)

GTN, gestational trophoblastic neoplasia.
Reproduced from Goldstein DP, Berkowitz RS, Bernstein MR. Management of molar pregnancy. *J Reprod Med* 1981;26:308, with permission.

Table 15.4 Prophylactic *Actinomycin D (Act-D)* after Evacuation or Hysterectomy for Molar Pregnancy

Furthermore, all 10 patients with local invasion achieved remission after only one additional course of chemotherapy. Prophylactic chemotherapy, therefore, not only prevented metastases, it reduced the incidence and morbidity of local uterine invasion. Kim et al. (22) performed a prospective, randomized study of prophylactic chemotherapy in patients with a complete mole and observed a significant decrease in persistent GTN in patients with high-risk mole who received prophylactic chemotherapy. Therefore, **prophylaxis may be particularly useful in the management of high-risk complete molar pregnancy, especially when hormonal follow-up is unavailable or unreliable.**

Follow-up

Human Chorionic Gonadotropin

Human chorionic gonadotropin is a predictable secretory product of the trophoblastic cell. Like the other glycoprotein hormones—luteinizing hormone (LH), follicle-stimulating hormone, and thyroid-stimulating hormone—hCG is composed of two polypeptide chains (a and b) attached to a carbohydrate moiety. There is considerable cross-reactivity between hCG and LH because they share indistinguishable a chains. Each of the b chains of these four glycoprotein hormones is biochemically unique and confers biologic and immunologic specificity. The b-subunit radioimmunoassay is the most reliable assay available for the management of patients with GTN and is particularly useful in quantitating low levels of hCG without substantial interference from physiologic levels of LH.

After molar evacuation or hysterectomy with the mole *in situ*, patients should be followed by weekly determinations of b-subunit hCG levels until these are normal for 3 consecutive weeks and then by monthly determinations until the levels are normal for 6 consecutive months. The normal postmolar b-hCG regression curve is presented in Fig. 15.1.

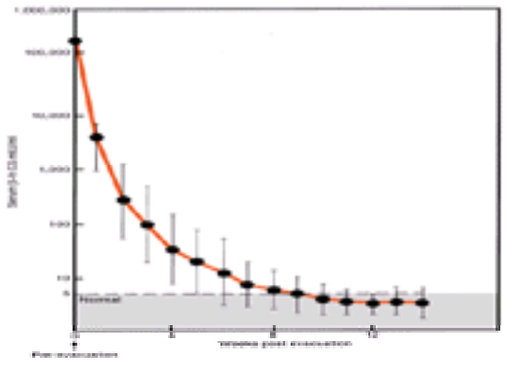


Figure 15.1 Normal regression curve of beta-subunit human chorionic gonadotropin (b-hCG) after molar evacuation. (Reprinted from Morrow CP, Kletzky OA, DiSaia PJ, Townsend DE, Mishell DR, Nakamura RM. Clinical and laboratory correlates of molar pregnancy and trophoblastic disease. *Am J Obstet Gynecol* 1977;128:424–430, with permission.)

Contraception

Patients are encouraged to use effective contraception during the entire interval of gonadotropin follow-up. Intrauterine devices should not be inserted until the patient achieves a normal hCG level, because of the potential risk of uterine perforation. If the patient does not desire surgical sterilization, the choice is to use either hormonal contraception or barrier methods.

The incidence of postmolar GTN has been reported to be increased among patients who used oral contraceptives before gonadotropin remission (23). However, data from both the NETDC and the Gynecologic Oncology Group (GOG) indicate that these agents do not increase the risk of postmolar trophoblastic disease (24,25). In addition, the contraceptive method did not influence the mean hCG regression time. It appears that oral contraceptives may be safely prescribed after molar evacuation during the entire interval of hormonal follow-up.

Malignant Gestational Trophoblastic Neoplasia

Nonmetastatic Disease

Locally invasive GTN develops in 15% of patients after evacuation of a complete mole and infrequently after other gestations (10). These patients usually present clinically with one or more of the following:

1. Irregular vaginal bleeding
2. Theca lutein cysts
3. Uterine subinvolution or asymmetric enlargement
4. Persistently elevated serum hCG levels

The trophoblastic tumor may perforate through the myometrium, causing intraperitoneal bleeding, or erode into uterine vessels, causing vaginal hemorrhage. Bulky, necrotic tumor may involve the uterine wall and serve as a nidus for infection. Patients with uterine sepsis may have a purulent vaginal discharge and acute pelvic pain.

After molar evacuation, persistent GTN may exhibit the histologic features of either hydatidiform mole or choriocarcinoma. After a nonmolar pregnancy, however, persistent GTN always has the histologic pattern of choriocarcinoma. Histologically, choriocarcinoma is characterized by sheets of anaplastic syncytiotrophoblast and cytotrophoblast with no preserved chorionic villous structure.

Placental-Site Trophoblastic Tumor Placental-site trophoblastic tumor is an uncommon but important variant of GTN that consists predominantly of intermediate trophoblast and a few syncytial elements (26). These tumors produce small amounts of hCG and human placental lactogen relative to their mass, and tend to remain confined to the uterus, metastasizing late in their course. In contrast to other trophoblastic tumors, placental-site tumors are relatively insensitive to chemotherapy. High cure rates can be achieved with early diagnosis and surgical resection.

Metastatic Disease

Metastatic GTN occurs in 4% of patients after evacuation of a complete mole and is infrequent after other pregnancies (10). Metastasis is usually associated with choriocarcinoma, which has a tendency toward early vascular invasion with widespread dissemination. Because trophoblastic tumors are often perfused by a network of fragile vessels, they are frequently hemorrhagic. Symptoms of metastases may therefore result from spontaneous bleeding at metastatic foci. Sites of metastatic spread are shown in Table 15.5.

Lungs	80%
Vagina	30%
Pelvis	20%
Brain	10%
Liver	10%
Bowel, kidney, spleen	<5%
Other	<5%
Undetermined*	<5%

*Persistent human chorionic gonadotropin titer after hysterectomy.
Reproduced from Berkowitz RS, Goldstein DP. Pathogenesis of gestational trophoblastic neoplasms. Pathobiol Annu 1981;11:291, with permission.

Table 15.5 Relative Incidence of Common Metastatic Sites

Pulmonary At the time of presentation, 80% of the patients with metastatic GTN show lung involvement on chest radiographs. Patients with pulmonary metastases may have chest pain, cough, hemoptysis, dyspnea, or an asymptomatic lesion on chest radiographs. Respiratory symptoms may be of acute onset, or they may be protracted over many months.

Gestational trophoblastic neoplasia produces four principal radiographic patterns in the lungs:

1. An alveolar or “snowstorm” pattern
2. Discrete, rounded densities
3. Pleural effusion
4. An embolic pattern caused by pulmonary arterial occlusion

Because respiratory symptoms and radiographic findings may be dramatic, the patient may be thought to have primary pulmonary disease. Some patients with extensive pulmonary involvement have minimal or no gynecologic symptoms because the reproductive organs may be free of trophoblastic tumor. Regrettably, the diagnosis of GTN may be confirmed only after thoracotomy has been performed, particularly in patients with a nonmolar antecedent pregnancy.

Pulmonary hypertension may develop in patients with GTN secondary to pulmonary arterial occlusion by trophoblastic emboli. Although patients with pulmonary hypertension may be very symptomatic, the chest film may reveal only minimal changes.

Vaginal Vaginal metastases are present in 30% of patients with metastatic tumor. These lesions are usually highly vascular and may appear reddened or violaceous. They can bleed vigorously if sampled for biopsy, so attempts at histologic confirmation of the diagnosis should be resisted. Metastases to the vagina may occur in the fornices or suburethrally and may produce irregular bleeding or a purulent discharge.

Hepatic Liver metastases occur in 10% of patients with disseminated trophoblastic tumor. Hepatic involvement is encountered almost exclusively in patients with protracted delays in diagnosis and extensive tumor burdens. Epigastric or right upper quadrant pain may develop if metastases stretch Glisson's capsule. Hepatic lesions are hemorrhagic and friable and may rupture, causing exsanguinating intraperitoneal bleeding.

Central Nervous System Ten percent of metastatic trophoblastic disease involves the brain. Cerebral involvement is usually seen in patients with far advanced disease; virtually all patients with brain metastases have concurrent pulmonary and/or vaginal involvement. Because cerebral lesions may undergo spontaneous hemorrhage, patients may have acute focal neurologic deficits.

Staging

An anatomic staging system for GTN has been adopted by the International Federation of Gynecology and Obstetrics (FIGO; Table 15.6). It is hoped that this staging system will encourage the objective comparison of data among various centers.

Stage I	Confined to uterine corpus
Stage II	Metastases to pelvis and vagina
Stage III	Metastases to lung
Stage IV	Distant metastases

Table 15.6 Staging of Gestational Trophoblastic Neoplasia

Stage I includes all patients with persistently elevated hCG levels and tumor confined to the uterine corpus.

Stage II comprises all patients with metastases to the vagina and/or pelvis.

Stage III includes all patients with pulmonary metastases with or without uterine, vaginal, or pelvic involvement. The diagnosis is based on a rising hCG level in the presence of pulmonary lesions on a chest film.

Stage IV patients have far advanced disease with involvement of the brain, liver, kidneys, or gastrointestinal tract. These patients are in the highest-risk category, because they are most likely to be resistant to chemotherapy. In most cases, their disease follows a nonmolar pregnancy and has the histologic pattern of choriocarcinoma.

Prognostic Scoring System

In addition to anatomic staging, it is important to consider other variables to predict the likelihood of drug resistance and to assist in selection of appropriate chemotherapy (3). A prognostic scoring system, based on one developed by Bagshawe, has been proposed by the World Health Organization and reliably predicts the potential for resistance to chemotherapy (Table 15.7).

	Score			
	0	1	2	4
Age (yr)	<39	>39		
Antecedent pregnancy	H. mole	Abortion	Term	
Interval between end of antecedent pregnancy and start of chemotherapy (mo)	<4	4–6	7–12	>12
Human chorionic gonadotropin (IU/L)	$<10^3$	10^3–10^4	10^4–10^5	$>10^5$
ABO groups		O or A	B or AB	
Largest tumor, including uterine (cm)	<3	3–5	>5	
Site of metastases		Spleen Kidney	Gastrointestinal tract Liver	Brain
No. of metastases		1–3	4–8	>8
Prior chemotherapy			1 drug	2 drugs

The total score for a patient is obtained by adding the individual scores for each prognostic factor. Total scores of 4 or less risk; 5–7 is middle risk; 8 or 9 high risk.
Reproduced from Bagshawe KD. Treatment of high-risk, choriocarcinoma. *J Reprod Med* 1980;24:181–185, with permission.

Table 15.7 Scoring System Based on Prognostic Factors

When the prognostic score is 8 or more, the patient is categorized as high risk and requires intensive combination chemotherapy to achieve remission. Patients with stage I disease usually have a low-risk score, and those with stage IV disease have a high-risk score, so that the distinction between low and high risk applies mainly to patients with stage II or III disease.

Diagnostic Evaluation

Optimal management of persistent GTN requires a thorough assessment of the extent of the disease before the initiation of treatment. All patients with persistent GTN should undergo a careful pretreatment evaluation, including:

1. A complete history and physical examination
2. Measurement of the serum hCG value
3. Hepatic, thyroid, and renal function tests
4. Determination of baseline peripheral white blood cell and platelet counts

The metastatic work-up should include:

1. A chest radiograph
2. An ultrasonogram or a computed tomographic (CT) scan of the abdomen and pelvis
3. A CT or magnetic resonance imaging (MRI) scan of the head
4. Measurement of cerebrospinal fluid (CSF) hCG level if any metastatic disease is present and the head CT scan is negative
5. Selective angiography of abdominal and pelvic organs if indicated

Liver ultrasonography and CT scanning of the liver document most hepatic metastases in patients with abnormal liver function tests. CT or MRI of the head has facilitated the early diagnosis of asymptomatic cerebral lesions (27).

In patients with choriocarcinoma and/or metastatic disease, hCG levels should be measured in the CSF to exclude cerebral involvement if the CT scan of the brain is negative. The plasma/CSF hCG ratio tends to be less than 60 in the presence of cerebral metastases (28). However, a single plasma/CSF hCG ratio may be misleading because rapid changes in plasma hCG levels may not be promptly reflected in the CSF.

Stool guaiac tests should also be routinely performed in patients with persistent GTN. If the guaiac test is positive or if the patient reports gastrointestinal symptoms, a complete radiographic evaluation of the gastrointestinal tract should be undertaken.

Pelvic ultrasonography appears to be useful in detecting extensive trophoblastic uterine involvement and may also aid in identifying sites of resistant uterine tumor (29). Because ultrasonography can accurately and noninvasively detect extensive uterine tumor, it may help to select patients who will benefit from hysterectomy. When the uterus contains large amounts of tumor, hysterectomy may substantially reduce the tumor burden and limit the exposure to chemotherapy needed to induce remission as well as eliminate the potential for hemorrhage or infection (30).

Management of Malignant Gestational Trophoblastic Disease

Stage 1

The NETDC protocol for the management of stage I disease is presented in Table 15.8. The selection of treatment is based primarily on whether the patient wishes to retain fertility.

Initial	MTX-FA; if resistant, switch to Act-D or hysterectomy with adjuvant chemotherapy
Resistant	Combination chemotherapy or hysterectomy with adjuvant chemotherapy; local uterine resection; pelvic intraarterial infusion
Follow-up hCG	Weekly until normal for 3 wk, then monthly until normal for 12 mo
Contraception	12 consecutive mo of normal hCG values

MTX, methotrexate; FA, folinic acid; Act-D, actinomycin D; hCG, human chorionic gonadotropin.
Modified from Goldstein DP, Berkowitz RS, eds. *Gestational trophoblastic neoplasms: clinical principles of diagnosis and management*. Philadelphia: WB Saunders, 1982:1–301, with permission.

Table 15.8 Protocol for Treatment of Stage I Gestational Trophoblastic Neoplasia

Hysterectomy Plus Chemotherapy

If the patient no longer wishes to preserve fertility, hysterectomy with adjuvant single-agent chemotherapy may be performed as primary treatment. Adjuvant chemotherapy is administered for three reasons:

1. To reduce the likelihood of disseminating viable tumor cells at surgery
2. To maintain a cytotoxic level of chemotherapy in the bloodstream and tissues in case viable tumor cells are disseminated at surgery
3. To treat any occult metastases that may already be present at the time of surgery

Chemotherapy can be administered safely at the time of hysterectomy without increasing the risk of bleeding or sepsis. At the NETDC, 29 patients were treated with primary hysterectomy and a single course of adjuvant chemotherapy, and all have achieved complete remission with no additional therapy.

Hysterectomy is also performed in all patients with a *placental-site trophoblastic tumor.* Because placental-site tumors are resistant to chemotherapy, hysterectomy for presumed nonmetastatic disease is the only curative treatment. To date, infrequent patients with a metastatic placental-site tumor have been reported to be in sustained remission after treatment with combination chemotherapy (31).

Chemotherapy Alone

Single-agent chemotherapy is the preferred treatment in patients with stage I disease who desire to retain fertility. Primary single-agent chemotherapy was administered at the NETDC to 453 patients with stage I GTN, and 416 (91.8%) achieved complete remission. The remaining 37 patients with resistant disease subsequently attained remission after combination chemotherapy or surgical intervention.

When patients are resistant to single-agent chemotherapy and wish to preserve fertility, combination chemotherapy should be administered. If the patient is resistant to both single-agent and combination chemotherapy and wants to retain fertility, local uterine resection may be considered. When local resection is planned, a preoperative ultrasonogram, MRI, and/or arteriogram may help to define the site of the resistant tumor.

Follow-up

All patients with stage I lesions should be followed with:

1. Weekly measurement of hCG levels until they are normal for 3 consecutive weeks
2. Monthly hCG values until levels are normal for 12 consecutive months
3. Effective contraception during the entire interval of hormonal follow-up

Stages II and III

Low-risk patients are treated with primary single-agent chemotherapy, and high-risk patients are managed with primary intensive combination chemotherapy. A protocol for the management of patients with stage II and III disease is presented in Table 15.9.

Low risk*	
Initial	MTX-FA; if resistant, switch to Act-D
Resistant to both single agents	Combination chemotherapy
High risk*	
Initial	Combination chemotherapy
Resistant	Second-line combination chemotherapy
Follow-up hCG	Weekly until normal for 3 wk, then monthly until normal for 12 mo
Contraception	Until there have been 12 consecutive mo of normal hCG values

MTX, methotrexate; FA, folinic acid; Act-D, actinomycin D; hCG, human chorionic gonadotropin.
*Local resection optional.
Modified from Goldstein DP, Berkowitz RS, eds. Gestational trophoblastic neoplasms: clinical principles of diagnosis and management. Philadelphia: WB Saunders, 1982:1–381, with permission.

Table 15.9 Protocol for Treatment of Stages II and III Gestational Trophoblastic Neoplasia

All 27 patients with stage II disease treated at the NETDC achieved remission. Single-agent chemotherapy induced complete remission in 16 (84.2%) of 19 low-risk patients. Three patients with resistant disease were cured with combination chemotherapy. In contrast, only two of eight high-risk patients achieved remission with single-agent treatment, the others requiring combination chemotherapy and local resection.

Vaginal Metastases

Vaginal metastases may bleed profusely because they are highly vascular and friable. When bleeding is substantial, it may be controlled by packing of the hemorrhagic lesion or by wide local excision. Arteriographic embolization of the hypogastric arteries may also be used to control hemorrhage from vaginal metastases.

Pulmonary Metastases

Of 135 patients with stage III disease managed at the NETDC, 134 (99%) attained complete remission. Gonadotropin remission was induced with single-agent chemotherapy in 72 of 89 (80.9%) patients with low-risk disease. All patients who were resistant to single-agent treatment subsequently achieved remission with combination chemotherapy and/or local pulmonary resection.

Thoracotomy Thoracotomy has a limited role in the management of stage III disease. However, if a patient has a persistent viable pulmonary metastasis despite intensive chemotherapy, thoracotomy may be used to excise the resistant focus. A thorough metastatic work-up should be performed before surgery to exclude other sites of persistent disease. Fibrotic pulmonary nodules may persist indefinitely on radiographs of the chest, even after complete gonadotropin remission has been attained. In patients undergoing thoracotomy for resistant disease, postoperative chemotherapy should be administered to treat potential occult sites of micrometastases.

Hysterectomy

Hysterectomy may be required in patients with metastatic GTN to control uterine hemorrhage or sepsis. Furthermore, in patients with extensive uterine tumor, hysterectomy may substantially reduce the trophoblastic tumor burden and thereby limit the need for multiple courses of chemotherapy.

Follow-up

Follow-up monitoring for patients with stage II and III disease is the same as for patients with stage I disease.

Stage IV

A protocol for the management of stage IV disease is presented in Table 15.10. These patients are at greatest risk for development of rapidly progressive and unresponsive tumors despite intensive multimodal therapy. They should all be referred to centers with special expertise in the management of trophoblastic disease.

Initial	Combination chemotherapy
Brain	Whole-head irradiation (3,000 cGy) Craniotomy to manage complications
Liver	Resection to manage complications
Resistant*	Second-line combination chemotherapy
	Hepatic arterial infusion
Follow-up hCG	Weekly until normal for 3 wk, then monthly until normal for 24 mo
Contraception	Until there have been 24 consecutive mo of normal hCG values

hCG, human chorionic gonadotropin.
*Local resection optional.
Modified from Goldstein DP, Berkowitz RS, eds. *Gestational trophoblastic neoplasms: clinical principles of diagnosis and management*. Philadelphia: WB Saunders, 1980:1–301, with permission.

Table 15.10 Protocol for Treatment of Stage IV Gestational Trophoblastic Neoplasia

All patients with stage IV disease should be treated with primary intensive combination chemotherapy and the selective use of radiation therapy and surgery. Before 1975, only 6 of 20 patients (30%) with stage IV disease treated at the NETDC attained complete remission. Since 1975, however, 14 of 18 patients (77.8%) with stage IV tumors have achieved gonadotropin remission. This gratifying improvement in survival has resulted from the use of primary combination chemotherapy in conjunction with radiation and surgical treatment.

Hepatic Metastases

The management of hepatic metastases is particularly challenging and problematic. If a patient is resistant to systemic chemotherapy, hepatic arterial infusion of chemotherapy may induce complete remission in selected cases. Hepatic resection may also be required to control acute bleeding or to excise a focus of resistant tumor.

Cerebral Metastases

If cerebral metastases are diagnosed, whole-brain irradiation (3,000 cGy in ten fractions) should be instituted promptly. The risk of spontaneous cerebral hemorrhage may be lessened by the concurrent use of combination chemotherapy and brain irradiation because irradiation may be both hemostatic and tumoricidal (32).

Craniotomy Craniotomy may be required to provide acute decompression or to control bleeding and should be performed to manage life-threatening complications in the hope that the patient ultimately will be cured with chemotherapy. Infrequently, cerebral metastases that are resistant to chemotherapy may be amenable to local resection. Fortunately, most patients with cerebral metastases who achieve sustained remission generally have no residual neurologic deficits (33).

Follow-up

Patients with stage IV disease should be followed with:

1. Weekly determination of hCG levels until they are normal for 3 consecutive weeks
2. Monthly determination of hCG levels until they are normal for 24 consecutive months
3. Effective contraception during the interval of hormonal follow-up

These patients require prolonged gonadotropin follow-up because they are at increased risk of late recurrence.

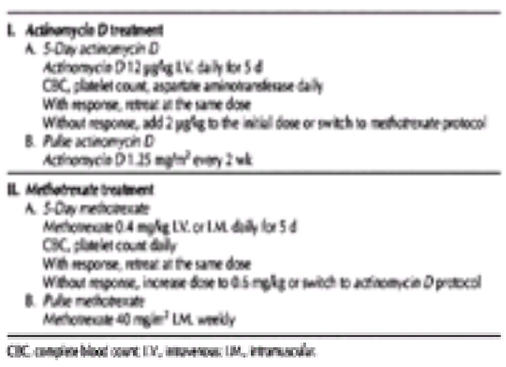
An algorithm for the management of GTN is presented in Fig. 15.2.

Figure 15.2 Management of gestational trophoblastic neoplasia. GTN, gestational trophoblastic neoplasia; hCG, human chorionic gonadotropin; RT, radiation therapy.

Chemotherapy

Single-Agent Chemotherapy

Single-agent chemotherapy with either *Act-D* or *methotrexate (MTX)* has achieved comparable and excellent remission rates in both nonmetastatic and low-risk metastatic GTN (34). There are several protocols available for the treatment of patients with *Act-D* or *MTX* (Table 15.11).



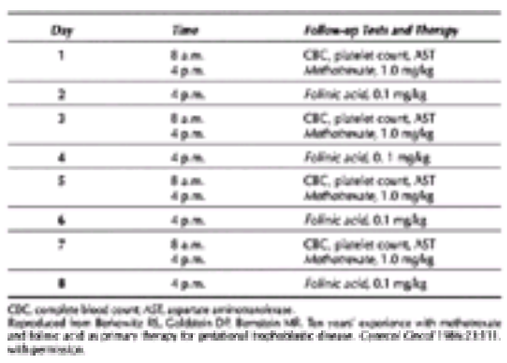
I. Actinomycin D treatment	
A. 5-Day actinomycin D	
Actinomycin D 12 μg/kg I.V. daily for 5 d	
CBC, platelet count, aspartate aminotransferase daily	
With response, retreat at the same dose	
Without response, add 2 μg/kg to the initial dose or switch to methotrexate protocol	
B. Pulse actinomycin D	
Actinomycin D 1.25 mg/m² every 2 wk	
II. Methotrexate treatment	
A. 5-Day methotrexate	
Methotrexate 0.4 mg/kg I.V. or I.M. daily for 5 d	
CBC, platelet count daily	
With response, retreat at the same dose	
Without response, increase dose to 0.6 mg/kg or switch to actinomycin D protocol	
B. Pulse methotrexate	
Methotrexate 40 mg/m² I.M. weekly	

CBC, complete blood count; I.V., intravenous; I.M., intramuscular.

Table 15.11 Single-Drug Treatment

Actinomycin D can be given every other week in a 5-day regimen or in a pulse fashion, and *MTX* can be given similarly in a 5-day regimen or weekly in a pulse fashion. No study has compared all of these protocols with regard to success, but the morbidity is comparable. The selection of chemotherapy should be influenced by the associated systemic toxicity. An optimal regimen should maximize response rate while minimizing morbidity.

In 1964, Bagshawe and Wilde (35) first reported the administration of *MTX* with *folinic acid (MTX-FA)* in GTN to limit systemic toxicity, and subsequently it has been confirmed that *MTX-FA* is both effective and safe in the management of GTN (36) (Table 15.12).



Day	*Time*	*Follow-up Tests and Therapy*
1	8 a.m. 4 p.m.	CBC, platelet count, AST Methotrexate, 1.0 mg/kg
2	4 p.m.	Folinic acid, 0.1 mg/kg
3	8 a.m. 4 p.m.	CBC, platelet count, AST Methotrexate, 1.0 mg/kg
4	4 p.m.	Folinic acid, 0.1 mg/kg
5	8 a.m. 4 p.m.	CBC, platelet count, AST Methotrexate, 1.0 mg/kg
6	4 p.m.	Folinic acid, 0.1 mg/kg
7	8 a.m. 4 p.m.	CBC, platelet count, AST Methotrexate, 1.0 mg/kg
8	4 p.m.	Folinic acid, 0.1 mg/kg

CBC, complete blood count; AST, aspartate aminotransferase.
Reproduced from Berkowitz RS, Goldstein DP. Hampton MB. Ten years' experience with methotrexate and folinic acid as primary therapy for gestational trophoblastic disease. Gynecol Oncol 1986;23:111. with permission.

Table 15.12 Protocol for Therapy with *Methotrexate and Folinic Acid "Rescue"*

Methotrexate with *folinic acid* has been the preferred single-agent regimen in the treatment of GTN at the NETDC since 1974. An evaluation of 185 patients treated in this manner between 1974 and 1984 revealed that complete remission was achieved in 162 patients (87.6%), and 132 of the 162 patients (81.5%) required only one course of *MTX-FA* to attain remission (36). *MTX-FA* induced remission in 147 of 163 patients (90.2%) with stage I GTN and in 15 of 22 patients (68.2%) with low-risk stages II and III GTN. Resistance to therapy was more common in patients with choriocarcinoma, metastases, and when pretreatment serum hCG levels exceeded 50,000 mIU/mL. After treatment with *MTX-FA*, thrombocytopenia, granulocytopenia, and hepatotoxicity developed in only 3 (1.6%), 11 (5.9%), and 26 (14.1%) patients, respectively. *MTX-FA* therefore achieved an excellent therapeutic outcome with minimal toxicity and attained this goal with limited exposure to chemotherapy.

Administration of Single-Agent Treatment

The serum hCG level is measured weekly after each course of chemotherapy, and the hCG regression curve serves as the primary basis for determining the need for additional treatment.

After the first treatment:

1. Further chemotherapy is withheld as long as the hCG level is falling progressively.
2. Additional single-agent chemotherapy is not administered at any predetermined or fixed time interval.

A second course of chemotherapy is administered under the following conditions:

1. If the hCG level plateaus for more than 3 consecutive weeks or begins to rise again
2. If the hCG level does not decline by 1 log within 18 days after completion of the first treatment

If a second course of *MTX-FA* is required, the dosage of *MTX* is unaltered if the patient's response to the first treatment was adequate. **An adequate response is defined as a fall in the hCG level by 1 log after a course of chemotherapy.** If the response to the first treatment is inadequate, the dosage of *MTX* is increased from 1.0 to 1.5 mg/kg/day for each of the four treatment days. If the response to two consecutive courses of *MTX-FA* is inadequate, the patient is considered to be resistant to *MTX*, and *Act-D* is promptly substituted in patients with nonmetastatic and low-risk metastatic GTN. If the hCG values do not decline by 1 log after treatment with *Act-D*, the patient is also considered resistant to *Act-D* as a single agent. She must then be treated intensively with combination chemotherapy to achieve remission.

Combination Chemotherapy

MAC III

In the past, the preferred combination drug regimen at the NETDC was MAC III (triple therapy), which included *MTX-FA*, *Act-D*, and *cyclophosphamide (Cytoxan; CTX)* (37). However, triple therapy proved to be inadequate as an initial treatment in patients with metastases and a high-risk prognostic score. Data from the GOG, M. D. Anderson Hospital, and the NETDC indicated that triple therapy induced remission in only 21 (49%) of 43 patients with metastases and a high-risk score (score >8) (38,39 and 40).

EMA-CO

Etoposide was reported to induce complete remission in 56 (93%) of 60 patients with nonmetastatic and low-risk metastatic GTN (41). In 1984, Bagshawe (42) first described a new combination regimen that included *etoposide*, *MTX*, *Act-D*, *CTX*, and *vincristine* (EMA-CO; Table 15.13), and reported an 83% remission in patients with metastases and a high-risk score (42). Bolis et al. (43) confirmed that primary EMA-CO induced complete remission in 76% of the patients with metastatic GTN and a high-risk score. Furthermore, Rustin et al. (44) reported remission with EMA-CO in 13 (87%) of 15 patients with brain metastases.

	Regimen
Course 1 (EMA)	
Day 1	*VP-16* (etoposide) 100 mg/m², I.V. infusion in 200 mL of saline over 30 min *Actinomycin D*, 0.5 mg, I.V. push *Methotrexate*, 100 mg/m², I.V. push, followed by a 200 mg/m² I.V. infusion over 12 hr
Day 2	*VP-16* (etoposide) 100 mg/m², I.V. infusion in 200 mL of saline over 30 min *Actinomycin D*, 0.5 mg, I.V. push *Folinic acid*, 15 mg, I.M. or orally every 12 hr for 4 doses beginning 24 hr after start of methotrexate
Course 2 (CO)	
Day 8	*Vincristine*, 1.0 mg/m², I.V. push *Cyclophosphamide*, 600 mg/m², I.V. in saline

I.V., intravenous; I.M., intramuscular
This regimen consists of two courses (a course 1 is given on days 1 and 2; its course 2 is given on day 8. Course 1 might require overnight hospital stay; course 2 does not. These courses can usually be given on days 1 and 2, 8, 15, and 16, 22, etc., and the intervals should not be extended without cause.
Reproduced from Bagshawe KD. Treatment of high-risk choriocarcinoma. *J Reprod Med* 1984;29:811, with permission.

Table 15.13 EMA-CO Regimen for Patients with Gestational Trophoblastic Neoplasia

The EMA-CO regimen is usually well tolerated, and treatment seldom has to be suspended because of toxicity.

The EMA-CO regimen is now the preferred primary treatment in patients with metastases and a high-risk prognostic score. If patients become resistant to EMA-CO, remission may still be achieved by substituting *etoposide* and *cisplatin* for *CTX* and *vincristine* on day 8 (45). The optimal combination drug protocol will most likely include *etoposide*, *MTX*, and *Act-D* and perhaps other agents, administered in the most dose-intensive manner. *Vinblastine, bleomycin*, and *cisplatin* also effectively induced remission in four of seven patients who were resistant to triple therapy (46).

Duration of Therapy

Patients who require combination chemotherapy must be treated intensively to attain remission. Combination chemotherapy should be given as often as toxicity permits until the patient achieves three consecutive normal hCG levels. After normal hCG levels are attained, at least two additional courses of chemotherapy are undertaken to reduce the risk of relapse.

Secondary Tumors

Investigators have reported an increased risk of secondary tumors, including leukemia, colon cancer, melanoma and breast cancer, in patients treated with chemotherapy for gestational trophoblastic tumors (47). The increased risk of secondary tumors has been attributed to the inclusion of etoposide in combination chemotherapy. The increased incidence of colon cancer, melanoma, and breast cancer was not apparent until more than 5, 10, and 25 years after therapy, respectively.

Subsequent Pregnancies

Pregnancies after Hydatidiform Mole

Patients with hydatidiform moles can anticipate normal reproduction in the future (48). From 1965 to 1996, patients who were treated at the NETDC for complete molar gestation had 1,234 subsequent pregnancies that resulted in 845 full-term live births (68.5%), 93 premature deliveries (7.5%), 11 ectopic pregnancies (0.9%), 7 stillbirths (0.6%), and 17 repeat molar pregnancies (1.4%). First- and second-trimester spontaneous abortions occurred in 223 pregnancies (18.1%). There were 38 therapeutic abortions (3.1%). Major and minor congenital malformations were detected in 38 infants (3.1%). Primary cesarean section was performed in 56 of 340 (16.5%) term or premature births from 1979 to 1996. **Patients with a complete molar pregnancy therefore should be reassured that they are at no increased risk of obstetric complications, either prenatally or intrapartum in later pregnancies. Although data concerning subsequent pregnancies after a partial mole are limited, the information is also reassuring.**

When a patient has had a hydatidiform mole, she is at increased risk of molar pregnancy in subsequent conceptions (48). Approximately 1 in 100 patients has at least two molar gestations. Later molar pregnancies are characterized by worsening histologic type and increased risk of postmolar GTN. After two episodes of molar pregnancy, patients may still achieve a normal full-term gestation in a later pregnancy.

Therefore, for any subsequent pregnancy, we recommend:

1. A pelvic ultrasonogram during the first trimester to confirm normal gestational development
2. A thorough histologic review of the placenta or products of conception
3. An hCG measurement 6 weeks after completion of the pregnancy to exclude occult trophoblastic neoplasia

Pregnancies after Persistent Gestational Trophoblastic Neoplasia

Patients with GTN who are treated successfully with chemotherapy can expect normal reproduction in the future (48). Patients who were treated with chemotherapy at the NETDC from 1965 to 1996 reported 504 subsequent pregnancies that resulted in 348 term live births (69.0%), 27 premature deliveries (5.4%), 5 ectopic pregnancies (1.0%), 8 stillbirths (1.6%), and 5 repeat molar pregnancies (1.0%) (48). First- and second-trimester spontaneous abortions occurred in 84 pregnancies (16.7%). There were 25 therapeutic abortions (5.0%). Major and minor congenital anomalies were detected in only ten infants (2.0%). Primary cesarean section was performed in 56 (19.9%) of 281 subsequent term and premature births from 1979 to 1996. It is particularly reassuring that the frequency of congenital malformations was not increased, although chemotherapeutic agents are known to have teratogenic and mutagenic potential.

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16 Breast Disease

Philip I. Haigh and Armando E. Giuliano

An understanding of the pathophysiology of breast disorders, skill at detecting and diagnosing breast cancer, and an appreciation of the numerous options for treating breast cancer are essential for the practicing gynecologist. In this chapter, common benign conditions that mimic malignancy, as well as the diagnosis and management of invasive and preinvasive cancer of the breast, are discussed.

Detection

Physical Examination

Breast tumors, particularly cancerous ones, are usually asymptomatic and are discovered only by physical examination or screening mammography. It is important to record the physical findings of routine breast examination in the medical record for future reference.

Inspection

Inspection is done initially while the patient is seated comfortably with her arms relaxed at her sides. The breasts can be compared for symmetry, contour, and skin appearance. Edema or erythema can be identified easily, and skin dimpling or nipple retraction can be demonstrated by having the patient raise her arms above her head, then press her hands on her hips, thereby contracting the pectoralis muscles. Tumors that distort Cooper's ligaments may lead to skin dimpling with these maneuvers (Fig. 16.1).

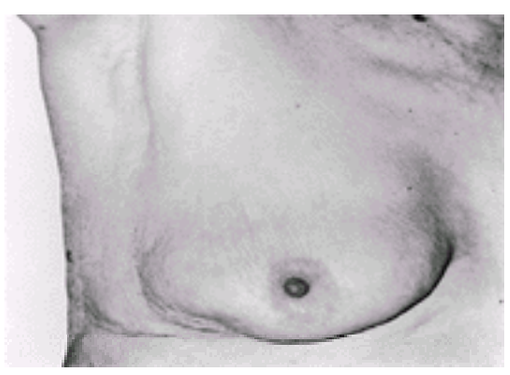


Figure 16.1 Retraction of the skin of the lower, outer quadrant seen only on raising the arm. A small carcinoma was palpable.

Palpation

With the patient seated, each breast should be methodically palpated. An easily reproducible method is to palpate the breast in enlarging concentric circles until the entire breast is palpated. Palpation should be performed with the flat portion of the fingers rather than the tips. While the patient is seated, the examiner may palpate the pendulous breast bimanually by placing one hand between the breast and the chest wall and gently palpating the breast between both examining hands. The axillary and supraclavicular areas should be palpated for enlarged lymph nodes. The entire axilla, the upper outer quadrant of the breast, and the axillary tail of Spence are palpated for possible masses.

The patient is then asked to lie down and raise her arm over her head. The entire breast again is palpated methodically, with the examiner being certain to examine from the clavicle to the costal margin. Placement of a pillow or towel beneath each scapula to elevate the side being examined is important for women with large breasts, because when such women lie flat the breast tends to fall laterally, making palpation of the lateral hemisphere more difficult.

The major features to be identified are tenderness, nodularity, and dominant masses. Most patients have normally nodular breast parenchyma. The nodularity is diffuse, although predominantly in the upper, outer quadrants where there is more breast tissue. The nodules are small, similar in size, and indistinct. Breast cancer, by comparison, is usually a nontender, firm mass, with unclear margins, that feels distinct from the surrounding nodularity. A malignant mass may be fixed to the skin or to the underlying fascia.

During the premenstrual phase, most women have increased innocuous nodularity and engorgement of the breast, which can obscure an underlying lesion. If the physician cannot confirm the patient's finding, the examination should be repeated again in 1 month or after her next menstrual period.

Breast Self-Examination

Breast self-examination (BSE) is advocated as a screening procedure in the hope that breast cancers will be diagnosed at an early stage, leading to a decreased mortality rate. However, there is no evidence to date for this effect from BSE. Only preliminary results are available from ongoing trials in Leningrad and Shanghai that randomized women to either BSE instruction or to a control group. The Leningrad trial suffered from lack of compliance with BSE, and therefore results are not easily interpretable (1). The Shanghai trial randomly assigned over 250,000 women to either BSE instruction (with high participation and proficiency confirmed) or no intervention (2). The number of breast cancers diagnosed in each group was similar, and tumors were equivalent in size and stage. A greater number of benign lesions were detected in the BSE instruction group. Mortality rates at 5 years from entry were similar. Longer follow-up of this trial is required, but there will likely be little, if any survival benefit because of the lack of a stage shift in the intervention group.

In spite of insufficient evidence regarding a survival benefit, it is still appropriate to support BSE as a simple measure to heighten the awareness that women have about changes that may occur in their breasts. BSE supplements screening by clinical breast examination and mammography, and should not be used in isolation.

Although young women have a low incidence of breast cancer, it is important to teach BSE early so that it becomes habitual when they are older. Premenopausal women should examine their breasts monthly during the week after their menses. The reasons most women do not perform BSE are complex, but reassurance, support, and patient education may encourage women to overcome psychological barriers. BSE can also be used by women who have been treated for breast cancer, as a supplemental method to aid in detecting recurrences.

The woman should inspect her breasts while standing or sitting before a mirror, looking for any asymmetry, skin dimpling, or nipple retraction. Elevating her arms over her head or pressing her hands against her hips to contract the pectoralis muscles will highlight any skin dimpling. While standing or sitting, she should carefully palpate her breasts with the fingers of the opposite hand. This may be performed while showering, because soap and water may increase the sensitivity of palpation. Finally, she should lie down and again palpate each quadrant of the breast, as well as the axilla.

Breast Imaging

The two most common and important imaging techniques for the early detection of malignancy are mammography and ultrasonography. Thermography is an outdated technique that is no longer used but frequently emerges in a new and better form only to be discarded again. Newer techniques using magnetic resonance imaging (MRI) and nuclear scintigraphy are emerging and may become applicable in the near future.

Mammography

The original mammographic technique used industrial film and low-kilovoltage equipment, which resulted in radiation doses of almost 10 cGy to the skin (3). Theoretically, this dose may be high enough to induce a small number of cancers among women undergoing screening mammography. Improvements in film and equipment have resulted in a significantly lower dose of radiation and an improved image quality, so the risk of inducing malignancy by mammography has been virtually eliminated.

Mammography is the best method of detection for a nonpalpable breast cancer but occasionally misses some palpable or ultrasonographically detected malignancies. Bilateral mammography is mandatory in the following circumstances:

1. In all patients with a dominant mass, even if biopsy is planned, to exclude disease in the opposite breast
2. In all patients with axillary or supraclavicular lymphadenopathy
3. Before cosmetic breast operations

Mammography produces high-quality images of the breast (Fig. 16.2). With a good technique and well maintained, modern equipment, a film screen mammogram delivers only 0.02 to 0.03 cGy to the mid-breast, with a total skin dose of 0.2 to 0.3 cGy (4,5).

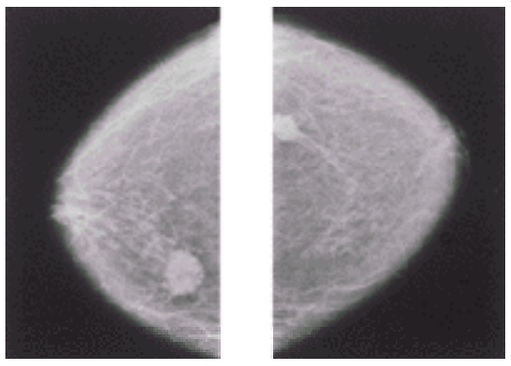


Figure 16.2 Bilateral film screen mammograms showing typical carcinoma in each breast, illustrating the importance of bilateral mammography in the work-up of a clinically apparent mass.

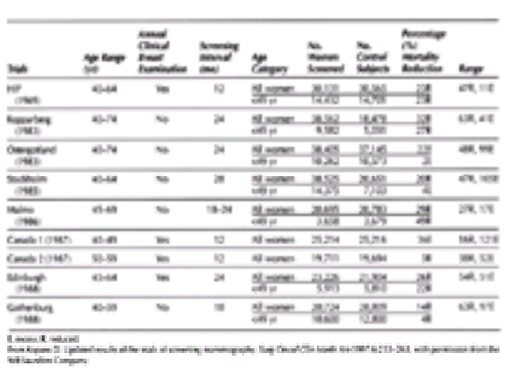
Mammography should be performed only by radiologists who are skilled in its interpretation and who are capable of obtaining good images with good equipment. Vigorous compression of the breast is necessary to obtain good images, and patients should be forewarned that breast compression is uncomfortable.

Signs of Malignancy The most common signs of breast cancer seen on mammography are:

1. A cluster of small calcifications
2. A mass seen as an area of increased radiodensity
3. An area of breast parenchymal distortion
4. Skin thickening or edema

These signs may be obvious even to the untrained, or they may be subtle, appreciated only by the most skilled radiologist. **The findings of malignancy can also be seen with benign lesions, leading to a false-positive rate of 15% to 20%** (6). False-negative mammograms occur particularly in young women with dense breast parenchyma and little fat (4,7). If there are clinically abnormal signs, biopsy of the breast must be performed regardless of the mammographic findings (8).

Screening Mammography **Nine randomized, controlled trials have been performed in the United States, Europe, and Canada that strongly support routine screening mammography in women older than 50 years of age for the early diagnosis of, and reduction in, mortality from breast cancer** (Table 16.1). The evidence is less powerful for screening women between the ages of 40 and 49 years, although the Canadian National Breast Screening Study (CNBSS 1) is the only trial that was specifically designed to investigate screening in that age cohort. An update at 10.5 years from entry into the CNBSS trial shows no impact on mortality from breast cancer in women who are in their fifth decade (9). Some of the other trials do show a benefit with subgroup analysis. When the eight randomized, controlled trials for women screened before 50 years of age were pooled and analyzed in a meta-analysis, the mortality rate for this group of women was found to be reduced significantly by 18% (10).



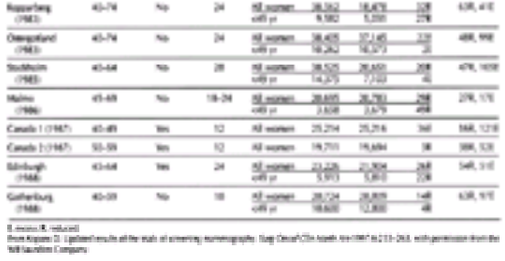


Table 16.1 Randomized Trials of Screening Mammography for Breast Cancer

Screening Guidelines **On the basis of these studies, the American Cancer Society recommends annual mammography for women beginning at 40 years of age.** Clinical breast examination should also be conducted close to the time of the regularly scheduled mammogram (11).

Ultrasonography

Both hand-held and automated breast ultrasonography are popular imaging techniques. Although early reports suggested cancer detection rates nearly as high as those achieved with film screen mammography, repeat studies have failed to show any value for ultrasonography as a screening technique (12).

There is no role for surveying the entire breast using ultrasound; it should be used as an adjunct to scrutinize an area of interest identified as abnormal by mammography or clinical examination. Microcalcifications usually are not detected ultrasonographically, but with new equipment malignant calcifications may be seen. Masses are more difficult to detect in fatty breasts using ultrasound, and this makes mammography more useful in the fatty breasts of older women. In dense breasts seen typically in premenopausal women, ultrasonography may be useful in identifying noncalcified cancers in areas of clinical concern.

Hand-held or real-time ultrasonography is 95% to 100% accurate in differentiating solid masses from cysts (12). In clinical practice, this is of limited value, because a dominant mass should be studied by biopsy, and a needle aspiration can be performed on a cystic mass if it is palpable. Aspiration of fluid is far less expensive than ultrasonography, and when needle aspiration cytologic testing is used, hand-held ultrasonography adds little to the evaluation. The primary role of hand-held ultrasonography is in the evaluation of a benign-appearing, nonpalpable density identified by mammography. If such a lesion proves to be a simple cyst, no further work-up is necessary. However, hand-held ultrasonography may aid in fine-needle aspiration (FNA) biopsy or preoperative localization of nonpalpable lesions.

Magnetic Resonance Imaging

Magnetic resonance imaging is gaining more recognition as an adjunct to mammography for diagnosing lesions in specific clinical scenarios. In general, the specificity of MRI for the diagnosis of breast cancer is low, and false-positive rates are high. MRI may be useful in patients with dense breasts, silicone implants, or postlumpectomy scarring that makes evaluation by mammography difficult (13). In women who have an occult primary breast cancer presenting as axillary adenopathy, there is some promise that MRI can localize these lesions, therefore allowing breast-conserving surgery (14,15).

Scintigraphy

Advances in nuclear medicine have contributed to interest in assessing various radiopharmaceuticals as candidates for breast cancer imaging. ^{99m}*Tc-methoxyisobutylisonitrile*, initially used for assessing cardiac function, shows some promise in breast cancer diagnosis, but its role is yet to be defined (16). Similarly, ^{18}*F-fluorodeoxyglucose*, which has been used for detecting metastases from many other tumors, may have an application in the diagnosis of primary breast cancer. Both appear to lack sensitivity for the detection of small tumors, but with technical refinements, the detection of these tumors may improve.

Benign Breast Conditions

Fibrocystic Disease (Fibrocystic Mastopathy)

The most common breast problem seen in practice is fibrocystic disease. This term refers to a spectrum of clinical signs and symptoms and histologic changes and is not precise. The clinical significance, relationship to cancer, and management of this problem are often misunderstood. In the past, the term *mammary dysplasia* was commonly used. However, the use of this term is misleading. **The essential part of the evaluation of the woman with symptoms of fibrocystic disease is to exclude malignancy, because the diagnosis of fibrocystic disease is otherwise of little clinical significance** (17).

Clinical Presentation

Symptoms and Signs Fibrocystic disease usually appears in women between the ages of 25 and 50 years with multiple, tender, palpable masses that fluctuate with the menstrual cycle. Usually the breasts are most tender and the masses largest just before the menses, and the signs and symptoms abate in the week after menstruation. The symptoms usually abate with menopause. **More than 50% of women between the ages of 25 and 50 years have clinical findings compatible with the diagnosis of fibrocystic disease (17).**

Evaluation The evaluation of a woman with probable fibrocystic disease must exclude malignancy. If physical examination reveals diffuse nodularity, predominantly in the upper, outer quadrants, with no mass being dominant, a mammogram and repeat examination after the next menstrual cycle are all that is necessary. If there is a dominant mass, biopsy is imperative if it does not resolve.

If a clear, watery, colorless, or greenish nipple discharge is found in patients with fibrocystic disease, it should be tested for blood by means of a standard guaiac or Hemoccult test and for cytologic status. If the discharge is not bloody and from multiple ducts, it is most likely benign.

Pathology The histologic features of fibrocystic disease are extremely variable (18). At operation, the surgeon may see fluid-filled cysts or firm, fibrous tumors. A typical cyst is smooth, with blue-green or yellow fluid, and usually there are multiple cysts of varying sizes. Sometimes firm, fibrous tissue has the appearance of a malignancy. Microscopically, the histologic features are extremely pleomorphic, and almost always there is more than one histologic finding. The dominant microscopic features are cysts, sclerosing adenosis, epithelial hyperplasia, and fibrosis.

In most studies of biopsies and autopsies, 60% to 90% of breasts show one or more of these histologic features (19). Probably 80% to 90% of breast biopsies will show some cyst formation. **Most of the histologic findings can be found in asymptomatic women, which lends support to the concept that fibrocystic disease is not really a disease.** It is, however, of value to know whether the epithelium is hyperplastic or atypical.

Cancer and Fibrocystic Disease

Initial evidence for an association was the common histologic finding of fibrocystic disease and malignancy together in the same breast (19,20). However, because one in every eight women has breast cancer in her lifetime, and because 80% to 90% of biopsies show fibrocystic disease, it is not surprising that these two entities frequently coexist. Other studies have shown an increased incidence of prior breast biopsies in women with cancer (21), but the increased incidence in these patients may be a reflection of increased surveillance.

In a study by Dupont and Page (21) to evaluate the relationship between fibrocystic disease and breast cancer, 10,366 women who underwent biopsy from 1950 to 1968 were followed for a median of 17 years. Approximately 70% of the biopsies showed nonproliferative changes, whereas 30% showed proliferative breast disease. Cytologic atypia was present in 3.6% of the cases. Women with nonproliferative disease had no increased risk of breast cancer. **Women with proliferative breast disease and no atypical hyperplasia had a breast cancer risk that was approximately twice that of women with nonproliferative breast lesions. For patients whose biopsy showed atypical hyperplasia, the risk was approximately five times that of women with nonproliferative disease.**

These histologic criteria also were correlated with other risk factors. Family history added little risk for women with nonproliferative breast disease. However, a family history of breast cancer and atypia resulted in a breast cancer risk that was 11 times that for women with nonproliferative breast disease and no family history. Cysts did not increase the risk of breast cancer, but cysts and a family history of breast cancer increased the risk approximately threefold.

Benign Tumors

Intraductal Papilloma

Intraductal papilloma is a benign lesion that is usually solitary and found arising in a major duct close to the nipple in the subareolar location. Presenting most commonly in the fourth decade, the patient usually complains of a unilateral bloody or serous nipple discharge. **The most common etiology of bloody nipple discharge without an associated mass is an intraductal papilloma** (22). Examination often successfully produces discharge from the affected duct by compressing the breast close to the nipple in the affected quadrant. The actual lesion is usually not palpable because it rarely is larger than 5 mm. Mammography should be performed to rule out other abnormalities in the breast because a malignancy may present with bloody nipple discharge.

Treatment **Local excision of the lesion and duct from which it arises is the treatment of choice.** This can be performed using local anesthesia through a paraareolar incision. A lacrimal probe can be used to assist in locating the offending duct. If the duct is not identified, total duct excision can be performed through the same incision. The presence of atypical hyperplasia in a papilloma increases the subsequent risk of invasive breast cancer equivalent to that of proliferative disease with atypia (23).

Fibroadenoma

Fibroadenomas are the most common benign tumors of the breast. They usually occur in young women and may occur in teenagers (21). Before the age of 25 years, fibroadenomas are more common in the breast than are cysts. They rarely occur after menopause, although occasionally they are found, often calcified, in postmenopausal women. It is postulated that they are responsive to estrogen stimulation (21).

Symptoms and Signs Fibroadenomas may be multiple. Clinically, a young patient usually notices a mass while showering or dressing. Most masses are 2 to 3 cm in diameter, but they can grow to an extremely large size (i.e., the giant fibroadenoma). On physical examination, they are firm, smooth, and rubbery. They do not elicit an inflammatory reaction, are freely mobile, and cause no dimpling of the skin or nipple retraction. They are often bilobed. Mammographically, they have typical benign-appearing features with smooth, clearly defined margins. Occasionally, in older women, coarse calcifications can be seen within the fibroadenoma. Only rare cases of carcinoma developing in a fibroadenoma have been reported.

A study by Dupont et al. (24) showed that a fibroadenoma may be associated with a slightly increased risk of breast cancer, which persisted more than 20 years after the diagnosis of the fibroadenoma. Often morphologically variable, fibroadenomas that displayed the histologic features of cysts, sclerosing adenosis, epithelial calcifications, or papillary apocrine changes were associated with an increased risk of invasive cancer compared with fibroadenomas without these complex features. In addition, the study also found that breast cancer was more likely to develop if the adjacent parenchyma showed proliferative disease. Reassuringly, **the patients who had a simple fibroadenoma without complex histologic features and with no proliferative disease in the adjacent parenchyma were at no increased risk for development of invasive cancer.**

Treatment Once a fibroadenoma is suspected, its diagnosis should be confirmed by either excisional biopsy or FNA cytologic analysis. Complete excision under local anesthesia can treat the lesion and confirm the absence of malignancy, but usually is not necessary. Alternatively, a fibroadenoma diagnosed by clinical examination, imaging, and FNA may be followed. In younger women, fibroadenomas may diminish in size or even totally resolve, and therefore excision can be avoided (25,26).

Benign Phyllodes Tumor

Phyllodes tumors, previously named *cystosarcoma phyllodes*, are fibroepithelial tumors characterized by hypercellular stroma combined with an epithelial component lining clefts or cysts. Clinically, phyllodes tumors tend to occur in the fifth to sixth decade (27). These lesions are rarely bilateral and usually appear as isolated masses that are difficult to distinguish clinically from a fibroadenoma. Size is not a diagnostic criterion, although phyllodes tumors tend to be larger than fibroadenomas, probably because of their rapid growth. There are no good clinical criteria by which to distinguish a phyllodes tumor from a fibroadenoma (28).

Pathology **Phyllodes tumors have been classified as benign, borderline, and malignant.** The histologic distinction between fibroadenoma, benign phyllodes tumor, and malignant phyllodes tumor can be very difficult (28). Pathologic criteria describing features of the stromal component have been used to help distinguish between the benign and malignant spectrum. Tumor margins, whether pushing or infiltrative, degree of stromal cellularity or overgrowth, presence of tumor necrosis, cellular atypia, and number of mitoses are all used to assign benignity or malignancy (29). **Those tumors that are judged by the pathologist to be benign tend to recur locally in up to 10% of patients, whereas malignant phyllodes tumors may recur locally in up to 40%, but also can metastasize to the lungs** (30,31 and 32). Axillary lymph node metastases are extremely unusual. Often, the appearance of metastases is the first sign that a phyllodes tumor is malignant. True soft tissue sarcomas occur in the breast but are rare.

Treatment **Treatment of phyllodes tumors should consist of wide, local excision** (28,31). Massive tumors or large tumors in relatively small breasts and those malignant tumors with particularly infiltrative margins may require mastectomy. Mastectomy should be avoided whenever possible, however, and axillary lymph node dissection is not indicated. Typically, a patient undergoes an excisional biopsy of a mass believed to be a fibroadenoma, but histologic examination reveals a phyllodes tumor. When the pathologic diagnosis is malignant phyllodes tumor, a complete reexcision of the area should be undertaken so that the prior biopsy site and any residual tumor are excised. Radiation therapy is of unknown value and probably should be avoided.

Breast Cancer

Breast cancer accounts for approximately 30% of all new cancer cases in women and is second only to lung cancer as the leading cause of cancer deaths in women. In 2000 in the United States, an estimated 182,800 new cases of invasive breast cancer will be diagnosed in women, with approximately 40,800 deaths (33). In the United States, the overall lifetime risk for development of breast cancer in women is one in eight (34). However, the longer a woman lives free of breast cancer, the less likely it is she will have breast cancer in the remaining years of her life. **There has been a significant increase in the incidence of breast cancer in the United States during the past 50 years, but this correlates with the increased use of screening mammography. The mortality rate, however, remained fairly flat from 1973 to 1990, with an increase of only 1.5%, followed by a relatively sharp decline from 1991 to 1995** (35). Screening mammography has also resulted in a decrease in size of breast cancer at diagnosis, with close to one third of cancers having a size of 1 cm or less (36). Not surprisingly, the proportion of cases with ductal carcinoma *in situ* (DCIS) has increased, and it is predicted that in the next decade these trends will continue.

Predisposing Factors

Age

The likelihood for development of breast cancer increases steadily with age. Before the age of 25 years, breast cancer is rare; this age group accounts for fewer than 1% of all cases of breast cancer. After the age of 30 years, there is a sharp increase in the incidence, with a small plateau between the ages of 45 and 50 years (37). Women between 40 and 50 years of age may have a lower mortality rate from the disease than older women (38).

Prior History of Cancer

One of the strongest single risk factors for the development of a primary breast cancer is the previous diagnosis of a contralateral breast cancer. At autopsy, microscopic breast cancer has been found in the contralateral breast in approximately 50% of women treated for invasive breast cancer (39). However, clinical breast cancer can be detected in the contralateral breast in only 5% to 8% of patients. *Lobular carcinoma* has a higher incidence of bilaterality than does *ductal carcinoma.*

Family History

Any family history of breast cancer increases the overall relative risk (40). However, women whose mothers or sisters had breast cancer after menopause are not at significantly increased risk, whereas women whose mothers or sisters had bilateral premenopausal breast cancer have at least a 40% to 50% likelihood of acquiring the disease. If the patient's mother or sister had unilateral premenopausal breast cancer, the likelihood of the patient having breast cancer is approximately 30%.

Inherited Breast Cancer Syndromes

Most breast cancers occur sporadically without a recognizable hereditary association. However, **approximately 5% to 10% of all breast cancers arise in genetically susceptible individuals who have inherited one or more mutations in genes that are transmitted in an autosomal dominant fashion** (41). This translates to approximately 18,000 cases per year in the United States. These hereditary breast cancer syndromes are considered to be a subset of familial breast cancer. *BRCA1*, mapped to chromosome 17q21, and *BRCA2*, located on chromosome 13q12-13, are two tumor suppressor genes that have been identified, and when mutated may be responsible for up to 90% of inherited breast cancers (42). Mutations of the *BRCA1* gene carry a lifetime risk of up to 87% for the development of breast cancer and 44% for ovarian cancer (43,44). An increased risk also exists for the development of colon cancer. This mutated gene is responsible for approximately half of all patients with hereditary early-onset breast cancer syndrome and most of those with breast-ovarian cancer syndrome. A particular mutation in *BRCA1*, the frameshift mutation at position 185 producing a deletion of adenine and guanine (185delAG), has been implicated in approximately 20% of Ashkenazi Jewish women in whom breast cancer develops before the age of 40 years (45,46). The *BRCA2* gene is often responsible for the early-onset breast cancer syndrome not associated with *BRCA1* (41,47). These genes are large and many different mutations may occur, which are associated with highly variable risks for the development of breast, ovarian, and other cancers (48).

There are other hereditary syndromes associated with breast cancer with autosomal dominant transmission, such as Li-Fraumeni syndrome, Cowden's disease, Muir-Torre syndrome, and hereditary nonpolyposis colon cancer. These are each associated with an abnormal gene that is responsible for producing a recognized phenotype. These syndromes contribute to only a small fraction of hereditary breast cancers seen in clinical practice.

Reproductive and Hormonal Factors

A number of studies have shown a relationship between early menarche, late menopause, and breast cancer (49,50,51 and 52). The median age at menarche is lower for women with breast cancer than for those who never have the disease (52). **The longer a woman's reproductive phase, the higher the risk for development of breast cancer** (50). No clear association has been found between the risk of breast cancer and menstrual irregularity or duration of menses. Lactation does not affect the incidence of breast cancer, but childbearing definitely does (51). **Women who have never been pregnant have a higher risk of breast cancer than those who are multiparous.** However, it is the age at first childbirth that alters the incidence of breast cancer, with the older primigravida having a higher incidence (51).

There have been conflicting reports concerning the effect of oral contraceptives and hormonal replacement therapy on the incidence of breast cancer. Many studies have shown no adverse effect of oral contraceptives on breast cancer incidence, whereas some have shown an increased incidence. **A large meta-analysis of 54 epidemiologic studies found convincing evidence that a small increased relative risk of breast cancer exists in women who were either currently using oral contraceptives or who had stopped for less than 10 years** (53). A diminution in relative risk occurred throughout 9 years after cessation. There was no excess risk 10 or more years after stopping use. Furthermore, those breast cancers in the women who had ever used oral contraceptives were more likely to be localized to the breast. No risk factors such as family history or reproductive history changed the results when related to the time since cessation. Similarly, the duration of use, age at first use, and the dose and type of hormone were not important features.

Studies on the use of estrogens to treat menopausal symptoms have also generated great debate regarding a possible increase in breast cancer incidence. An analysis of the participants in the Nurses' Health Study revealed that the risk of breast cancer was increased among women who were currently using either estrogen alone or in combination with a progestin, with relative risks of 1.32 and 1.41, respectively (54). However, in a separate analysis of data generated from the same study, **current hormone users had a lower risk of death from all causes than women who had never used hormones** (55). **The reduction in mortality was largely attributed to a reduction in cardiovascular mortality,** especially in participants with multiple coronary risk factors. With 10 or more years of use, the benefit was much less apparent because of the increase in deaths from breast cancer.

An overview of five meta-analyses supports a slight increase in risk of breast cancer for current hormone users, but no significant increase in women who were previous users compared with never-users of hormone replacement (56). **This slight increase in risk of breast cancer from hormone replacement therapy obviously must be balanced with the improved quality of life achieved in reducing postmenopausal symptoms.**

The decision to initiate hormone replacement therapy is influenced by the estimated risk of breast cancer and the variable mortality reduction when such factors as cardiac risks are considered. Duration of use must be individualized with each patient, taking into consideration the symptoms of menopause, the risk for harm, which will likely increase with prolonged use, and the survival benefit, which will likely diminish over time.

Diet and Obesity

Marked differences in the incidence of breast cancer among women in different geographic areas have been correlated with mean annual per capita consumption of various nutrients. Obesity and high-fat diets in particular have been used to explain the marked differences in international incidences of breast cancer (57). **However, it is not clear that obesity is a specific risk factor because most studies have not clearly separated obesity from other known risk factors** (52). A large pooled analysis of seven cohort studies including 337,819 women that compared those in the highest quintile of total fat intake with those in the lowest quintile found no evidence of a positive association between fat intake and risk of breast cancer (58). In the same study, relative risks associated with the type of fat intake and cholesterol ingested also were not significantly different.

There is inconclusive evidence that a high-fiber diet may protect against breast cancer, but two large, prospective trials in the United States did not find any association between fiber intake and the risk of breast cancer (59,60). It has also been postulated that the antioxidant activity of vitamins A, C, and E may provide a cellular defense against DNA damage induced by reactive oxygen species (61). However, two large cohort studies have found little evidence that these vitamins have any role in influencing breast cancer risk (62,63).

Alcohol

Alcohol consumption may increase the risk of breast cancer (64). A pooled analysis of seven prospective case–control studies from the United States (Nurses' Health Study, Iowa Women's Health Study, New York State Cohort), Canada (CNBSS), The Netherlands (Netherlands Cohort Study), and Sweden (Sweden Mammography Cohort) was performed. From a total of 322,647 women with follow-up to 11 years, this pooled study found a linear increase in the relative risk of breast cancer, from 9% to 41%, in women with a daily alcohol consumption of 10 g/day (approximately one drink per day) to those who consumed 60 g/day (approximately five drinks per day), respectively, compared with nondrinkers (65). The type of alcoholic beverage did not influence relative risk estimates.

Diagnosis

Breast cancer may occur anywhere in the breast, but it is most commonly found in the upper, outer quadrant, where there is more breast tissue. Extension of the “tail of Spence” into the axilla further increases the likelihood that a tumor will develop in this quadrant.

Most breast cancers are discovered by the patient when she feels a painless mass. Less commonly, the tumor is found by the physician during a routine breast examination. Rarely, the patient may have an axillary mass and no obvious malignancy in the breast, or the abnormality may be found on a screening mammogram without a palpable tumor. Conversely, the findings on mammography may raise the suspicion that a palpable lesion is a breast cancer (66,67).

Physical examination alone is quite inaccurate for the diagnosis of most breast cancers. In older women with fatty breasts in which the tumor is more obvious, the diagnosis can be made more accurately by physical examination, whereas younger women with dense, often nodular breasts are extremely difficult to examine. An area of thickening amid normal nodularity may be the only clue to an underlying malignancy. Skin dimpling, nipple retraction, or skin erosion is usually obvious, but these are late signs and, fortunately, are unusual at presentation. Algorithms for the evaluation of breast masses in premenopausal and postmenopausal women are presented in Fig. 16.3 and Fig. 16.4.

Figure 16.3 Schematic evaluation of breast masses in premenopausal women.

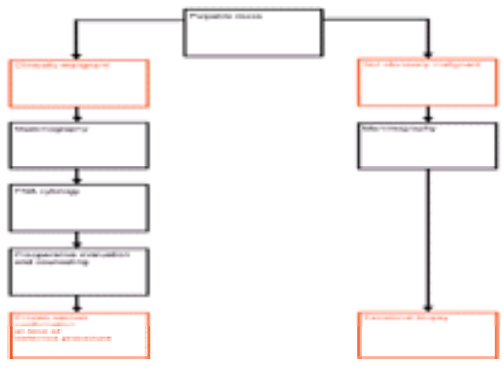


Figure 16.4 Schematic evaluation of breast masses in postmenopausal women.

A dominant breast mass in a woman of any age must be approached as a possible carcinoma. Approximately 30% to 40% of lesions thought clinically to be malignant are found to be benign on histologic examination (66). **Conversely, 15% to 20% of lesions believed clinically to be benign are proven malignant by open biopsy** (67). **Clinical judgment is insufficient to undertake definitive treatment of carcinoma.**

Fine-Needle Aspiration Cytologic Testing

Fine-needle aspiration is performed with a 20- or 22-gauge needle. **The technique has a high diagnostic accuracy, with a 10% to 15% false-negative rate and a rare but persistent false-positive rate** (68).

If a mass appears to be malignant on physical examination and/or mammography, FNA cytologic evaluation can aid the clinician in discussing alternatives with the patient. A negative FNA cytologic diagnosis often must be followed with excisional biopsy. Most clinicians are reluctant to perform a mastectomy on the basis of FNA cytologic results because of the rare false-positive diagnosis. An FNA cytologic diagnosis of a fibroadenoma in a young woman can be used to follow the mass safely.

Biopsy

Image-Guided Core-Needle Biopsy The refinement of core-needle biopsy (CNB) has enabled the procurement of tissue for accurate histopathologic diagnosis of nonpalpable mammographic or ultrasonographic lesions using a less invasive procedure than open biopsy. CNB retrieves a specimen in which abnormal tissue architecture and invasion can be identified and therefore may be preferable to FNA. Indications for stereotactic CNB are the same as for open biopsy. After high-quality mammographic images of nonpalpable lesions have been obtained, those that are suspicious or highly suggestive of malignancy should be sampled for biopsy.

Since the mid-1990s, a number of studies have shown sensitivity and specificity ranges of 85% to 100% for diagnosing breast cancer using stereotactic CNB (69). When microcalcifications are sampled, specimen radiography must be performed to ensure they are present in the tissue removed.

Technical issues such as a very small breast or a lesion that is too deep or very superficial may make the procedure difficult. A lesion in a breast that has a silicone implant is probably best diagnosed with an open biopsy to avoid implant rupture. Hand-held CNB under ultrasonic guidance is simpler and less expensive than stereotactic CNB and does not require special equipment.

Open Biopsy Although a definitive diagnosis can be made in most cases using CNB, some patients require subsequent open biopsy if CNB is not indicated or inadequate, or the pathologic results are equivocal. Similarly, if benign diagnoses of radial scar or atypical ductal hyperplasia are made after CNB, follow-up open biopsy is indicated because of the coexistence of malignancy in 20% and 50% of cases, respectively (69). Most importantly, the biopsy results must correlate with the clinical and mammographic results, and any discrepancy warrants additional biopsy, either repeat CNB or open biopsy.

Open biopsy can usually be performed in the outpatient setting with the aid of local anesthesia. The following steps are undertaken:

1. ***Local anesthesia is used to infiltrate the skin and subcutaneous tissue surrounding the palpable mass.*** Intravenous sedation often aids in easing anxiety.
2. ***An incision is made directly over the mass.*** It should be planned to allow an ellipse of skin to be either excised with the mastectomy or placed cosmetically so that partial mastectomy can be performed through the same incision. Paraareolar incisions are best avoided, particularly if the tumor is far from the areola and excision would result in contamination of a large segment of breast with malignant cells.
3. ***Once the skin and underlying tissue are incised, the mass can be gently grasped with Allys forceps or with a stay suture and delivered into the operative field.***
4. ***The mass should be totally excised whenever possible.*** Large masses that are difficult to excise totally with local anesthesia can be incised. However, a frozen section should be obtained to confirm that malignant tissue has been obtained with an incisional biopsy.
5. ***Once the mass is excised, adequate hemostasis is achieved and the incision is closed.*** A cosmetically superior result is achieved if the breast parenchyma is not reapproximated deeply. The most superficial subcutaneous fat can be reapproximated with fine, absorbable sutures. The skin is best closed with a subcuticular suture or Steri-Strips to achieve the most cosmetically pleasing result. Usually no drain is necessary.

Mammographically Localized Biopsy Open biopsy after failed CNB or of mammographically detected nonpalpable lesions that are not amenable to image-guided CNB can be difficult, and the procedure requires the cooperation of the surgeon and the mammographer. **The technique relies on the placement of a needle or specialized wire into the breast parenchyma at or near the site of the suspected abnormality.** Many mammographers also inject a biologic dye to assist localization further. The surgeon then reviews the films with the mammographer and localizes the abnormality with respect to the tip of the wire or needle. An incision is made directly over this area, and that small portion of the breast that is suspected of containing the mammographic abnormality is excised. A mammogram of the surgical specimen is performed to be certain that the abnormality has been excised.

Two-Step Approach The two-step approach involves initial biopsy followed by subsequent definitive treatment. This has been facilitated by stereotactic CNB. In addition, women who do have cancer can discuss the alternative forms of therapy and obtain a second opinion, if desirable, before undergoing definitive treatment. Psychologically, it is preferable for the patient to be involved in the planning of her therapy.

For patients with obvious malignancy in whom mastectomy is the treatment of choice, it is reasonable to obtain a biopsy specimen and a frozen section, to be followed immediately with mastectomy. The treatment can be discussed in advance in such patients.

Pathology and Natural History

Numerous histologic types of breast cancer can be identified microscopically (18,70). **The malignancy arises either in the ducts or in the lobules.** With some exceptions, it appears that most *lobular carcinomas* have their origin within the small terminal ducts of the lobules. *Ductal carcinomas* usually arise from the larger ducts or the intralobular ducts. However, the distinction between lobular and intraductal carcinoma is based more on the histologic appearance than on the site of origin.

The cancer may be either invasive (infiltrating ductal carcinoma, infiltrating lobular carcinoma) or *in situ* [DCIS or lobular carcinoma *in situ* (LCIS)]. The histologic subtypes (i.e., scirrhous, tubular, medullary) often referred to by the pathologist are usually morphologic distinctions among the various patterns of infiltrating ductal carcinoma.

The most common histologic diagnosis is infiltrating ductal carcinoma, type not specified. This histologic type accounts for 60% to 70% of the breast cancers in the United States (70). Mammographically, it is characterized by a stellate appearance with microcalcifications. Macroscopically, there are gritty, chalky streaks within the substance of the tumor that most likely represent necrosis, whereas microscopically, there is invasion of the surrounding fat. There is often a fibrotic response surrounding the invasive carcinoma.

Other types of infiltrating ductal carcinoma are far less common. ***Medullary carcinoma*** accounts for approximately 5% to 8% of breast carcinomas, arises from larger ducts within the breast, and has a dense lymphocytic infiltrate. The tumor may be a slow-growing, less aggressive malignancy than the usual infiltrating ductal carcinoma. ***Mucinous (colloid) carcinoma*** accounts for fewer than 5% of all breast cancers. Grossly, the tumor may have areas that appear mucinous or gelatinous. ***Infiltrating comedo carcinoma*** accounts for fewer than 1% of breast malignancies and is an invasive cancer characterized by foci of necrosis, which, when cut grossly, exude a comedo, necrotic substance. Usually comedo carcinomas are *in situ* malignancies. ***Papillary carcinoma*** is used to describe a predominantly noninvasive ductal carcinoma. However, these tumors may be invasive; when invasive components are present, they should be called *invasive papillary carcinomas.* ***Tubular carcinoma*** is a well differentiated breast cancer that accounts for fewer than 1% of all breast malignancies. ***Adenoid cystic carcinomas*** are extremely rare and are similar histologically to those seen in the salivary glands. They tend to be well differentiated and to metastasize late (70).

Growth Patterns

The growth potential of a breast cancer and the immunologic resistance of the individual woman to the malignancy vary widely among patients and at different stages of the disease. **Estimates of the doubling time of breast cancer range from several weeks for rapidly growing tumors to months or years for slowly growing ones.** If the doubling time of a breast tumor was constant and a tumor originated from one cell, a doubling time of 100 days would result in a 1-cm tumor in approximately 8 years (71) (Fig. 16.5). During this preclinical phase, tumor cells may be circulating throughout the body.

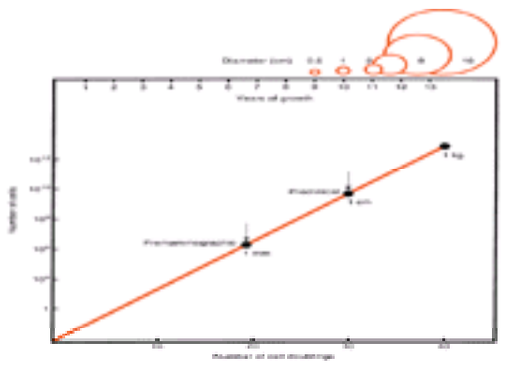


Figure 16.5 Growth rate of breast cancer, indicating long preclinical phase. (From Gullino PM. Natural history of breast cancer: progression from hyperplasia to neoplasia as predicted by angiogenesis. *Cancer* 1977;39:2699. Copyright 1977 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.)

Because of the long preclinical tumor growth phase and the tendency of infiltrating lesions to metastasize early, many clinicians view breast cancer as a systemic disease at the time of diagnosis. However, many women can be treated successfully with surgery alone for breast cancer, and some women have been cured even in the presence of palpable axillary disease. For this reason, a pessimistic attitude that breast cancer is systemic and incurable at the time of diagnosis is unwarranted.

A more realistic approach may be to view breast cancer as a two-compartment disease: one is the primary tumor in the breast with all the inherent problems of local and regional extension and primary tumor control, and the other consists of the systemic metastases with their life-threatening consequences.

Although the natural history of breast cancer can involve metastases to any organ, 85% of women with metastatic breast cancer have involvement of bone, lungs, or liver (72,73 and 74). If any of these sites are involved, metastases in other organs are highly likely. The use of systemic chemotherapy is altering the common sites of metastases, and more unusual metastatic sites are being seen with greater frequency. Bone metastases can give rise to pathologic fractures and/or hypercalcemia, and hypercalcemia develops in approximately 5% to 10% of women with metastatic breast cancer (73).

Staging

After the diagnosis of breast cancer has been established, either cytologically or histologically, the clinical stage of the disease should be determined. **The TNM (tumor–nodes–metastases) system has been recommended by the International Union Against Cancer and the American Joint Committee on Cancer and is presented in Table 16.2 and Table 16.3** (75). **This system has the advantage of being both a preoperative clinical staging system and a postoperative or pathologic staging system.**

Table 16.2 TNM System for Staging of Breast Cancer

Stage 0	T_{is}	N_0	M_0
Stage I	T_1*	N_0	M_0
Stage IIA	T_0	N_1	M_0
	T_1*	N_1*	M_0
	T_2	N_0	M_0
Stage IIB	T_2	N_1	M_0
	T_3	N_0	M_0
Stage IIIA	T_0	N_2	M_0
	T_1*	N_2	M_0
	T_2	N_2	M_0
	T_3	N_1	M_0
	T_3	N_2	M_0
Stage IIIB	T_4	Any N	M_0
	Any T	N_3	M_0
Stage IV	Any T	Any N	M_1

†T_1 includes T_{1mic}.
‡The prognosis of patients with N_{1mi} is similar to that of patients with pN_1. Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, IL. The original source for this material is the AJCC cancer staging manual. 5th ed. Philadelphia: Lippincott-Raven, 1997.

Table 16.3 TNM Stage Grouping of Breast Cancer

Preoperative Evaluation

The extent of preoperative work-up varies with the initial stage of the disease (76). For most patients with small tumors, no palpable lymph nodes (TNM stage I or II), and no symptoms of metastases, the preoperative evaluation should consist of:

1. Bilateral mammograms
2. Chest radiograph
3. Complete blood count
4. Screening blood chemistry tests

A routine *bone scan* and *liver scan* are not necessary unless symptoms or abnormal blood chemistry suggest bone or liver metastases. For patients with clinical stage II disease, a bone scan should be obtained, but a liver scan is not necessary unless symptoms or liver function tests suggest liver metastasis. Patients with clinical stage III or IV disease should have both a bone scan and a liver scan. A bone marrow biopsy should be performed if there is obvious bone marrow dysfunction but metastases are not evident on bone scan. Some advocate a bone marrow aspiration biopsy as an important prognostic test that may supplant axillary dissection for staging (77).

Treatment

Mastectomy

The traditional treatment of breast cancer has been surgical, but the type of operation used has remained a controversial and highly emotional issue. Before Halsted in the 19th century, surgical treatment of breast cancer was haphazard, and it varied from local excision alone to total mastectomy (78). Halsted devised the radical mastectomy in an attempt to treat carcinoma of the breast rationally based on his understanding of breast cancer as a local infiltrative process. The radical mastectomy was planned to remove the entire breast, the underlying pectoral muscles, and the axillary lymph nodes in continuity (79) (Fig. 16.6). However, the initial operation was designed to treat patients who had palpable axillary lymph nodes, and lesions that were at least clinical stage III.

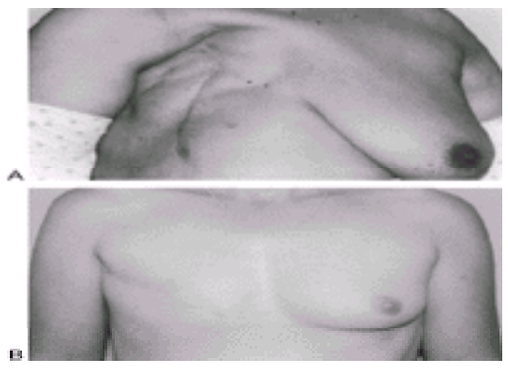


Figure 16.6 Defect after radical mastectomy (A), **compared with modified radical mastectomy** (B).

During the 20th century, extensions and modifications of the radical mastectomy were devised to remove more local and regional tissue. Supraclavicular node dissections were added to the radical mastectomy (80). In addition, supraclavicular, mediastinal, and internal mammary lymph node dissections were performed, with high mortality rates (81).

Urban (82) added an *en bloc* internal mammary lymph node dissection to the standard radical mastectomy. This technique became popular and is the operation commonly referred to as the *extended radical mastectomy.* The extended radical mastectomy has not produced an enhanced overall survival (83). Few patients without grossly involved axillary lymph nodes have involvement of internal mammary nodes, and current understanding of the biologic behavior of breast cancer makes such locally destructive surgical endeavors unnecessary.

Modified Radical Mastectomy

In an attempt to improve the functional and cosmetic results of the radical mastectomy, a modification in which the pectoralis major muscle is preserved was developed (Fig. 16.6B) (84,85). The removal of the breast is similar to that of the radical mastectomy; however, removal of the skin and the axillary lymph node dissection are not as extensive, and there is usually no need for skin grafting.

The advantage of the modified radical mastectomy is a better functional and cosmetic result. The radical mastectomy has been essentially replaced by the modified radical mastectomy, which remains the most common operation performed for this disease. There is no difference in survival between the two operations (86).

Total (Simple) Mastectomy

Total mastectomy is the removal of the entire breast, nipple, and areola without removal of the underlying muscles or axillary lymph nodes. The low-lying lymph nodes in the upper, outer portion of the breast and low axilla usually are included in the specimen. This form of treatment results in local control rates that are comparable with those of radical or modified radical mastectomy, but failure to examine the axillary lymph nodes microscopically makes this operation less desirable in general because the addition of adjuvant chemotherapy improves survival in certain patients with positive nodes.

Breast-Conserving Surgery

Radiation therapy alone without excision of the tumor is associated with a high local failure rate (87,88,89 and 90). Veronesi et al. (91,92) reported the first major, prospective, randomized trial comparing standard surgery with a combination of surgery and modern radiotherapeutic techniques. Patients were randomly assigned to either (a) quadrantectomy, axillary lymph node dissection, and postoperative radiation; or (b) the standard Halsted radical mastectomy. Only patients whose tumors were smaller than 2 cm and not centrally located and who had no clinical evidence of axillary lymph node disease ($T_1N_0M_0$) were considered for this trial. The 701 women who were randomized to either of the two groups were comparable in age, tumor size, menopausal status, and histologic involvement of the axillary lymph nodes (92). After 8 years of follow-up, there have been no statistically significant differences between the two groups in either local control or overall survival (Table 16.4).

	Halsted (% ± SE)	*Quadrantectomy + RT* (% ± SE)
No. of patients	349	352
Overall survival	83 ± 2.2	85 ± 2.1
Disease-free survival	77 + 2.4	80 ± 2.4

RT, radiation therapy; SE, standard error of the mean.
Reprinted from Veronesi U, Zucali R, Luini A, et al. Local control and survival in early breast cancer: the Milan trial. Int J Radiat Oncol Biol Phys 1986;12:717–720. copyright © 1986, with permission from Elsevier Science.

Table 16.4 Halsted Radical Mastectomy versus Quadrantectomy, Axillary Dissection, and Radiation Therapy: Results of the Randomized Milan Trial

The National Surgical Adjuvant Breast and Bowel Project (NSABP) conducted a trial that extended these observations (93). Eligible patients could have a primary tumor no larger than 4 cm, with or without palpable axillary lymph nodes, provided that the lymph nodes were not fixed (i.e., stage I or II, T_1 or T_2, and N_0 or N_1). Patients were assigned randomly to (a) the modified radical mastectomy; (b) segmental mastectomy (lumpectomy) and axillary lymph node dissection; or (c) segmental mastectomy, axillary lymph node dissection, and postoperative radiation therapy (Fig. 16.7). Unlike the quadrantectomy, segmental mastectomy or "lumpectomy" consists of removing only the tumor and a small rim of normal surrounding tissue. Patients were considered ineligible if they were found to have microscopic involvement of the margins. A total of 1,843 women were randomized among the three treatment arms, and the groups were comparable. The lowest local recurrence rate (7.7%) was seen among patients treated with segmental mastectomy and postoperative radiation therapy, whereas it was predicted that 27.9% of the patients undergoing segmental mastectomy without radiation therapy would have a local recurrence within 5 years. Although the addition of radiation clearly improved the local control rate, no significant difference in overall survival or disease-free survival could be seen among the three treatment arms; there was a trend, however, in favor of patients who received radiation. **This NSABP study clearly shows that segmental mastectomy, axillary lymph node dissection, and postoperative radiation therapy were as effective as modified radical mastectomy for the management of patients with stage I and II breast cancer.** The high local recurrence rate without radiation therapy makes limited surgery alone unacceptable except in unusual circumstances.

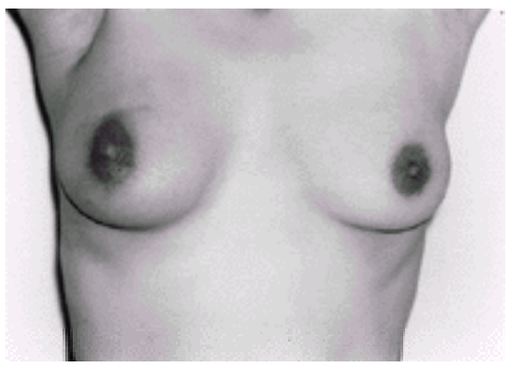


Figure 16.7 Appearance after lumpectomy, axillary dissection, and radiation therapy.

Axillary Lymph Node Dissection

Although the axillary nodal status remains the best predictor of patient survival, there are no noninvasive techniques to determine whether metastases are present. The procedure is therapeutic if metastases are present in the axilla because it provides excellent regional control, and also allows accurate staging for prognostic purposes and management decisions regarding adjuvant therapy.

Axillary dissection as part of breast-conserving surgery is performed through a separate incision just inferior to the hair-bearing area of the axilla. The axilla has been anatomically divided into three levels based on the relations to the pectoralis minor muscle. Most surgeons perform a level I and II dissection, removing all fatty and lymph node–bearing tissue from beneath and lateral to the pectoralis minor muscle. Cases in which lower levels in the axilla are free of metastases but the higher levels are involved, so-called *skip metastases*, are few (94). If at surgery palpable nodes are encountered in level III, that area medial to the pectoralis minor, then a complete level I, II, and III dissection should be performed.

A National Institutes of Health Consensus Development Conference (95) concluded that for early breast cancer, removal of level I and II nodes should be routine both for accurate staging and the prevention of axillary recurrences. With the advent of mammography, breast cancer size and nodal positivity at diagnosis are diminishing, with only approximately 30% of patients having involved axillary nodes detected by standard pathologic techniques (36). This has led some authorities to question the value of routine axillary dissection in patients with early invasive breast cancers (36). Complications are rare, but lymphedema of the arm continues to be problematic for 10% to 20% of patients, and it may occur any time after treatment.

Sentinel lymphadenectomy, a more recent development, is a minimally invasive procedure that accurately stages patients by removing one or two sentinel nodes, those lymph nodes that are most likely to contain tumor if metastasis has occurred. Before lumpectomy, a blue dye or radioisotope is injected close to the tumor and is transported into the lymphatics. A limited dissection is performed in the axilla to isolate the blue-stained or radioactive sentinel nodes. These sentinel nodes may be removed and analyzed using immunohistochemistry to identify small foci of metastases. It has been shown that if the sentinel node is free of tumor, then there is a high likelihood that the rest of the axillary nodes will also be free of tumor, thus abrogating the need for a complete lymph node dissection (96,97). The false-negative rate is low in experienced hands, and can be 0% with adherence to technical detail and proper patient selection (97). This procedure accurately stages the patient with little risk of lymphedema, which makes it an attractive, practical alternative to complete axillary lymph node dissection in node-negative women. **Sentinel lymphadenectomy must still be regarded as experimental, however, until formal, randomized, controlled trials compare it directly with complete axillary lymph node dissection.**

Adjuvant Radiation Therapy

Adjuvant radiation after breast-conserving procedures is essential for the achievement of recurrence rates equivalent to those obtained with mastectomy. The concept of total mastectomy and adjuvant radiation therapy was developed by McWhirter (98). Most prospective, randomized and historical control studies show that radiation therapy, when combined with radical surgery, improves local control but does not improve survival (99,100,101 and 102).

A prospective, randomized trial by the NSABP examined the role of postoperative radiation therapy (103). Patients were randomly assigned to therapy consisting of (a) total mastectomy, (b) radical mastectomy, or (c) total mastectomy with radiation therapy. This trial showed no difference in survival among the three groups of patients, although local control was improved in patients treated with total mastectomy and radiation therapy.

In the 1980s, failure to show any survival advantage for adjuvant radiation led to a decline in its use. Two randomized trials from Denmark and Canada have renewed interest in radiation in addition to chemotherapy after mastectomy because of evidence not only of reduced recurrence rates, but of improved survival in premenopausal node-positive women. In the Danish study, with a median follow-up of 10 years, overall survival was improved by 9% with the addition of radiation to the chest wall and all regional nodes, regardless of the number of involved nodes (104). In the Canadian study, with a follow-up of 15 years, the addition of radiation in a similar manner resulted in a 10% increase in breast-cancer specific survival (105). These studies have generated speculation that locoregional disease may give rise to further distant dissemination. Risks are likely increased with such wide-field radiation, notably to the heart if the left side of the chest is being treated, and these must be considered before routinely treating all such patients with radiation.

Adjuvant Systemic Therapy

The 10-year survival rate for women who have metastases in axillary nodes is only approximately 40% to 50%. The current hypothesis is that breast cancer can metastasize early, and patients can have clinically undetectable systemic micrometastases during primary surgery that are responsible for later recurrences (106). This motivated investigation into the use of systemic therapy as an adjuvant to local surgical treatment.

The results of many well designed, randomized trials support the use of adjuvant systemic therapy. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) has provided an overview and meta-analyses of these trials on the effects of adjuvant chemotherapy, *tamoxifen*, and ovarian ablation on recurrences and mortality (107,108 and 109).

Adjuvant Chemotherapy

Results available on 11,000 women in the trials that compared adjuvant polychemotherapy (more than one chemotherapeutic agent) versus no chemotherapy show that recurrence-free survival diverged early in women treated with polychemotherapy, with a statistically significant absolute reduction in recurrences of 8.4% at 10 years, with most of the effect attributable in the first 5 years (108). Death rates were reduced by polychemotherapy by 3.2% at 5 years and continued to diverge to 6.3% at 10 years, both highly significant differences. When subdivided into nodal status, the improved recurrence-free survival and mortality reduction that polychemotherapy imparted appeared to be greater in women with positive nodes.

When analyzed as a proportional reduction in annual risk, polychemotherapy overall reduced the recurrence rate and mortality by 28% and 16%, respectively, both of which are highly significant. Most trials used the standard regimen of *cyclophosphamide, methotrexate*, and *5-fluorouracil* (CMF) given for six cycles. Combination chemotherapy was more effective than single-agent therapy, and 6 months of polychemotherapy was found to be as effective as more prolonged treatment.

Finally, when subdivided according to patient age, the benefits were greater in younger women for both recurrence rates and mortality. However, even women aged 60 to 69 years had a 20% delay of breast cancer recurrence, a highly significant improvement in disease-free survival, and a 10% reduction in mortality, which was not statistically significant.

The available data from the EBCTCG meta-analysis support chemotherapy as an adjuvant modality for early breast cancer. Although it would seem that every woman might benefit from such a regimen, it is important to individualize the decision for chemotherapy. A woman who has a favorable tumor with negative nodes may derive only a small absolute benefit at the cost of excessive morbidity.

Alternate regimens with similar efficacy to CMF are frequently used, such as FAC [*5-fluorouracil, doxorubicin (Adriamycin)*, and *cyclophosphamide*], AC (*doxorubicin* and *cyclophosphamide*), or FEC (*5-fluorouracil, epirubicin*, and *cyclophosphamide*). AC given as four cycles has been shown in an NSABP trial to have equivalent disease-free survival and overall survival to CMF in node-positive patients with *tamoxifen*-resistant tumors (110).

Promising new agents are emerging as possible successors or supplements to these standard regimens. The most notable of these is *paclitaxel (Taxol)*, a member of the taxanes. *Paclitaxel* has been shown to have good activity in patients with metastatic breast cancer, and is not cross-resistant to *doxorubicin.* For these reasons, the NSABP B-28 trial and other similar large, randomized trials are accruing patients to evaluate the role of taxanes in the adjuvant setting (111). Interim analysis from a large, cooperative, randomized study has shown improved disease-free and overall survival rates in node-positive patients who were randomized to receive AC in combination with sequential *paclitaxel* compared with AC alone (112). Final results from this trial may make AC plus sequential *paclitaxel* the preferred adjuvant regimen.

Adjuvant Hormone Therapy

In 1998, the EBCTCG reported a meta-analysis of women who participated in any randomized trial of adjuvant *tamoxifen* versus no *tamoxifen* before 1990. Data were available on 37,000 women (109).

In the women whose tumors were estrogen receptor (ER) positive, the proportional reductions in recurrence and mortality rates from 5 years of *tamoxifen* were highly significant at 50% and 28%, respectively. These proportional reductions were much less for tamoxifen used for only 1 or 2 years. When subdivided by nodal status, the absolute recurrence and mortality reductions at 10 years of follow-up for node-positive patients were 15% and 11%, respectively, and for node-negative patients, 15% and 5.6%, respectively. Node-negative patients derived no benefit from 1 year of *tamoxifen.* A somewhat surprising finding was that although women younger than 50 years of age did not benefit from the use of 1 or 2 years of *tamoxifen*, they had substantial reductions in recurrence and mortality from using *tamoxifen* for 5 years.

Those patients whose disease was hormone receptor negative did not show any substantial benefit.

Although not designed fully to quantify all risks, the EBCTCG tabulated malignancy incidence for contralateral breast cancer, colorectal cancer, and endometrial cancer. **The women in trials who used *tamoxifen* for 5 years enjoyed a reduction of approximately 50% in contralateral breast cancer.** There was no evidence for an increase in colorectal cancer. Unfortunately, the incidence of endometrial cancer quadrupled. However, this translates to approximately half the absolute magnitude of reduction in contralateral breast cancer. Overall, the mortality from endometrial cancer from 10 years after randomization equated to approximately 2 deaths per 1,000 women (109).

The relative merits of tamoxifen combined with chemotherapy remain controversial. **An important finding of the meta-analysis was that tamoxifen, when added to chemotherapy, produced additional benefits over the same chemotherapy given alone, especially with 5 years of tamoxifen**(109). The power of this observation is less reliable, however, because of smaller numbers as further subdivisions are used. Chemoendocrine therapy has been examined more recently in trials comparing the addition of chemotherapy to tamoxifen versus *tamoxifen* alone. The International Breast Cancer Study Group performed a trial in postmenopausal node-positive patients, who were randomly assigned to *tamoxifen* alone or *tamoxifen* plus CMF given in three different strategies, and concluded that early CMF in addition to 5 years of *tamoxifen* reduced the risk of relapse by 33% in the patients with ER-positive tumors (113). Other trials of postmenopausal, node-positive women with tumors expressing ER did not show a benefit from adding CMF to *tamoxifen*, but this may be because of CMF dosing and scheduling differences, or the relatively short duration of *tamoxifen* administration (114,115 and 116).

In practice, oncologists are using systemic adjuvant therapy for most patients with early-stage breast cancer, with lymph node status becoming less influential. The factors that determine the patient's risk of recurrence are tumor size, estrogen and progesterone receptor status, nuclear grade, histologic type, proliferative rate, and oncogene expression (117). Table 16.5 summarizes these prognostic factors and their effect on recurrence.

Factor	*Increased Risk of Recurrence*
Size	Larger tumors
Histologic grade	High-grade tumors
DNA ploidy	Aneuploid tumors
Labeling index	High index (>7%)
S-phase fraction	High fraction (>6%)
Lymphatic/vascular invasion	Present
Cathepsin D	High levels
p53 tumor suppressor gene	High expression
HER-2/*neu* oncogene expression	High expression
Epidermal growth factor	High levels
Angiogenesis	High microvessel density

Table 16.5 Prognostic Factors in Node-Negative Breast Cancers

To help with the decision for adjuvant therapy, the proportional risk reduction in mortality should be translated into absolute benefit by calculating the number of deaths avoided per 100 women (107). For instance, if the 10-year risk of death from breast cancer is 10%, and if adjuvant chemotherapy reduces the mortality rate by 20%, the absolute increase in the number of patients alive will be two. On the other hand, if the 10-year risk of death is 50%, the same proportional reduction in mortality would mean ten extra lives saved.

The current recommendations for adjuvant chemotherapy and hormonal therapy in breast cancer can be summarized as follows (Table 16.6):

Patient Age	*Estrogen-Receptor Status*	*Level of Risk*	*Adjuvant Systemic Therapy**
<50 yr	Negative	Any	Chemotherapy
	Positive	Low	Hormonal therapy or Chemotherapy or Chemotherapy and hormonal therapy
	Positive	Moderate or high	Chemotherapy and hormonal therapy or Investigational therapies
	Unknown	Any	Chemotherapy and hormonal therapy
≥50 yr	Negative	Any	Chemotherapy
	Positive	Low	Tamoxifen or Chemotherapy and hormonal therapy
	Positive	Moderate or high	Chemotherapy and hormonal therapy or Investigational therapies
	Unknown	Any	Chemotherapy and hormonal therapy

*Chemotherapy consists of fluorouracil, doxorubicin, and cyclophosphamide (FAC); doxorubicin and cyclophosphamide (AC); or cyclophosphamide, methotrexate, and fluorouracil (CMF). Hormonal therapy consists of tamoxifen or ovarian ablation (either surgical or chemical). From Harris JR, Lippman ME, Veronesi U, Willett W: Breast cancer. *N Engl J Med* 1992;327:319–328. Copyright © 1992 Massachusetts Medical Society. All rights reserved.

Table 16.6 Summary of Adjuvant Systemic Therapy for Women With Breast Cancer

1. **Premenopausal women who have ER-negative tumors should be treated with adjuvant chemotherapy.**
2. **Premenopausal women with ER-positive tumors can be considered for hormonal therapy in addition to chemotherapy.**
3. **Postmenopausal patients who have negative lymph nodes and positive hormone receptor levels should be treated with adjuvant *tamoxifen* or both chemotherapy and *tamoxifen*. Those with positive lymph nodes should receive both *tamoxifen* and chemotherapy.**
4. **Postmenopausal women who have negative hormone receptor levels may be treated with adjuvant chemotherapy.**

In spite of all of the evidence, decisions for adjuvant therapy must rest with a well educated and well informed patient.

Hormonal Therapy for Metastatic Disease

Metastatic disease may respond to hormonal manipulation. The latter may involve ablative surgery, drugs that block hormonal receptor sites, or drugs that block synthesis of hormones (118,119). The usual course of the disease after initially responding to hormonal manipulation is progression when the drug is no longer effective. Sequential therapy using other drugs is instituted in a stepwise fashion. Responses usually diminish with each new line of therapy. Hormonal manipulation should not be attempted in women with ER-negative tumors or bulky, progressive visceral metastases. Such patients should receive cytotoxic chemotherapy.

Premenopausal Women In the premenopausal patient, *tamoxifen* has replaced bilateral oophorectomy as the primary hormonal approach because of its ease of administration and lack of morbidity. **Approximately 60% of premenopausal patients with ER-positive tumors respond to either *tamoxifen* or bilateral oophorectomy.** Chemical ovarian ablation using a gonadotropin-releasing hormone (GnRH) agonist can be used also as primary therapy. A randomized trial comparing oophorectomy to chemical ablation using the GnRH analog *goserelin* found similar response rates and overall survival in premenopausal patients with hormone receptor–positive metastatic breast cancer (120).

Patients who respond to *tamoxifen* or GnRH analogs should be treated with *megestrol acetate* if they have subsequent tumor progression. There are no data to support the newer selective aromatase inhibitors in premenopausal women. Oophorectomy is rarely performed for metastatic breast cancer.

Postmenopausal Women **Primary hormonal manipulation in the postmenopausal woman should consist of *tamoxifen*; approximately one third of patients respond** (121). When *tamoxifen* becomes ineffective, a selective aromatase inhibitor should be used, such as *anastrozole* or *letrozole*. These new aromatase inhibitors are highly selective and much less toxic than *aminoglutethimide*, an early, nonselective aromatase inhibitor. Two randomized trials have shown a survival benefit of *anastrozole* over *megestrol acetate* in women whose disease progressed while they were taking *tamoxifen* (122). Further endocrine manipulation is probably best performed with *megestrol acetate*, now relegated to a third-line drug.

Patients whose tumors do not respond to *tamoxifen* initially should be treated with chemotherapy. An exciting new modality in the treatment of metastatic breast cancer is the intravenous administration of a humanized monoclonal antibody against the HER-2/*neu* growth factor receptor. **Early data show relatively high response rates in patients with progressive metastatic breast cancer unresponsive to standard chemotherapy who were treated with anti-HER-2/*neu* antibodies combined with *cisplatin*** (123). Although only approximately 20% to 30% of breast cancers overexpress HER-2/*neu*, this novel treatment modality provides a model for further investigation into the use of other signal transduction pathways to modify the biologic behavior and expression of malignant cells.

Special Breast Cancers

Carcinoma *In Situ*

Both lobular carcinoma and ductal carcinoma may be confined by the basement membrane of the ducts. These *in situ* carcinomas do not invade the surrounding tissue and, in theory, lack the ability to spread. Because of their unusual natural history, they represent a special form of breast cancer and have resulted in considerable controversy.

Lobular Carcinoma In Situ If treated by biopsy alone, 25% to 30% of patients with LCIS, also known as *lobular neoplasia*, subsequently have invasive cancer equally in either the sampled or the contralateral breast. (124,125). Most subsequent invasive cancers, however, are infiltrating ductal carcinomas, with a small minority of infiltrating lobular carcinomas. LCIS is therefore considered a marker of increased risk for breast cancer, rather than a precursor lesion.

Most women with LCIS are premenopausal. The tumor typically is not a discrete mass, but it is a multifocal lesion in one or both breasts found incidentally at biopsy for a mass or mammographic abnormality unrelated to the LCIS. LCIS is usually managed after biopsy by careful observation, clinical breast examination, and mammography. **Patients should be informed that they have a higher risk for development of invasive breast cancer, and occasionally a patient may request bilateral prophylactic mastectomy.**

Ductal Carcinoma In Situ Ductal carcinoma *in situ* typically occurs in postmenopausal women. It may appear as a palpable mass that shows the typical features of an invasive ductal carcinoma, but usually it appears as a cluster of branched or Y-shaped microcalcifications. DCIS does not invade beyond the basement membrane. Unlike patients with LCIS, when treated with excisional biopsy alone, 30% to 60% of patients with DCIS will develop invasive cancer in the same breast (126). Axillary metastases occur in fewer than 5% of patients, indicating that an invasive component has been missed on biopsy. For small true DCIS, axillary dissection is not indicated. Approximately 5% of patients whose initial biopsy shows DCIS are found to have infiltrating ductal carcinoma when treated with mastectomy. The incidence of contralateral breast cancer in women with intraductal carcinoma is the same as in those with invasive ductal carcinoma (i.e., 5% to 8%) (127).

Although the standard treatment for DCIS has been modified radical mastectomy, more conservative surgery with or without radiation therapy has been performed with good results (128). Because there is no reason to remove lymph nodes, total mastectomy is preferable. However, no randomized trial has been performed comparing mastectomy with lumpectomy and radiation for DCIS.

The NSABP B-17 randomized trial comparing lumpectomy with or without radiation therapy for DCIS has provided important information. **At 8 years of follow-up, the overall recurrence rate for either invasive carcinoma or DCIS in the ipsilateral breast was reduced from 26.8% in those treated with excision only to 12.1% in the patients who received radiation** (129). The benefit of radiation was greatest for recurrent invasive carcinoma, with an 8-year reduction from 13.4% with excision alone to 3.9% with added radiation therapy. All patient subgroups benefited from radiation, including those with small nonpalpable tumors detected by mammography.

Paget's Disease

Sir James Paget described a nipple lesion comparable with eczema and recognized that this nipple change was associated with an underlying breast malignancy (130). The erosion results from invasion of the nipple and surrounding areola by characteristic large cells with irregular nuclei, which are called *Paget's cells.* The origin of these cells has been much debated by pathologists. However, they are probably extensions of an underlying carcinoma into the major ducts of the nipple–areolar complex. The initial invasion of the nipple may be associated with no visible changes. Often the patient notices a nipple discharge, which is actually a combination of serum and blood from the involved ducts.

The overall prognosis for patients with Paget's disease depends on the underlying malignancy. Those cases associated with an intraductal carcinoma alone have a very favorable prognosis, whereas those with infiltrating ductal carcinoma metastatic to the regional lymph nodes do poorly.

Treatment has almost always been total mastectomy and lymph node dissection, although breast-conserving surgery is now being investigated, particularly in patients with no palpable mass and a negative mammogram (131). With the knowledge from NSABP B-17 that DCIS can be treated successfully with lumpectomy followed by radiation, investigators are asking whether this information can be translated to the treatment of Paget's disease with underlying DCIS only. Limited data for the treatment of Paget's disease with segmentectomy of the nipple–areolar complex followed by radiation are encouraging (132).

Inflammatory Carcinoma

Inflammatory carcinoma of the breast initially appears to be an acute inflammation with redness and edema. The diagnosis of inflammatory cancer rather than infiltrating ductal carcinoma should be made when more than one third of the breast is involved by erythema and edema or when biopsy of this area shows metastatic cancer in the dermal lymphatics. There may be no distinct palpable mass because the tumor infiltrates through the breast with ill-defined margins. There may be a dominant mass, or there may even be satellite nodules within the parenchyma. Most of the tumors are very poorly differentiated, and mammographically, the breast shows skin thickening with an infiltrative process.

The initial step in management is a skin biopsy, and complete staging. **Mastectomy in the face of inflammatory carcinoma usually fails locally and does not improve survival. A combined-modality approach using chemotherapy, radiation therapy, and surgery is the recommended treatment in many centers.** Induction chemotherapy may be given, and if a good response is achieved, then modified radical mastectomy with postoperative radiation therapy to the chest wall, internal mammary nodes, and supraclavicular nodes, followed by additional chemotherapy, is one of many combined-modality options (133). If there is no response to induction chemotherapy, mastectomy should not be performed.

The prognosis for patients with inflammatory breast cancer remains poor.

Breast Cancer in Pregnancy

Breast cancer complicates approximately 1 in 3,000 pregnancies (134,135 and 136). Close to 10% of patients with breast cancer who are of reproductive age are pregnant when the diagnosis is made. **Initial studies suggested a significantly worse prognosis for patients with breast cancer diagnosed during pregnancy, but more recent studies suggest that, stage for stage, the prognosis is similar to that for nonpregnant patients.**

Breast cancer presents the same as in nonpregnant patients, most commonly with a palpable mass. However, there is often a delay in diagnosis, and often patients present with positive axillary nodes (137,138). Prompt biopsy of a mass using FNA, CNB, or excisional biopsy with local anesthesia, which is safe at any time during pregnancy, must be performed if there is clinical suspicion.

The treatment of breast cancer in the pregnant woman must be highly individualized. Considerations include the patient's age and desire to have the child. The overall prognosis should be considered, particularly when axillary lymph nodes are involved. Adjuvant chemotherapy can be teratogenic or lethal, particularly in the first trimester, but can be given later in pregnancy. The following are recommendations:

1. **Localized disease found during the first or second trimester of pregnancy is probably best treated with definitive surgery.** Radiation therapy should be avoided, thus nullifying the option of breast-conserving surgery. Chemotherapeutic agents freely cross the placenta, and none has been found to be totally safe. The decision to treat a patient with chemotherapy depends on the magnitude of benefit over the risks of treatment and the patient's desire to continue the pregnancy.
2. **Localized tumors found in the third trimester of pregnancy must be managed on an individual basis.** Initially, tumors should be excised while the patient is under local anesthesia. Early in the third trimester, definitive surgical treatment should be undertaken; if adjuvant chemotherapy is indicated, labor can be induced after fetal maturity and chemotherapy administered after delivery. However, the use of chemotherapy is becoming more prevalent in pregnant women who are in the third trimester, with no obvious adverse effects to the fetus (139,140). Radiation therapy can be delayed until after delivery. If delivery is imminent, standard therapy can be performed immediately postpartum.
3. **Should the breast cancer be diagnosed during lactation, lactation should be suppressed and the cancer treated definitively.**
4. **Advanced, incurable cancer should be palliated and pregnancy continued or interrupted, depending on the therapy necessary and the desires of the mother.**

Available retrospective evidence suggests that termination of pregnancy does not improve the prognosis for patients with potentially curable breast cancer.

Counseling regarding future childbearing for women who have had carcinoma of the breast is important. For those patients treated with adjuvant systemic chemotherapy, infertility can be a significant problem. Rates of amenorrhea in premenopausal patients may be as high as 40% to 70%, especially in older women (141). The ability to breastfeed after treatment with lumpectomy and radiation is also affected. Successful prolonged breastfeeding from the same breast occurs in approximately 25% of patients (142).

Although it has been generally assumed that subsequent pregnancies are detrimental because of the high levels of circulating estrogens, there is no clear difference in survival for women who become pregnant after the diagnosis of breast cancer (134,137,143). Most recurrences occur within the first 2 to 3 years after treatment, and it may be prudent for these patients to delay further pregnancy.

Prognosis

The most reliable predictor of survival for patients with breast cancer is the stage of disease at the time of diagnosis. The overall 5-year survival rate for patients with breast cancer is 70% to 75%. Stage I patients with small tumors and no evidence of regional spread have an 80% to 90% 5-year disease-free survival rate. When the axillary lymph nodes are involved with tumor (stage II), the survival rate drops to 22% to 63% at 5 years. Each involved axillary lymph node imparts a diminished overall survival rate when large groups of women with breast cancer are studied (Table 16.7). Large lesions (T_3) or lesions with skin involvement or fixation to the underlying fascia have a 5-year survival rate of only approximately 20% to 30% (144).

No. of Positive Axillary Nodes	No. of Patients	Survival Rate (%)	Recurrence Rate (%)
0	12,299	72	19
1	2,012	63	33
2	1,338	62	40
3	842	59	43
4	615	52	44
5	478	47	54
6–10	1,261	41	63
11–15	562	29	72
16–20	301	29	75
21+	235	22	82

From Fentiman T, Varsa L, Bedwani RN, Baker HW, McGregor FH, Murphy GP. Management and survival of female breast cancer: results of a national survey by the American College of Surgeons. *Cancer* 1980;45:2917–2924. Copyright 1980 American Cancer Society. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

Table 16.7 Five-Year Results by the Number of Pathologically Positive Axillary Nodes

Estrogen receptor–positive tumors may be less aggressive than ER–negative tumors. Patients with T_1N_0 lesions that are ER positive have a 5-year survival rate greater than 90%. In general, breast cancer appears to be somewhat more malignant in younger women than in older women; however, this may be because fewer younger women have ER–positive tumors. Other prognostic parameters—tumor grade, histologic type, and lymphatic or blood vessel involvement—have been proposed as important variables, but most microscopic findings other than lymph node involvement have correlated poorly with prognosis (145). Other biochemical and biologic factors such as ploidy, S-phase fraction, HER-2/*neu* oncogene amplification, and cathepsin D levels appear to have some prognostic significance (Table 16.5), especially in node-negative patients (146,147,148 and 149).

Chemoprevention

Tamoxifen was found to decrease the incidence of contralateral breast cancers as a secondary end point in an NSABP trial of adjuvant *tamoxifen* for breast cancer (150). For this reason, the NSABP conducted the Breast Cancer Prevention Trial (BCPT), which studied the efficacy of *tamoxifen* as a preventative agent in women who had never had breast cancer but were at high risk for development of breast cancer based on their risk profile. **In this double-blinded, randomized, controlled trial, 13,388 women were enrolled, and after a mean of 4 years of follow-up, women who received *tamoxifen* for 5 years had close to a 50% reduction in both noninvasive and invasive breast cancers compared with those women taking a placebo** (151). Offsetting these benefits were increased risks for development of endometrial cancer and deep venous thrombosis in the women older than 50 years of age. Unfortunately, no survival data will be produced from this trial.

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17 Preoperative Evaluation, Medical Management, and Critical Care

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The high incidence of medical problems in patients with gynecologic cancer at the time of presentation, coupled with the stresses of aggressive surgical and chemotherapeutic management, necessitate careful monitoring of the patients' medical status. The early identification, evaluation, and management of emerging medical problems are essential, especially in the perioperative period. Comprehensive preoperative evaluation is also critical. The most frequently encountered problems in patients with gynecologic cancers are discussed.

Preoperative Evaluation

The cornerstone of all medical management is the anticipation of specific problems. It is always better to have a management plan than to react to complications. Careful assessment of risk and monitoring of patients in the perioperative period minimizes morbidity and mortality.

Cardiovascular

Surgery can represent a major cardiovascular stress because of depression in myocardial contractility, changes in sympathetic tone induced by general anesthetic agents, and rapid changes in intravascular volume due to blood loss and “third spacing” of fluids. The magnitude of cardiovascular stress depends on patient characteristics, the nature of the operation, the duration of the operation, and whether it is elective or emergent (1,2,3,4,5,6,7,8,9,10 and 11).

Cardiovascular Risk Factors

The American College of Cardiology working with the American Heart Association (ACC/AHA) and the American College of Physicians (ACP) have both proposed guidelines for perioperative assessment of cardiac risk (6,7). Both guidelines rely on groups of clinical factors as the basis for the initial assessment. The original multifactorial risk index of Goldman et al. (4) was reevaluated, validated, and improved by Detsky et al. (11), who created a *modified multifactorial cardiac risk index* (Table 17.1) by studying outcomes in patients in whom a question of cardiac risk was raised. The points assigned to each factor represent the contribution to the risk. A larger number represents a factor with greater influence over the risk of cardiac complication or death. In that study, unstable ischemic heart disease, recent congestive heart failure, or critical aortic stenosis had the greatest influence. With use of the assigned points, three score classes were identified representing increasing cardiac risk (Table 17.2). In the setting of vascular surgery, angina, diabetes, and a Q wave on an electrocardiogram (ECG) have been proposed as additional clinical risk factors (5). **The modified cardiac risk index is a reasonable way to stratify patients for nonvascular surgery.**

Modified Multifactorial Risk Index	Points
Coronary artery disease	
MI within 6 mo	10
MI after 6 mo	5
CCS angina class III	10
CCS angina class IV	20
Alveolar pulmonary edema	
Within 6 mo	10
Ever	5
Valvular disease	
Suspected critical aortic stenosis	20
Electrocardiogram: rhythm other than sinus or sinus plus APBs on last preoperative ECG	5
More than 5 PVBs/min before surgery	5
Poor medical status*	5
Age >70 yr	5
Emergency operation	10
Total points	**135**

APB, atrial premature beat; CCS, Canadian Cardiovascular Society; ECG, electrocardiogram; MI, myocardial infarction; PVB, premature ventricular beat.
*Po_2, <60 mm Hg; Pco_2, >50 mm Hg; K <3.0 mEq/L; HCO_3^- <20 mEq/L; BUN >50 mg/dL; creatinine >3 mg/dL; abnormal aspartate aminotransferase; signs of chronic liver disease; bedridden from noncardiac cause.
Reproduced from Detsky AS, Abrams HB, McLaughlin JR, et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. J Gen Intern Med 1986;1:211, with permission.

Table 17.1 Risk Factors for Postoperative Cardiac Complications

Class (points)	Major Surgery[b]	Minor Surgery[b]	All Surgery[b]
I (≤15)	0.42	0.39	0.43
II (15–30)	3.58	2.75	3.38
III (>30)	14.93	12.20	10.60

[a]Derived from a series of patients in whom the overall cardiac complication rate (myocardial infarction, pulmonary edema, ventricular tachycardia or fibrillation requiring treatment, cardiac death) was 16%.
[b]Relative risk of a patient within one point class relative to all patients. The use of these data to predict the rate of postoperative cardiac complications requires the use of a nomogram.
Adapted from Detsky AS, Abrams HB, McLaughlin JR, et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. J Gen Intern Med 1986;1:211, with permission.

Table 17.2 Relative Risk Using Modified Cardiac Risk Factors [a]

An increasing point score is associated with increased risk. Each point class of the modified risk factor scale is associated with a likelihood ratio (Table 17.2). The likelihood ratio is the relative risk of cardiac complications in that point class, compared with the average risk of all patients being rated. The likelihood ratios therefore provide information on the risk of a given patient compared with all patients.

In using these data to predict postoperative cardiac complications, the surgeon must take into account that some surgical procedures have more inherent cardiac risk than others. **The nomogram in Fig 17.1 can be used to get a sense for how the intrinsic risks of particular types of surgery interact with patient-related factors.** Using a straight edge, the average cardiac complication of gynecologic oncology surgery is used as a left anchor. With the edge set through the patient's point score or likelihood ratio (from the modified index), the estimated postoperative complication rate is defined on the right.

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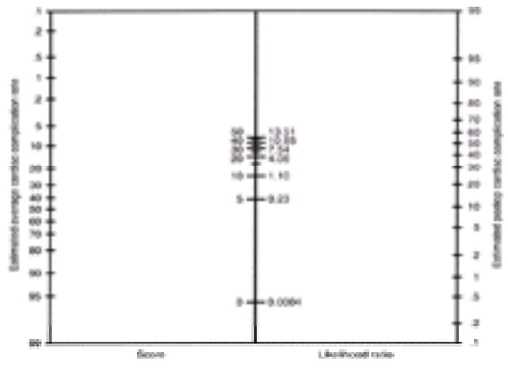

Figure 17.1 Nomogram for predicting postoperative cardiac complications. (Reproduced from Detsky AS, Abrams HB, McLaughlin JR, et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. *J Gen Intern Med* 1986;1:212, with permission.)

The overall cardiac complication rate varies among institutions, patient populations, and types of surgery. For comparison, the average cardiac complication rate was 11% in a study of patients undergoing abdominal aortic surgery (9), but 3.1% and 5.8% in studies of patients undergoing various noncardiac procedures (4,10). **The overall cardiac complication rate for gynecologic oncology operations is probably similar to that for general surgical operations, approximately 5% to 10%** (11).

The details of the calculations are not as important as the concept that important patient risk factors have been identified and that they appear to be valid. In evaluating patients with gynecologic malignancies for cardiac disease, it should also be kept in mind that because of the protective effects of estrogens, ischemic heart disease typically develops a decade or so later in women than in men. Thus, a 60-year-old woman in general has the same cardiac risk as a 50-year- old man.

An algorithm for the risk assessment and management of patients for significant perioperative cardiac events [e.g., myocardial infarction (MI) or death] is shown in Fig. 17.2. This algorithm is based on both the ACC/AHA and ACP guidelines and removes the complexity of issues related to vascular surgery that are not applicable to gynecologic oncology surgery.

Figure 17.2 Cardiovascular evaluation. CHF, congestive heart failure; *, severe aortic stenosis—would require catheterization; **, decision based on American Heart Association guidelines, independent of need for surgery; ***, noninvasive evaluation of ischemic disease prior to nonvascular surgery is not supported by evidence.

The algorithm can be seen to have eight levels.

1. The first level suggests that patients with true surgical emergencies have no time for cardiac evaluations and will go to surgery.
2. The second level is related to an important publication demonstrating significant improvement in 6-month mortality rates in patients with known or suspected ischemic heart disease treated with *atenolol* before surgery (8). Because of these data, all appropriate patients should be considered for b-blocker therapy. Patients who benefit include those with prior MI, angina, or positive stress tests, or those who have two or more of certain risk factors (age ³ 65 years, hypertension, current smoking, cholesterol >240, or diabetes). An important corollary of this study is that patients already taking b-blockers must certainly continue them in the perioperative period. Intravenous *atenolol* can be used if the bowel does not function.
3. In level three, a group of patients has recently undergone coronary revascularization. Such patients have a risk similar to that of the general population and do not need any further work-up in the absence of recurrent symptoms.
4. Level four anticipates a group of patients who recently have had cardiac evaluation. That evaluation needs only to be reviewed, and if no further evaluation is needed, the patient may proceed with surgery.
5. At level five, the remaining patients have their intrinsic cardiac risk assessed by the modified cardiac risk index. Common sense is needed to deal with the unexpected situation not anticipated by the risk index (e.g., the patient has a heart block with symptomatic bradycardia), but these situations are rare. In general, patients in the lowest point classifications (class I, <15 points) can proceed with surgery.
6. At level six are the patients in higher point classes who could benefit from further evaluation. It is the extent of that evaluation that is somewhat difficult to define. Patients with unstable angina or other ischemic syndromes unresponsive to therapy usually require cardiac catheterization, but this would be true regardless of the need for surgery. There is no evidence that noninvasive cardiac evaluations of ischemic disease such as *dipyridamole thallium* imaging or *dobutamine* stress echocardiography have value in the assessment of patients undergoing nonvascular surgery (12). It is also apparent that some combinations of risk index factors might be of more concern than others.
7. At level seven, there may be reason to delay surgery and treat patients with ischemic heart disease, congestive heart failure, arrhythmias, and the like. Some patients with poor medical status benefit from delay and correction of these problems.
8. Finally, at level eight there is the final determination of whether the patient is fit for surgery or if additional delay or cancellation is necessary.

Myocardial Infarction

Postoperative MI can be expected in 0.2% of patients undergoing surgery with general anesthesia (3,13,14). The risk factors for perioperative MI have been discussed previously and are related to the underlying risk of ischemic heart disease. In one older study, the risk of MI after anesthesia and general surgery was 27% if patients were operated on within 3 months of a previous infarction, 11% if the surgery was delayed 3 to 6 months, and 5% if surgery was delayed more than 6 months (1). Current cardiology practice, however, makes using this traditional 6-month cutoff less useful. Modern management of patients after MI includes revascularization, angioplasty, or very aggressive medical therapy with lipid-lowering agents and b-blocker use. Also, there is evidence that coronary artery bypass surgery lowers the risk substantially (15,16 and 17). With proper treatment, patients can undergo surgery 6 weeks after MI if necessary.

Postoperative MI can be painless in one third to one half of patients (1,15). **It can be seen throughout the first week, but its incidence is thought to peak on the third postoperative day** (3). Hence, it is prudent to identify patients at risk for postoperative MI and monitor them with daily ECGs, beginning in the immediate postoperative period and continuing at least through postoperative day 3. Troponin assays can be helpful for confirmation. Because the risk of perioperative MI is increased in patients who are subjected to intraoperative hypotension (1,13), measures must be taken to maintain high-risk patients in a normotensive state during surgery. If intraoperative hypotension (defined as a decrease in systolic blood pressure of 33% to 50% or more for at least 10 minutes) occurs, the patient should be considered at high risk of postoperative MI and monitored appropriately. Such reductions in blood pressure during surgery should be rare with modern anesthetic management.

Theoretically, b-blockers would be expected to facilitate the development of intraoperative hypotension because of the additive myocardial depressive effect of these medications with general anesthesia. However, it has been demonstrated that patients tolerate general anesthesia in the presence of continued b-blocker treatment (18), and that abrupt discontinuation of b-blocker medication is associated with a dangerous rebound syndrome (i.e., acute hypertension and angina), with the incidence of the syndrome peaking at 4 to 7 days after discontinuation of the drug (19). Furthermore, studies have shown that perioperative b-blocker use reduces late postoperative mortality. If anything, use of b-blockers in the perioperative period should be expanded.

Congestive Heart Failure

Patients with moderate or severe congestive heart failure should be treated before surgery with appropriate medications to optimize their cardiovascular status. In severe cases, particularly in patients with jugular venous distention, a third heart sound, or valvular heart disease, preoperative placement of a *pulmonary artery (Swan-Ganz) catheter* should be considered to allow cardiac function to be optimized and to aid in the intraoperative management of fluids and cardiac medications.

Heart Block

Third-Degree Heart Block **Patients who do not have permanent pacemakers and who have third-degree heart block at the time of presentation are at substantial risk of cardiopulmonary arrest during surgery.** Typically, they are unable to mount an appropriate pulse response to the vasodilatation and decreased myocardial contractility induced by general anesthesia or to the volume depletion induced by surgical blood loss. Patients with complete heart block should not be subjected to general surgery without appropriate medical consultation, and strong consideration should be given to preoperative placement of a pacemaker.

Bifascicular Block In patients with lower degrees of heart block, specifically *bifascicular block (right heart block with left axis deviation)*, the risk of development of a higher degree of ventricular block during surgery is not significantly increased, provided there is no history of previous third-degree heart block or syncope. Such patients rarely require insertion of a temporary pacemaker (15,20). Patients with bifascicular block who have a history of third-degree heart block should be managed for complete heart block with preoperative cardiology evaluation and pacemaker insertion.

A new bifascicular block developing in the setting of acute MI carries a high risk of progression to complete heart block. If this problem occurs after surgery, the patient should be considered at significant risk for the development of complete atrioventricular block. Such patients require a cardiology consultation and insertion of a temporary pacemaker (21).

Patients with permanently implanted pacemakers should have a preoperative cardiology evaluation to allow examination of all pacemaker functions. This precaution ensures that backup demand pacemaker failure will not be uncovered unexpectedly with the vagotonic stimuli associated with general anesthesia in abdominal surgery (22).

Pacemakers can sense the electromagnetic impulses created by electrocautery, especially when the electrocautery plate is close to the pacemaker unit. It is prudent to place the indifferent electrocautery electrode as far as possible from the chest and to use electrocautery sparingly. An added precaution consists of keeping a magnet available in the operating room to convert a pacemaker rapidly from the demand to a fixed pacing mode (23).

Endocarditis Prophylaxis

In general, patients with structural cardiac valvular abnormalities, either congenital or acquired, should be treated with prophylactic antibiotics while undergoing procedures that are likely to result in transient bacteremia. Endocarditis prophylaxis is not needed in patients with mitral valve prolapse without accompanying mitral regurgitation. **In gynecologic oncology, operations in which there is a possibility of bowel or vaginal incision should be considered appropriate for endocarditis prophylaxis. Assuming normal renal function and no *penicillin* allergy, appropriate prophylaxis includes intravenous *ampicillin* 2 g and *gentamicin* 1.5 mg/kg given 30 minutes before surgery, and then *ampicillin* 1 g intravenously 6 hours later. In patients who are allergic to *penicillin*, 1 g of intravenous *vancomycin* can be substituted for the *ampicillin*** (24).

Hypertension

The significance of mild to moderate hypertension in patients undergoing surgery remains controversial. This controversy stems from the difficulty in sorting out the risk of hypertension *per se* from the risk of hypertension in the setting of hypertensive or atherosclerotic heart disease.

A large, prospective study suggests that uncomplicated mild to moderate hypertension, regardless of treatment status, does not impose an added risk for postoperative cardiac or renal complications (15,25). However, the presence of hypertension may be of consequence because such patients frequently demonstrate marked intraoperative blood pressure lability and postoperative hypertensive episodes. Blood pressure lability and postoperative hypertension are more frequently associated with major vascular surgery and should be less of a problem with gynecologic surgery.

The causes of perioperative hypertension are presented in Table 17.3. Patients with both hypertensive and atherosclerotic heart disease may be at greater risk than those with uncomplicated hypertension alone. Two studies suggest that postoperative MI may be more frequent in patients with hypertension who have underlying heart disease (1,13). In these patients, postoperative MI was related to thoracic and upper abdominal procedures, anesthesia time in excess of 3 to 4 hours, and significant intraoperative hypotension. As is the case for cardiac complications, the type of surgery is important in understanding the risk of hypertension. Hypotension remains a concern in patients with coronary artery disease, especially if spinal anesthesia is used.

Cause	Recognition
Chronic hypertension	History, medication review
Laryngoscopy and intubation	Situation
Inadequate anesthesia	Situation
Inadequate ventilation	Arterial blood gas
Pain or anxiety	Patient examination and interview
Bladder distention	Bladder palpation
Emergence from anesthesia	Situation
Excessive fluid administration	Operating room records, patient examination
Postoperative fluid mobilization	Situation, patient examination
Acute cardiac events (e.g., congestive heart failure)	Patient examination, electrocardiogram, chest radiograph
Pheochromocytoma (rare—can be occult)	Unusual clinical responses
Malignant hyperthermia	Unusual clinical responses, fever

Table 17.3 Causes of Perioperative Hypertension

Hypertensive management begins with identification, followed by development of a plan for control. The patient's preoperative blood pressure should be controlled as well as possible (26). In general, all antihypertensive medications should be given on the morning of surgery. The question of whether chronic diuretics should be given has not been settled, but most clinicians do not give them. Although diuretic use is associated with volume depletion and hypokalemia, the importance of correcting mild degrees of diuretic-induced hypokalemia in the absence of significant heart disease is somewhat controversial (27). Repletion should never be rapid and is safest by the oral route or by adjustment of medication.

In the postoperative period, many patients, especially the elderly, need less antihypertensive medication because of the salutary effects of bed rest and relative sodium restriction (28,29). It is wise to plan on reinstating drugs stepwise, beginning with the most active agent at approximately half the usual dose and finally adding the diuretic, if used, sometime later. Patients whose only antihypertensive drugs are *thiazide* diuretics are best observed in the immediate postoperative period. Certain drugs, such as *propranolol* and *clonidine*, have well recognized abrupt withdrawal syndromes that can lead to acute myocardial ischemia (especially *propranolol*) or hypertension (especially *clonidine*), or both. These drugs should be given orally on the morning of surgery and reinstated as soon as possible after surgery. The use of transdermal *clonidine* for those patients who are stabilized on *clonidine* is useful in some cases, but not routinely. Patients who need antihypertensive therapy in the immediate preoperative period should not be treated with diuretics because of the associated hypovolemia and hypokalemia.

Pulmonary

General anesthesia and abdominal surgery can compromise respiratory function in all patients. In patients with preexisting lung disease, this added stress can precipitate potentially fatal pulmonary complications. **Pathophysiologic processes associated with surgery include** (30,31,32,33,34 and 35):

1. A decrease in lung volume, including vital capacity
2. A decrease in functional residual capacity
3. Shallow, rapid respiration with decreased sighing and atelectasis
4. An alteration in ventilation and perfusion relationships, with a decrease in arterial oxygen saturation
5. A decreased clearance of bacteria because of decreased coughing and impaired ciliary function

These impairments in normal lung function can persist into the second postoperative week and are related to pain, analgesic medications, the supine position, and tight abdominal bandages (36). Postoperative pulmonary complications can occur in up to 70% of high-risk patients undergoing upper abdominal surgery. These include pneumonia and deterioration of arterial blood gases secondary to atelectasis and altered pulmonary physiology (37).

Pulmonary Risk Factors

There are no multivariate studies of pulmonary risk factors in gynecologic oncology. **However, sufficient data exist to identify a number of clinical factors associated with perioperative pulmonary complications during abdominal surgery** (36,38,39,40,41,42,43,44,45 and 46). **These are:**

1. The anatomic site of surgery (upper abdominal and thoracic surgery having the most complications)
2. Smoking cigarettes
3. Chronic obstructive pulmonary disease (COPD)
4. Asthma
5. Hypercapnia
6. Obesity (the effect is less certain)
7. Prolonged anesthesia time
8. Normal aging (although the effect is less certain)
9. Poor general health status

Spirometry **Well done, prospective, clinical studies on spirometry as a predictor of surgical risk are lacking. Even so, the literature suggests the following** (44,45 and 46):

1. As a group, patients with abnormal spirometry results are at risk for complications.
2. The degree of spirometric abnormalities does not predict the degree of risk.
3. In patients with COPD, there is probably no degree of spirometric abnormality that prohibits surgery.
4. General preoperative screening with spirometry is not effective.

Abdominal surgery is associated with significant risk of pulmonary complications. After surgery, vital capacity is reduced by 50% to 60% and functional residual capacity is reduced by 20% to 30%. Approximately one third of these changes may be related to supine positioning. In one study of patients undergoing upper abdominal surgery without any prophylactic measures (40), 48% had postoperative pulmonary complications. This complication rate was reduced considerably by any of several prophylactic measures, but was still approximately 20% in the treatment groups. The mechanisms responsible for the high rate of pulmonary complications after upper abdominal surgery have been a subject of great interest. Studies have emphasized that diaphragmatic dysfunction secondary to reduced phrenic nerve output may be an important factor (37).

Current smokers with a history of smoking cigarettes for more than 20 pack-years, or more than one pack a day, appear to have an increased rate of postoperative pulmonary complications. To ameliorate this risk, patients undergoing major oncologic surgery need to stop smoking for at least 8 weeks before the surgery (41).

Patients with COPD are at increased risk of postoperative complications. In this group of patients, an increased risk has been associated with:

1. A forced vital capacity less than 70% of predicted
2. A forced expiratory volume in 1 second less than 70% of predicted
3. A maximum voluntary ventilation less than 50% of predicted
4. Hypercapnia

However, most of the studies on which these cutoff values are based have serious flaws in methodology (46). There is agreement that patients with chronic lung disease, as a group, do have more postoperative pulmonary complications. Among patients with COPD, however, the predictive value of abnormal spirometry to identify the subgroup at risk of postoperative complications is poor (43,45). Spirometery has not been useful for general screening to predict complications in patients without COPD. In a prospective study (44), 82 cases and 82 control subjects underwent abdominal surgery. It was found that abnormal chest findings on examination were highly associated with pulmonary risk, but that abnormal spirometric findings were not associated with risk. To the extent that obtaining screening spirometry helps to identify all patients with underlying lung disease who can then receive appropriate preventive measures, a benefit should accrue. **Spirometry may be useful in patients with pulmonary symptoms that remain unexplained after initial clinical evaluation.** A program of preoperative and postoperative treatment that includes smoking cessation, antibiotics, bronchodilators, and chest physiotherapy has been shown to reduce complications significantly (47). Early ambulation is also important.

Normal aging has traditionally been considered a risk factor for pulmonary complications. Physiologic changes associated with normal aging include a reduction in vital capacity, mild hypoxemia, and possible loss of protective airway reflexes (2). However, there is evidence suggesting that, when controlled for comorbidity and pulmonary function (48), age *per se* may not confer a significant independent risk.

There is an increased risk of pulmonary complications associated with obesity. Physiologically, the obese have reduced *functional residual capacity* and a reduced *effective residual volume* (46,48). The reduced effective residual volume frequently results in normal tidal breathing below the closing volume (the lung volume at which airways are believed to undergo closure) and produces a widening of the arterial-alveolar gradient and hypoxemia. Obesity is associated with postoperative atelectasis (49). Pneumonia is associated with patient weight over 115 kg (50). Postoperative hypoxemia may be more severe or prolonged (51). Even modest weight loss (e.g., 5 to 10 kg) may reduce the rate of complications (52).

Anesthesia time greater than 3 to 4 hours has been reported as a pulmonary risk (1), even when the site of surgery is considered (15). For upper abdominal incisions, some older data are conflicting (53).

In practical terms, the preoperative pulmonary evaluation should be directed first at identifying the clinical risk factors (47,54,55,56,57 and 58).

1. Patients with chronic pulmonary disease should be free of acute infection (e.g., bronchitis) and should be treated with preoperative antibiotics if necessary.
2. Smoking cessation should be encouraged, ideally 8 weeks before surgery.
3. Weight loss is useful and should be encouraged, but it has unproven benefit, is difficult to accomplish, takes time, and usually is not practical, given the urgency of oncologic surgery.
4. Although screening spirometry cannot substitute for history taking and examination, candidates for screening include those patients with symptoms suggestive of pulmonary disease.
5. Patients with spirometric abnormalities should have blood gas determinations.
6. Elderly patients who have no symptoms probably do not need screening spirometry before extrafascial hysterectomy, although mild hypoxemia and a propensity to atelectasis should be assumed.
7. Patient education is important and should emphasize familiarization with the management plans, especially such respiratory maneuvers as incentive spirometry.
8. Incentive spirometry, because it is inexpensive, effective, and without complications, should be ordered for all patients with risk factors, including the elderly who are otherwise free of symptoms.

In the preoperative and postoperative management of high-risk patients, intermittent positive-pressure breathing is not superior to the use of simple incentive spirometry, and it may increase the risk of complications (55).

A summary of guidelines to reduce pulmonary complications is presented in Table 17.4. An algorithm for the perioperative management of patients with lung disease is presented in Fig. 17.3. Patients with asthma deserve special comment. **Asthmatic patients are at increased risk of postoperative complications but can do well with proper preparation and postoperative care** (54). The major problems involve exacerbation of asthma, especially as a result of endotracheal intubation or in the immediate postoperative period, and proper steroid coverage is essential if adrenal suppression is suspected. The basic preoperative goal is absence of wheezing on examination, which usually corresponds to the patient's best physical status and pulmonary function. Achievement of this goal may require adjustment of oral or inhaled steroids, inhaled b-adrenergic agonist, and/or oral *theophylline.* Modern ambulatory therapy for patients with chronic asthma emphasizes the use of inhaled steroids to suppress bronchial hyperresponsiveness and b-agonists for the symptomatic relief of acute exacerbation.

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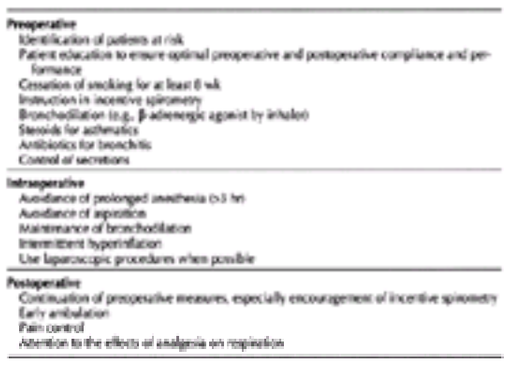


Table 17.4 Measures to Reduce Pulmonary Complications

Figure 17.3 Pulmonary evaluation and postoperative care. COPD, chronic obstructive pulmonary disease; *, refers to measures to reduce pulmonary complications (see Table 17.4).

Stable asthmatic patients who take steroids should receive their usual inhaled dose, or their oral dose should be given intravenously the morning of surgery. b-Agonist inhalational therapy (e.g., *albuterol*, 2.5 mg/3 mL of normal saline solution or with the patient's own metered-dose inhaler) is also indicated. In the recovery room, exacerbations should be treated initially with b-agonist inhalational therapy. If wheezing persists, intravenous steroids in modest doses (e.g., *prednisone* 30 to 60 mg every 6 to 8 hours) may be added. Patients with adrenal suppression need appropriate coverage (see section on Corticosteroids, later). Postoperative b-agonist therapy should be continued for all patients.

Diabetes Mellitus

Diabetes mellitus affects approximately 5% of the adult population in the United States. It is now believed that type I diabetes is an autoimmune disease. **People with type I diabetes have a near-total lack of insulin and become ketoacidotic if *insulin* is withheld.** They are usually, but not always, young. **People with type II diabetes are not insulin deficient and thus are not prone to ketoacidosis. The problem in type II diabetes is usually one of relative insulin resistance.** Patients with type II diabetes are usually older and overweight. Both groups may experience the complications listed in Table 17.5. Many elderly patients have mild type II diabetes of recent onset related to obesity, are well controlled with diet or oral hypoglycemic drugs, and have few overt complications, but may have occult atherosclerotic vascular disease.

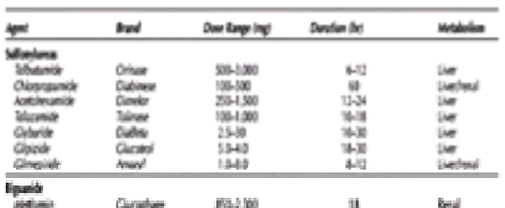
Complication	*Importance*
Cataracts	Decreased vision
Retinopathy	Decreased vision
Nephropathy	Nephrotic syndrome, hyperkalemia, metabolic acidosis, reduced glomerular filtration rate
Peripheral neuropathy	Decreased peripheral nociception, susceptibility to infection
Autonomic neuropathy	Orthostatic hypotension, gastropathy (delayed gastric emptying, diarrhea), uropathy (urinary retention, overflow incontinence, infection), cardiorespiratory arrest
Coronary artery disease	Silent ischemia, myocardial infarction
Vascular disease	Peripheral arterial insufficiency, coronary artery disease, stroke

Table 17.5 Complications of Diabetes

The management of diabetes begins with some understanding of the factors that influence perioperative glucose metabolism (59,60,61,62 and 63). Insulin is the principal glucose-lowering hormone; cortisol, glucagon, growth hormone, and catecholamines are the principal glucose-raising hormones. In the preoperative period, stress and the “dawn” phenomenon may elevate blood glucose. The dawn phenomenon is early-morning hyperglycemia resulting from nocturnal surges of growth hormone. During surgery, cortisol and growth hormone levels rise. In this period, there is hyperglycemia in diabetic and nondiabetic patients alike. This is caused by glycogenolysis, inhibition of glucose uptake, and decreased insulin release. After surgery, in nondiabetic patients, the hyperglycemia is brought under control by increased endogenous insulin release over a period of 4 to 6 hours. Patients with diabetes may need additional exogenous *insulin.*

In addition to these hormonal factors, several other factors are important in modulating the blood glucose level in the perioperative period. Inactivity, stress, and intravenous glucose infusions tend to raise blood glucose. Decreased caloric intake and semistarvation tend to lower blood glucose. Because the net effect of these factors is sometimes difficult to anticipate, it is important frequently to monitor blood glucose levels.

Oral Hypoglycemics There are many more oral agents being used to treat diabetes than in the past (Table 17.6). Sulfonylureas such as *glyburide (Diabeta)* remain the most popular. Most sulfonylureas are primarily excreted by the liver. These drugs are typically withheld 24 to 48 hours before surgery depending on their half-life. They can be restarted when the patient starts eating after bowel function returns. The biguanide *metformin (Glucophage)* is being used more frequently. However, *metformin* should not be used in the perioperative period, and probably should be avoided altogether in systemically ill gynecologic oncology patients. There is a serious risk of lactic acidosis if renal function declines as a result of chemotherapy, dehydration, congestive heart failure, sepsis, radiologic contrast agents, or third spacing. It should not be used in patients with liver disease. *Acarbose (Precose)* is a complex oligosaccharide glucosidase inhibitor that delays the digestion of ingested carbohydrates. There is little use for this drug in the perioperative period. *Repaglinide (Prandin)* is a meglitinide that stimulates release of insulin from the pancreas. Its safe use depends on stable renal and hepatic function. Finally, the thiazolidinedione *troglitazone (Rezulin)* improves peripheral use of glucose. There is concern over its safety because of hepatic toxicity, and thus it is a second-line agent used in combination with other drugs. Because treatment of gynecologic oncology patients may influence liver enzyme levels, monitoring for toxicity is problematic. Its use in patients with gynecologic cancer is not recommended. *Rosiglitazone (Avandia)* and *pioglitazone (Actose)* are newer thiazolidinediones that should have little or no hepatic toxicity.



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Agent	Brand	Dose Range (mg)	Duration (hr)	Metabolism
Sulfonylurea				
Tolbutamide	Orinase	500–3,000	6–12	Liver
Chlorpropamide	Diabinese	100–500	60	Liver/renal
Acetohexamide	Dymelor	250–1,500	12–24	Liver
Tolazamide	Tolinase	100–1,000	10–18	Liver
Glyburide	Diabeta	2.5–20	10–30	Liver
Glipizide	Glucotrol	5.0–40.0	18–30	Liver
Glimepiride	Amaryl	1.0–8.0	6–12	Liver/renal
Biguanide				
Metformin	Glucophage	850–2,300	10	Renal
Glucosidase inhibitor				
Acarbose	Precose	25–100	2 (minimal absorption)	Gastrointestinal
Meglitinide				
Repaglinide	Prandin	0.5–16	1	Liver/renal
Thiazolidinedione				
Troglitazone	Rezulin	200–600	16–34	Liver
Rosiglitazone	Avandia	4.0–8.0	3–4	Liver
Pioglitazone	Actose	15–45	16–24	Liver/renal

Table 17.6 Characteristics of Oral Hypoglycemics

Management

The goal of management is a blood glucose value of not more than 180 to 240 mg/dL. This level is chosen because severe glucosuria (and risk of dehydration) is prevented. Furthermore, experimental studies suggest that glucose levels greater than 240 mg/dL may impair the function of leukocytes (62). Finally, experimental studies suggest that hypoinsulinemia may impair wound healing.

Details of the management of the diabetic patient who is taking an oral sulfonylurea hypoglycemic agent are presented in Table 17.7. Patients with very well controlled diabetes who take oral agents are at risk of hypoglycemia if an oral hypoglycemic agent is given while the caloric intake is reduced. This is why the oral agent should be withheld on the day of surgery. Oral agents with a long duration of action should be withheld longer. As is the case with patients who are taking *insulin*, care must be taken to restart the normal daily dose while the patient is hospitalized because the usual dose of oral agent given in the setting of reduced caloric intake may lead to hypoglycemia. This management plan relates to patients who the surgeon plans to send after surgery to a general hospital ward. The strategy of this plan is to use short-acting *insulin* only as needed and then restart the outpatient regimen when the patient starts eating.

Preoperative
1. Plan for surgery early in the day
2. Hold oral hypoglycemic on day of surgery; long-acting drugs (e.g., chlorpropamide) should be held for 48 hr
3. Measure early a.m. glucose; use sliding-scale insulin for glucose >200–250 mg/dL)
Intraoperative
5. Measure intraoperative glucose frequently (e.g., every 2 hr)
Postoperative
6. Measure recovery room glucose (use sliding-scale insulin for glucose >200–250 mg/dL)
7. Measure postoperative glucose every 6 hr (use sliding-scale insulin for glucose >200–250 mg/dL)
8. Return to previous regimen incrementally in a.m. if eating

Table 17.7 Details of Perioperative Diabetes Management for Well Controlled Patients Taking Oral Hypoglycemics

The management of the diabetic patient who takes *insulin* is presented in Table 17.8. **It is important to reduce the total daily dose of *insulin* because caloric intake on the day of surgery is reduced** (63) **(hence the recommendation that one third of the normal daily dose be given on the morning of surgery and another, similar dose 8 to 12 hours after the first).** If control of diabetes is known to be poor, one-half the normal daily dose can be given (unless the reason for the poor control is too much *insulin*). The need for additional *insulin* immediately after surgery is anticipated by measurement of glucose level in the recovery room. Care must be taken to restart the normal daily dose while the patient is hospitalized. Hypoglycemia may result if caloric intake is reduced because of discomfort or missed meals. The importance of postoperative blood glucose monitoring every 6 hours (or before each meal if the patient is eating) cannot be overemphasized. This allows the physician to make appropriate adjustments in therapy.

Preoperative
1. Plan for surgery early in the day
2. Measure early a.m. glucose (use sliding-scale insulin for glucose >200–250 mg/dL)
3. Use one third of NPH (or equivalent) insulin subcutaneously
4. Start D5W at 125 mL/hr
Intraoperative
5. Measure intraoperative glucose frequently (e.g., every 2 hr) and make adjustments
Postoperative
6. Measure recovery room glucose (use sliding-scale insulin for glucose >200–250 mg/dL)
7. Measure postoperative glucose every 6 hr (use sliding-scale insulin for glucose >250 mg/dL)
8. Use regular insulin according to sliding scale as needed
9. Use one third of NPH 8–12 hr after a.m. dose
10. Continue regimen until patient begins to eat (usually next morning)
11. Return to previous regimen incrementally beginning in a.m. if eating

Table 17.8 Details of Perioperative Insulin Management for Well Controlled Patients Taking Insulin

If a patient is critically ill after surgery, it is difficult to anticipate the *insulin* needs resulting from stress and varying caloric loads. Some poorly controlled patients may require urgent or emergency surgery. In these situations, continuous infusion of *insulin* by pump is probably worthwhile. The patient should be adequately hydrated (dehydration by itself potentiates hyperglycemia in diabetic patients secondary to alterations in renal clearance of glucose) and given 5 units of *insulin* by intravenous bolus. Regular *insulin* at 1 to 5 units per hour should be infused. At blood glucose levels below 250 mg/mL, 5% or 10% glucose in water should be infused to protect against hypoglycemia. Intravenous *insulin* requires constant monitoring.

Thyroid Disorders

***Hypothyroidism Hypothyroidism* is common and may go undetected in patients being prepared for surgery** (64). Symptoms include cold intolerance, recent or progressive constipation, hoarseness, fatigability, and changes in cognition. Signs include associated goiter, skin dryness, and a delayed relaxation phase of peripheral reflexes (best demonstrated in the Achilles tendon). Studies have suggested that unrecognized mild to moderate hypothyroidism is clinically important, but fears of hyponatremia, prolonged respirator dependency, hypothermia, delayed recovery from anesthesia, or death are probably unwarranted (65,66). One retrospective study suggested that such patients have more intraoperative hypotension, postoperative ileus, and confusion and that infection is less often accompanied by fever.

For patients who are suspected before surgery of being hypothyroid, thyroid hormone levels should be measured. Hypothyroid patients should be treated with replacement hormone and rendered euthyroid before surgery. In urgent situations, patients who are not myxedematous should be given 1 or 2 days of oral replacement before surgery, with careful postoperative follow-up.

Hyperthyroidism *Hyperthyroidism* can be a dramatic illness, with tachycardia, fever, and exophthalmos associated with goiter. Other common symptoms and signs include frequent weight loss, fatigue, diarrhea, heat intolerance, tremor, hyperreflexia, and muscle weakness. Hyperthyroidism may be occult in older patients. Unexplained tachycardia, weight loss, arrhythmias, or fever may be the only clinical indicators. With proper preparation (67), hyperthyroid patients undergoing thyroid surgery do well. However, there are scant data concerning the problems of the hyperthyroid patient undergoing nonthyroidal surgery such as radical hysterectomy. Exacerbation of the illness into a "thyroid storm" is the usual concern. Because of this, when any patient is suspected before surgery of being hyperthyroid, thyroid hormone levels should be measured. If the diagnosis is confirmed, elective surgery should be delayed until treatment has produced a euthyroid state. In the postoperative period, thyroid hormone levels should be measured when any patient has persistent unexplained tachycardia, fever, or tachyarrhythmias.

Corticosteroids

Patients taking corticosteroids or those who have taken them in the recent past should be evaluated for the need of supplemental corticosteroid coverage. In general, patients taking less than the equivalent of 7.5 mg *prednisone* daily or 40 mg of *prednisone* on alternate days (68) should not have adrenal suppression. This assumes that a short-acting steroid (e.g., *prednisone*) is given as a single dose on the morning of surgery. **The amount of steroid needed to cause adrenal suppression is the equivalent of 40 mg of *prednisone* or more daily for 1 to 2 weeks, or more than 7.5 mg of *prednisone* daily administered chronically. The recovery from adrenal suppression can take up to 9 months** (69). The details of recovery after short courses of high-dose steroid therapy have not been well studied.

Patients who have taken high doses of corticosteroids for more than 1 or 2 weeks within 9 months of surgery are candidates for supplemental steroid coverage. The symptoms of adrenal insufficiency in the postoperative patient can be nonspecific and include fever, nausea, ileus, weakness, and anorexia (70). Because of this, most clinicians err on the side of treatment because major complications associated with brief steroid coverage are rare.

A review concluded that the traditional regimen of corticosteroid coverage for elective surgery (100 mg of *hydrocortisone succinate* intravenously on call to the operating room and then the same dose repeated every 8 hours for 24 hours) is unnecessary. Basing their recommendations on endogenous steroid production during major stress, the authors concluded that even for the most extensive surgery, 100 to 150 mg of *hydrocortisone* or its equivalent each 24 hours was enough (71). **Regardless of the dose, and assuming that the patient is recovering from surgery uneventfully, the dose can be reduced by 50% the second day, and then placed back on her usual steroid dose on the third postoperative day.**

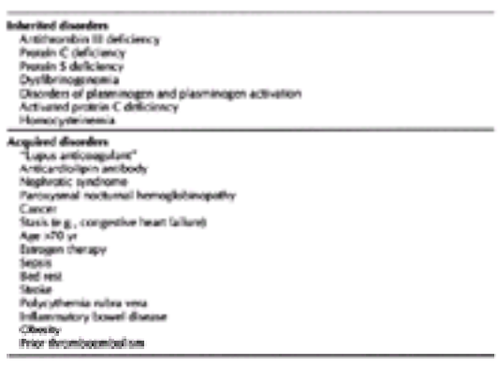
There are some patients (e.g., those with diabetes) in whom it is important to avoid the unnecessary use of steroids. In these patients, a normal adrenocorticotropic hormone (ACTH) stimulation test can be used to predict an adequate, but not necessarily normal, response to surgical stress (72). The procedure is to give 250 µg of ACTH intravenously or intramuscularly. The cortisol level is measured immediately before and 30 to 60 minutes after injection. A normal response is an increase of 12 to 20 µg/mL.

Thromboembolic Disease

Prophylaxis Patients hospitalized for oncologic treatment, and particularly those undergoing surgery for these diseases, are at substantial risk for thromboembolic disease. Patients can be stratified into risk groups according to clinical history. In one retrospective review, high-risk patients had a history of recent pulmonary embolism, extensive surgery for cancer, or orthopedic procedures of the lower limbs. Patients at moderate risk were 40 years of age or older or had undergone general surgery with longer than 30 minutes of anesthesia. These groupings were associated with the following rates of thrombosis and embolism without any prophylaxis (73):

Risk	Calf	Proximal	Fatal pulmonary embolism
High	40-80	10-20	1-5
Moderate	10-40	2-10	0.1-0.7
Low	<10	<1	<0.01

Because of these and other risks commonly associated with gynecologic malignancy (Table 17.9), thromboembolic prophylaxis should be considered in every patient undergoing surgery and those confined to prolonged bed rest. Most studies show low-dose *heparin* (5,000 units twice a day) and external pneumatic compression devices to be equally effective in reducing thrombotic risk. Several studies suggest these methods might be additive in their protective benefit (74,75). Those at particularly high risk might be candidates for low molecular weight *heparin, warfarin (Coumadin)*, or even placement of an inferior vena caval filter, although these methods of prevention have not been well studied in the gynecologic oncology population. Use of anticoagulation must be weighed carefully against bleeding risks in critically ill and postoperative patients.


Inherited disorders
Antithrombin III deficiency
Protein C deficiency
Protein S deficiency
Dysfibrinogenemia
Disorders of plasminogen and plasminogen activation
Activated protein C deficiency
Homocysteinemia

Acquired disorders
"Lupus anticoagulant"
Anticardiolipin antibody
Nephrotic syndrome
Paroxysmal nocturnal hemoglobinopathy
Cancer
Stasis (e.g., congestive heart failure)
Age >70 yr
Estrogen therapy
Sepsis
Bed rest
Stroke
Polycythemia rubra vera
Inflammatory bowel disease
Obesity
Prior thromboembolism

Table 17.9 Factors Related to Increased Risk of Thromboembolic Disease

Preoperative Testing

The question of how much preoperative laboratory testing is warranted has been the subject of considerable interest and debate (76,77,78,79,80,81 and 82). The data from these studies confirm that, unless clinical indicators are present, preoperative test results will likely be either normal, falsely positive, or truly positive with no relevance to clinical outcome (79). A study done predominantly in men without cancer (80) suggested that in stable patients, tests previously ordered in the past few months could be used to satisfy preoperative requirements. It is recognized that abnormalities do occur in symptom-free patients, but often these are either false-positive or true positive results that have no impact on surgical or anesthetic management. The latter case is especially true if age is used as a basis for test ordering.

Preoperative testing *per se* should be directed at uncovering abnormalities that have an impact on surgical or anesthetic management. However, general screening in a population of preoperative patients may often reveal abnormalities that reflect underlying medical conditions worthy of evaluation, although these abnormalities do not always affect surgical or anesthetic management.

Because the prevalence of test abnormalities does increase with age (Table 17.10), age itself is commonly used as a parameter for test ordering. In the older age groups undergoing surgery, many of the traditional preoperative tests can be justified (82). Younger patients in general need few of these tests.

Test	Indication
Chest radiograph	Age >60 yr or clinical history
Electrocardiogram	Age >40 yr or clinical history
Creatinine	Age >40 yr or clinical history
Glucose	Age >40 yr or clinical history
Hematocrit	All female patients
Complete urinalysis	Clinical history
Electrolytes	Clinical history
Prothrombin time	Anticoagulation or clinical history
Partial thromboplastin time	Anticoagulation or clinical history
Platelet count	Anticoagulation or clinical history

Adapted from Kaplan EB, Sheiner LB, Boeckmann AJ, et al. The usefulness of preoperative laboratory screening. JAMA 1985;253:3576, with permission.

Table 17.10 Example of the Increase in Prevalence of Preoperative Test Abnormalities by Age; Common Preoperative Laboratory Testing for Anesthesia and Surgery

Patients with widespread cancer, with or without prior therapy, can have associated coagulation abnormalities; therefore, screening for coagulation disturbances is worthwhile. Rappaport (83) argues that in the presence of a negative history, the activated partial thromboplastin time (aPTT) and platelet count constitute adequate coagulation screening for major surgical procedures. Studies have usually concluded that unexpected coagulation results are rare when the history and physical examination findings are negative (83,84). Patients with cancer may also have been treated with drugs that have toxic effects on the renal, cardiac, or respiratory systems. These patients would benefit from additional studies.

Screening for Hemostatic Defects

In a hemostatic history, the most important information involves the outcome of prior hemostatic stress and the family history. Minor surgical procedures should not have required transfusion, and a history of postoperative bleeding 2 or 3 days after surgery is also suspicious. Many patients have had tooth extractions. Bleeding should not last more than 24 hours and should not start again after stopping. A familial history of bleeding or suspected bleeding should be investigated. Large ecchymoses, especially if they are of recent onset, should be evaluated initially with a platelet count. Many older patients have senile purpura, a benign condition that is not associated with a hemostatic defect.

Von Willebrand's disease is the most common inherited disorder of hemostasis, occurring in as many as 1 in 800 people. The degree of bleeding tendency can vary over time in the same person because of changes in factor levels. In severe disease, the aPTT is elevated, but in milder forms it may be in the normal range (84). The template bleeding time can be used to screen for the most common form of von Willebrand's disease (type I).

Perioperative Antibiotics for Wound Infection Prophylaxis

Although prophylactic antibiotics for the prevention of wound infection are controversial, it is reasonable to administer 1 g *cefotetan* intravenously or intramuscularly just before surgery and then every 6 hours for two additional doses in patients undergoing extensive gynecologic oncology surgery. One study demonstrated that **preoperative antibiotics must be given within 2 hours of surgery to be effective** (85). In addition, if incision of the colon or rectum is anticipated, bowel preparation with *neomycin* and *erythromycin* base, coupled with mechanical cleansing of the bowel on the day before surgery, is prudent, as discussed in Chapter 19.

Critical Care

Cardiovascular

Hypertension

High blood pressure, both labile and persistent, is a common problem for acutely ill patients. **Perioperative hypertensive episodes occur in approximately 25% of hypertensive patients and occasionally in normotensive patients because of pain, anxiety, stress, medications, and other factors** (Table 17.4). Perioperative hypertension is most common during laryngoscopy and induction (primarily because of sympathetic stimulation) and immediately after surgery, often in the recovery room.

Patients with preexisting hypertension usually require continuation of their daily antihypertensive medication when they are brought into the hospital. These agents can be converted to an intravenous form or administered with minimal fluid down a gastric tube if the patient is not eating or drinking. The use of b-blockers as antihypertensives in the acute care setting may have additional benefits by decreasing the risks of atrial fibrillation and myocardial ischemia in vulnerable patients. At least one controlled trial has shown improved long-term morbidity and mortality with routine use of these agents after surgery (8). Sublingual, short-acting calcium channel blockers (e.g., *nifedipine*) should be avoided because their use can lead to reflex tachycardia and myocardial ischemia.

Steroid medications can sometimes cause hypertension in susceptible patients. Mild antihypertensives may be necessary until the steroid dose is lowered or discontinued.

Many hypertensive episodes resolve spontaneously (24). In some patients, postoperative hypertension is due to or exacerbated by pain, anxiety, or emergence from anesthesia. Patients with pain and anxiety are best treated with appropriate analgesics and anxiolytics. Adequacy of ventilation and stable cardiac status should be verified by examination, arterial blood gases, and ECG. Bladder distention can cause elevated blood pressure and should be relieved. Occasionally a patient may require a continuous intravenous infusion to control severe hypertension. Drugs with short half-lives are chosen to allow safe titration (the vasodilator *nitroprusside* or the b-blocker *esmolol* are two popular choices), and patients are changed over to longer-acting agents as their condition stabilizes (86).

Myocardial Injury and Ischemia

Many patients undergoing oncologic treatment have underlying coronary artery disease. The variable stresses in the postoperative period, or after receiving chemotherapy, can lead to myocardial injury or ischemia. Careful preoperative assessment may help predict which patients are most vulnerable to these events (7). The 1990s have seen remarkable progress in the management of what are now called *acute coronary syndromes*, that is, unstable angina and myocardial injury. The 12-lead ECG and repeat serum assays for myocardial necrosis (e.g., troponin I) allow rapid identification of patients undergoing such events (87). The benefits of aspirin therapy (88) and b-blockers (89) are now known to decrease the mortality and morbidity of these coronary syndromes, and these agents should be administered immediately, barring any contraindications. The use of “reperfusion” techniques with direct angioplasty or thrombolytic therapy has also shown benefit for many of these patients (90,91), although their use may be limited by availability or contraindications. The benefits of any of these treatments decline with time, and it is important to identify possible myocardial injury or ischemia promptly and begin appropriate treatment. **Once diagnosis and therapy for acute coronary syndrome is begun, continued close observation in the intensive care unit (ICU) is needed for possible complicating features such as arrhythmia, pulmonary edema, and shock.**

Arrhythmia

Every physician working in an acute care hospital should be familiar with the use of a defibrillator and the algorithms developed by the American Heart Association for advanced cardiac life support (92). Fluid shifts, electrolyte changes, and myocardial ischemia can put the patient receiving treatment for gynecologic malignancy at increased risk for heart rhythm abnormalities.

The tachyarrhythmias, both ventricular and supraventricular, can be quite dangerous and should be cardioverted immediately if the blood pressure is low or unstable. A variety of antiarrhythmic medications are available for chemical conversion and stabilization of these tachyarrhythmias. Many of these medications are proarrhythmic as well, and a search for an underlying cause of the rhythm disturbance should be performed. Often, when the electrolyte imbalance or other precipitant is corrected, these agents can be discontinued. Ventricular arrhythmias are typically managed in the acute setting with intravenous *lidocaine*, although multiple alternative agents are available. Supraventricular tachycardias may respond to vagal maneuvers or a rapid bolus of *adenosine*.

Atrial fibrillation is the most common postoperative tachyarrhythmia and deserves special mention. Once the blood pressure is stabilized in a patient with atrial fibrillation, attempts should be made to control heart rate. Popular drugs for rate control include b-blockers (if left ventricular function is preserved), *diltiazem*, or *digoxin*. Once heart rate and blood pressure are controlled, most clinicians would attempt chemical or electrical conversion of a new case of atrial fibrillation. Restoration of normal sinus rhythm often improves cardiac output (CO) and mitigates the risk of stroke from left atrial thrombus forming in the fibrillating chamber. Patients in atrial fibrillation lasting longer than a few days, and who have no contraindication, should be considered for anticoagulation to decrease their risk of cerebral vascular accident (93).

Bradyarrhythmias often arise from excessive vagal stimulation. Nausea, bladder distention, pain, and endotracheal tube manipulation can all stimulate excess vagal tone. As with tachyarrhythmias, attention to blood pressure is paramount. Those patients who develop hypotension should receive *atropine* and/or catecholamines. Patients not responding to these agents may need urgent transvenous pacemaker placement. Transcutaneous pacing can also be attempted if available at the bedside.

Shock

***Shock* is defined as a clinical syndrome in which the patient shows signs of decreased perfusion of vital organs, including alterations in mental status and oliguria.** In general, patients with shock have a substantial decrease in blood pressure, but no absolute value is used to define shock.

The therapeutic approach to these patients is facilitated by a functional classification of shock states. Each class of shock has its own pathophysiologic process and requires a different management strategy. Traditionally, four varieties of shock are described (94):

1. **Hypovolemic shock**—secondary to fluid losses and decreased cardiac filling pressures (e.g., postoperative bleeding or intravascular fluid redistribution)
2. **Distributive shock**—secondary to inappropriate “vasodilation” and venous pooling (e.g., sepsis syndrome, anaphylaxis, decreased vasomotor tone from spinal anesthesia, adrenal insufficiency from steroid withdrawal)
3. **Cardiogenic shock**—secondary to decreased myocardial contractility and function (e.g., acute MI or ischemia and/or congestive heart failure)
4. **Obstructive shock**—secondary to mechanical obstructions in the cardiovascular circuit (e.g., pulmonary embolism, cardiac tamponade)

Common causes of shock in the perioperative management of gynecologic malignancy include:

1. **Hemorrhage (hypovolemic)**
2. **Sepsis (distributive)**
3. **Postoperative MI (cardiogenic)**
4. **Pulmonary embolus (obstructive)**

Critically ill patients may have mixed or uncertain shock syndromes. Invasive hemodynamic monitoring systems have been developed to assist clinicians in managing these patients. The most popular system for hemodynamic monitoring is the pulmonary artery catheter, a balloon-tipped catheter that is inserted percutaneously through a large central vein and then threaded into position through the right side of the heart into one of the pulmonary arteries. With the balloon inflated, the catheter occludes a pulmonary artery subdivision. The left atrial filling pressure is then transmitted through a continuous column of blood to the catheter tip and measured by a transducer. This measurement is termed the ***pulmonary artery occlusion pressure (PAOP)*, or *wedge pressure.*** In addition to pressure tracings obtained in this manner, most of these catheters also have thermistors at their tips allowing right ventricle CO measurements. These measurements are typically performed with aliquots of cool saline injected through a proximal port on the catheter, and temperature changes are then measured distally.

Despite its frequent use, the pulmonary artery catheter has not been well studied in terms of patient benefit, and some observational studies suggest it may not improve outcome in critically ill patients (94,95 and 96). A careful physical examination and consideration of the clinical situation often reveal the etiology of a patient's shock syndrome. Therapy should typically begin without invasive hemodynamic measurement, although these instruments are still frequently used in the ICU, particularly in patients with known or suspected myocardial dysfunction.

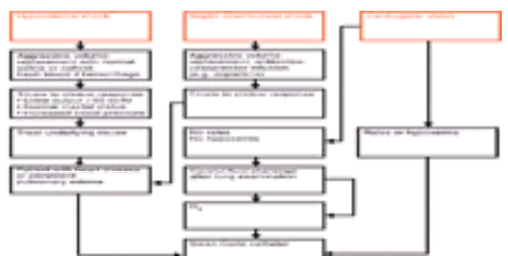
With a pulmonary artery catheter in place, CO values can then be compared with blood pressure changes across the peripheral vasculature **[mean arterial blood pressure (MAP) to central venous pressure (CVP) differences]** to estimate degrees of systemic vascular resistance (SVR). These values are often calculated at the bedside using the following formula (80 is used as a correction factor):

$$\mathbf{SVR = [(MAP - CVP)/CO] \times 80}$$

In a healthy 60-kg woman, the SVR is expected to be near 1,100 dynes/second/ cm^{-5}. Differences in body size are often adjusted for by “indexing” *CO* and therefore ***SVR*** values ***(cardiac index = CO divided by body surface index).*** Clinicians are wise to keep in mind that such calculations depend on multiple measurements, many of them lacking perfect precision or accuracy.

Regardless of whether measured directly with a pulmonary catheter, each of the shock states has an expected hemodynamic profile. Therapy is therefore targeted to the underlying defect in cardiovascular performance:

1. **Hypovolemic shock** is treated with crystalloid or colloid infusion to improve CVP and PAOP such that stroke volume and therefore CO and perfusion to vital organs are improved. There is no consistent evidence that colloid has any benefits over crystalloid for this purpose. Hypovolemic shock is the most common form of shock in the surgical patient, and treatment of the hypotensive, oliguric patient typically begins with a “fluid trial.”
2. **Distributive shock** often requires vasopressor management with catecholamines active at the a receptors on the vasculature. This helps restore adequate resistance (SVR) against which CO can create a perfusing blood pressure. Equally important, however, is to begin treatment of the presumed cause of the vasodilation: antibiotics for cases of suspected sepsis, steroids if secondary adrenal insufficiency is a possibility, or withdrawal of the offending agent and antiinflammatory treatment if the patient might be having an allergic response.
3. **Cardiogenic shock** is characterized by inadequate CO, such that inotrope management with catecholamine and dopaminergic compounds is often necessary to maintain adequate contractility. Vasodilator therapy is often helpful in cardiogenic shock because it unburdens the failing heart's afterload and allows contractility to improve without excessive cardiac work, which might exacerbate myocardial ischemia.
4. **Obstructive shock** can be difficult to manage and might require a combination of measures to maintain adequate filling pressures and contractility. Like distributive shock, it is important to attempt reversal of the precipitant (e.g., anticoagulation for pulmonary embolism, pericardiocentesis for tamponade) because the patient's ultimate outcome depends on this. An algorithm for the management of shock syndromes is shown in Fig. 17.4, although critically ill patients may often develop mixed disturbances in hemodynamics.



contractility. Like distributive shock, it is important to attempt reversal of the precipitant (e.g., anticoagulation for pulmonary embolism, pericardiocentesis for tamponade) because the patient's ultimate outcome depends on this. An algorithm for the management of shock syndromes is shown in Fig. 17.4, although critically ill patients may often develop mixed disturbances in hemodynamics.

Figure 17.4 Management of hypotension. PCWP, pulmonary capillary wedge pressure; SVR, systemic vascular resistance.

Respiratory Failure

Respiratory failure can be defined as a failure of gas exchange, that is, failure of the respiratory system to accomplish the exchange of oxygen and carbon dioxide between ambient air and red blood cells in amounts required to meet the body's metabolic needs. Respiratory syndromes characterized by difficulty in oxygenation of the blood are grouped under the umbrella term, *hypoxic respiratory failure*, and those with difficulty removing carbon dioxide from the blood are described as *ventilatory failure*. It is often helpful for assessment and therapy to consider these as separate duties, although in reality they are closely connected. The arterial blood gas is used to determine the degree and type of gas exchange failure and should be performed as part of the initial evaluation. Patients with respiratory failure initially have abnormal mental status (agitation, somnolence, and disorientation) and physical findings may include tachycardia, hypertension, and occasionally cyanosis and sweating (Fig. 17.5).

Figure 17.5 Management of respiratory failure. ABG, arterial blood gases; PCWP, pulmonary capillary wedge pressure; CPAP, continuous positive airway pressure; PEEP, positive end-expiratory pressure; SIMV, synchronized intermittent mandatory ventilation; AC, assist control; F_IO_2, fraction of inspired oxygen.

Common causes of respiratory failure in the perioperative management of gynecologic malignancy include:

1. **Nervous system depression secondary to sedative or analgesic medications**
2. **Bronchospasm**
3. **Pneumonia**
4. **Pulmonary edema**
5. **Lymphangitic spread of cancer**
6. **Respiratory muscle weakness**

Hypoxic Respiratory Failure

Hypoxic respiratory failure is usually caused by a mismatch between inhaled gas and blood circulation in the lung parenchyma. Blood circulating in areas of mismatch is relatively deoxygenated. The degree of hypoxic respiratory failure can be characterized by the alveolar–arterial oxygen gradient. This value is determined by measuring the arterial oxygen tension with a blood gas, and then calculating the alveolar oxygen tension using known values for the fraction of inspired air that consists of oxygen (dependent on ambient barometric pressure and amount of oxygen supplementation) and the amount of carbon dioxide tension in the alveolus (calculated by measuring the arterial carbon dioxide tension on blood gas and adjusting for the expected exchange into the alveolus to maintain metabolic processes). This calculation is frequently performed at bedside using the following alveolar gas equation:

$$\text{Alveolar } P_{O_2} = \text{Inspired } O_2 \text{ concentration} - \text{alveolar } CO_2 \text{ concentration}$$

$$\text{Alveolar } P_{O_2} = (F_{IO_2} \times [\text{barometric pressure} - \text{water vapor pressure*}]) - (P_{aCO_2} \text{ arterial} \times 1.25)$$

*713 mm Hg at sea level

Without oxygen supplementation at sea level, the inspired oxygen concentration is approximately 150 mm Hg. Normal P_{aCO_2} is 40 mm Hg in arterial blood. Therefore, the alveolar oxygen concentration by the preceding equation is approximately 100 mm Hg. This would then be compared with the measured arterial oxygen concentration on a blood gas sample to describe the ***alveolar–arterial gradient (alveolar P_{O_2} – arterial P_{O_2}).*** The alveolar–arterial difference in oxygen concentration increases with age, but typically does not exceed 20 mm Hg. A gradient wider than 20 mm Hg is the hallmark of hypoxic respiratory failure.

Treatment of hypoxic respiratory failure involves improving oxygenation of arterial blood as well as attempting correction of the underlying mismatch in lung function. Interventions to improve oxygenation include supplemental oxygen by nasal cannula or mask, or by positive-pressure breathing for refractory hypoxemia. Positive airway pressure serves in part to inflate partially or totally collapsed regions of the lung, often with dramatic improvement in oxygenation. On a mechanical ventilator, different manipulations can be made to increase air way pressures. Most commonly, this is done by increasing ***positive end-expiratory pressure (PEEP).*** Additional methods to help reverse underlying ventilation-perfusion mismatch in hypoxic respiratory failure are as follows:

1. Bronchodilators for bronchospasm
2. Diuretics for excess lung edema
3. Antibiotics for pneumonia
4. Chest physiotherapy for atelectasis
5. Anticoagulants for pulmonary embolism

Ventilatory Failure

Ventilatory failure occurs in patients who fail to “excrete” adequate carbon dioxide from their lungs. These problems typically do not arise from mismatch at the alveolar–capillary level, but more likely from failure of the lungs to effectively pump gas out of the respiratory circuit. As P_{CO_2} builds up in the alveoli, the arterial P_{CO_2} begins to rise as well. Hypercarbia on the blood gas measurement is the hallmark of ventilatory failure. “Pump” dysfunction can occur anywhere from the medulla to the diaphragm to the thickened or destroyed airways of the patient with COPD. Typical scenarios for the oncology patient include the oversedated patient with inadequate respiratory rate or the weakened patient unable to pump air adequately through diseased lungs.

Treatment of ventilatory failure consists of reversing any precipitants, and if these are not readily correctable, providing adequate tidal volume and respiratory rate with invasive or noninvasive ventilation techniques. This is typically administered through an endotracheal tube with a mechanical ventilator, although there is increasing interest in the use of noninvasive masks to administer continuous or phasic positive airway pressure in certain situations (97).

Chronic Respiratory Failure

Some patients with gynecologic malignancy may have adapted to chronic respiratory insufficiency. These patients with chronic lung disease may have abnormal alveolar–arterial oxygen gradients or carbon dioxide tensions as their baseline equilibrium. Chronic hypoxemia leads to elevated hemoglobin and improved oxygen delivery chemistry, and these patients are not in acute distress unless their P_{O_2} dips into the 50 mm Hg range. **Chronic lung disease can lead to carbon dioxide retention, which is compensated by a metabolic alkalosis. Increasing oxygen supplementation beyond that necessary to maintain hemoglobin saturations at the patient's baseline can sometimes lead to worsening pump function in patients with chronic CO_2 retention.** Likewise, improving ventilation by mechanical means to a "normal" P_{CO_2} on blood gas measurement may lead to dangerous alkalemia in such a patient with chronic lung disease who was in acid–base balance at a higher P_{CO_2}. The goal in oxygenation and ventilation in patients with chronic respiratory insufficiency should be to maintain their baseline status.

Adult Respiratory Distress Syndrome

One pattern of severe respiratory failure that deserves special mention is the adult respiratory distress syndrome (ARDS). This is a pattern of lung injury that can be precipitated by direct damage (aspiration) or can occur as part of a septic syndrome and resulting lung inflammation. It is characterized by severe hypoxemia and markedly decreased lung compliance thought to be secondary to diffuse capillary leakage into the lung parenchyma. The chest radiograph has the appearance of pulmonary edema, although direct measurement with a pulmonary catheter typically shows low or normal PAOP. Management typically involves mechanical ventilation with PEEP for oxygenation, minimizing fluid overload, and avoiding high peak airway pressures and nosocomial complications (98). Despite aggressive support, the mortality rate from this syndrome remains high (99).

Mechanical Ventilation

Physicians working with critically ill patients need to understand the principles of mechanical ventilation. Postoperative patients sometimes remain on mechanical ventilation until they are stabilized. Even apparently stable oncologic patients on the wards are often at risk for hypoxic and ventilatory failure that can progress to the need for positive-pressure ventilation.

Mechanical ventilation is typically performed by placement of an endotracheal tube, although tight-fitting masks are sometimes used in patients who are awake enough to protect their airways (noninvasive positive-pressure ventilation) (87). There has been a proliferation in both the types and terminology for mechanical ventilation over the years, often leading to some confusion. Despite the many modalities, little is known about improved benefits from one ventilator setting versus another in terms of long-term outcome (100).

A basic understanding of ventilator management can be divided into two realms (much like the understanding of respiratory failure)—ventilation and oxygenation. **Management of ventilation requires adjusting when and how often the machine delivers a breath (with every patient effort, or on a timer) and how it delivers that breath (either as a preset volume, or applying a preset pressure).** These settings are chosen to help the clinician accomplish two goals: full or partial support of the patient's breathing efforts, and ensuring adequate ventilation without excessive airway pressures. Management of oxygenation requires adjustment of the fraction of inspired oxygen delivered into the lungs and the end-expiratory airway pressure settings. These values are also set to achieve adequate blood oxygen saturation without damaging the lungs.

When the machine is set to deliver a full mechanical breath with each patient effort, the patient is receiving fully supported ventilation. Typically, a backup respiratory rate is set, but the patient can breathe as often as she wants and receives a fully supported tidal breath each time. This is typically called ***assist control (AC)*** ventilation. When the machine is set to deliver only a certain number of breaths each minute, the patient needs to breathe without full machine support for any additional respirations above the set rate. This is considered partially supported ventilation and is most typically set as ***synchronized intermittent mandatory ventilation (SIMV).*** The mechanical breath itself can be delivered as a preset volume with each breath, so-called ***volume control ventilation.*** This ensures an adequate tidal volume but risks increased airway pressures if the lungs become difficult to inflate because of increased airway resistance or lung stiffness. **High airway pressures can cause barotrauma, such as pneumothorax, and most physicians attempt to keep peak airway pressures less than 35 cm H_2O** (101). Instead of volume control, the mechanical breath can be administered as a preset pressure; this is usually termed ***pressure control*** (or in a slightly different mode, ***pressure support***). This avoids the risks of increased airway pressures but may provide smaller tidal volumes with each breath if lung mechanics (or patient efforts) change. **Arterial blood gases are typically followed for patients on mechanical ventilation, and adjustments are made in the aforementioned settings to keep the patient's arterial carbon dioxide level near her baseline value.**

When adjusting oxygenation settings on the ventilator, most critical care physicians attempt to lower the fraction of inspired oxygen to below 65%. Values above this for prolonged periods are believed to be damaging to lung parenchyma (102). The addition of PEEP often increases the functional reserve capacity of the diseased lung and allows F_{IO_2} reductions. PEEP should be titrated to maximize oxygenation in respiratory failure, although some caution is needed because higher values can begin to precipitate barotrauma from increased peak pressures, as noted previously. In some forms of acute respiratory failure, such as ARDS, additional measures may be tried for refractory hypoxemia, including lengthening the inspiratory time on the ventilator cycle. Unfortunately, like many interventions that have been tried for this syndrome, this has not been shown in any prospective trials to improve long-term outcome (100).

Once the cause of respiratory failure is improved or improving, and the patient is judged hemodynamically stable, attempts to remove the patient from mechanical ventilation should begin. This process has become known as *weaning*, although it does not need to be as slow as this appellation suggests. Although clinicians have looked at many screening methods for identifying patients who are ready to come off mechanical ventilation, none offers perfect sensitivity or specificity. **Traditional weaning criteria such as negative inspiratory force less than 25 cm and minute ventilation less than 10 L/minute have poor predictive value** (103). **The bedside test with best predictive accuracy may be the *rapid shallow breathing test*, which divides *respiratory rate* (breaths per minute) by *tidal volume* (liters) measured with the patient removed briefly from ventilatory support. Values less than 105 breaths/minute/L have shown more than 90% positive predictive value** (104). Perhaps most useful in determining a patient's readiness for extubation is a trial of spontaneous breathing with little or no support from the ventilator. Patients who can tolerate this for 2 hours with acceptable blood gases should be considered for extubation if they can protect their airway and maintain oxygenation (105). Early extubation can help avoid nosocomial pneumonia as well as other complications associated with the mechanical ventilator and a prolonged ICU stay.

Renal Insufficiency, Fluids, and Electrolytes

Oliguria and Acute Renal Failure

The first sign of new or worsening renal dysfunction is often low urine output or rising serum creatinine concentration. ***Oliguria*** **is defined as a urine output of less than 400 mL/day.** ***Acute renal failure*** **has been variably defined, but typically reflects a significant fall in glomerular filtration reflected in a creatinine increasing to twice its baseline value** (106). **In the hospital setting, acute oliguria or renal failure is usually caused by hypovolemia, decreased CO, postoperative kidney injury, or the use of nephrotoxic drugs.** (107). **Patients with malignancy are also at increased risk for acute kidney injury from ureteral obstruction and tumor lysis syndrome.**

The causes of oliguria and/or acute renal failure are grouped into three categories: prerenal, intrinsic, and postrenal. Initial evaluation attempts to group the patient into one of these classes. The physical examination should exclude orthostatic blood pressure changes, evidence of liver disease, a palpable bladder, and an elevated postvoid residual urine volume as determined by bladder catheterization. Laboratory evaluation of the oliguric patient should include determinations of urinary and serum sodium and creatinine concentrations, urine osmolality, and microscopic urinalysis. Unfortunately, urinary electrolyte studies are uninterpretable in a patient who has been receiving diuretics or is glucosuric.

Postrenal causes of oliguria or acute renal failure arise from obstruction of the urinary tract. If this remains a suspicion even after a urethral catheter is placed, an ultrasound can be ordered, which may show characteristic dilation of the collection system above the obstruction. Although quite specific, this finding may not be present in all cases of ureteral obstruction, and additional radiographic tests may be needed (108). Percutaneous or cystoscopic stenting is often performed for cases of acute ureteral obstruction.

Prerenal azotemia can often be diagnosed with urinary indices: it tends to be associated with high urine osmolality, low urinary sodium, and a high urine-to- plasma creatinine ratio. **The best urinary index for distinguishing prerenal from other causes of oliguria is the fractional excretion of filtered sodium ($F_{ex}Na$).** This can be calculated from sodium and creatinine concentrations as follows:

$$F_{ex}Na = [(\text{Urine sodium} \times \text{plasma creatinine})/(\text{Plasma sodium} \times \text{urine creatinine})] \times 100$$

Prerenal azotemia **is associated with a fractional excretion for sodium of less than 1%, whereas obstructive uropathy and most forms of intrinsic renal failure [except pigment- or radiocontrast-induced acute tubular necrosis (ATN)] are associated with levels greater than 2%** (109). Causes of prerenal oliguria and acute renal failure include hypovolemia due to fluid losses or redistribution, cardiogenic shock, or renal vasculature abnormalities caused by stenosis, obstruction, or disruption of renal vasculature autoregulation (this is believed to be the culprit in renal failure associated with hepatic failure). Patients with a history or physical examination suggestive of volume depletion, or urinary indices consistent with prerenal azotemia, should be treated with fluid administration and frequent examination for evidence of volume overload. Characteristic urinary indices for prerenal and other causes of acute renal failure are listed in Table 17.11.

	Prerenal Azotemia	*Acute Oliguric Renal Failure*	*Acute Nonoliguric Renal Failure*	*Acute Obstructive Uropathy*	*Acute Glomerulonephritis*
Urine osmolality, mosm/kg H_2O	518 ± 15	369 ± 20	343 ± 17	393 ± 39	385 ± 60
Urine sodium, mEq/L	18 ± 3	68 ± 5	50 ± 5	69 ± 10	22 ± 6
Urine/plasma urea nitrogen	18 ± 7	3 ± 0.5	7 ± 1	8 ± 4	11 ± 4
Urine/plasma creatinine	45 ± 6	17 ± 2	17 ± 2	15 ± 4	40 ± 7
Fractional excretion of filtered sodium	0.4 ± 0.1	7 ± 1.4	3 ± 0.5	6 ± 2	0.6 ± 0.2

[illegible] Reproduced and adapted from Miller TR, Anderson RJ, Linas SC, et al. Urinary diagnostic indices in acute renal failure: a prospective study. Ann Intern Med. 1978;89:47–50., with permission.

Table 17.11 Urinary Diagnostic Indices[a]

Once prerenal and postrenal causes of renal dysfunction have been excluded, the patient likely has intrinsic disease of the kidney. Most of these cases are caused by *ATN*, although a small percentage of patients may have interstitial nephritis or a form of glomerulonephritis (106). Urinalysis may suggest the etiology: red blood cell casts in the sediment are diagnostic of glomerulonephritis, “muddy” and cellular casts are suggestive of ATN, and eosinophils in the urine (stained with Wright's stain) are diagnostic of interstitial nephritis induced by drugs.

Acute tubular necrosis is usually caused by either ischemia or toxins. Many drugs are known nephrotoxins, including many chemotherapeutic agents. Clinicians attempt to avoid nephrotoxicity by careful dosing and avoidance of hypovolemia. Use of a saline intravenous bolus shortly before administering radiocontrast dye, for instance, has been shown to decrease the known risk of ATN from these agents (110). One cause of intrinsic renal failure that should be considered in any oncology patient being treated with chemotherapy is ***tumor lysis syndrome*****, which is caused by the rapid death of large numbers of tumor cells and the sudden release of intracellular phosphate.** Most commonly seen in lymphoma, it can occur in solid malignancies that respond dramatically to chemotherapeutic agents. When recognized, it is an indication for urgent hemodialysis.

Management of patients with an acutely rising serum creatinine includes discontinuation of any nephrotoxic medications and adjustment of continuing medications to the patient's new creatinine clearance. The treating physician also needs to ensure adequate volume status yet avoid volume overload, and pay careful attention to serum electrolytes and acid–base status. Many clinicians believe maintaining urine output is helpful in management of acute renal failure, and administer diuretics (and often low-dose *dopamine*) when volume status is restored. Whether this improves outcome is debated, but, if successful, this strategy can make volume management easier and potentially avoid hemodialysis (111). Sometimes the use of renal replacement therapy (hemodialysis) is needed for patients whose volume status, electrolyte imbalance (particularly hyperkalemia and hyperphosphatemia), and acidemia cannot be controlled. This therapy might also be used for patients with decreasing mental status (uremic encephalopathy), bleeding (uremic platelet dysfunction), or pericarditis. Patients who are hemodynamically unstable might benefit from continuous techniques (continuous venovenous hemodialysis or ultrafiltration) rather than intermittent therapy (112). An algorithm for managing oliguria and/or rising serum creatinine is shown in Fig. 17.6.

Figure 17.6 Management of a rising serum creatinine.

Acid–Base Disorders

Disorders of acid–base homeostasis are common in critical care medicine, and accurate interpretation of these disorders is important for successful management. For an exhaustive review of acid–base disorders, the reader is referred to several excellent summaries (113,114). The human body requires tight regulation of acid–base balance despite ongoing metabolic processes that produce substantial acid loads. It does this with several buffering systems, all of which are in balance and reflect any disturbances. The most important, and most easily measured, is the bicarbonate–carbonic acid equilibrium, which is reflected in serum bicarbonate measurement and carbon dioxide tension (which is in equilibrium with carbonic acid). Changes in these measurements from baseline reflect changes in acid or base balance.

Changes in serum P_{CO_2} reflect either primary lung disorders (hyperventilation or hypoventilation) and resulting respiratory disturbances in acid–base balance, or attempts by the lungs to compensate for matching changes in bicarbonate concentration in the blood (metabolic disturbances). Hyperventilation as a primary disturbance results in a low carbon dioxide gas concentration in the blood and resulting respiratory alkalemia. Hypoventilation as a primary disturbance raises carbon dioxide tension in the blood and causes a *respiratory acidemia*. On the other hand, when the primary acid–base disturbance is not caused by the respiratory system itself, the patient's ventilatory system attempts to keep the pH balanced by hyperventilation or hypoventilation and creates compensatory changes in the P_{CO_2}. By studying the serum pH and comparing changes in the serum carbon dioxide tension to changes in the serum bicarbonate, the clinician is often able to distinguish primary respiratory alkalemia and acidemia (as well as their duration) from compensation (113,114). Bedside nomograms have been designed for this purpose as well.

Primary changes in the serum bicarbonate concentration often reflect processes initially less obvious than primary lung disturbances. A decreased measured serum bicarbonate concentration, called a *metabolic acidosis*, is a common finding in critically ill patients. ***Metabolic acidosis* is defined as a decrease in serum bicarbonate level and occurs as a primary disorder or as a compensation for a respiratory disturbance.** Typically, the first step in evaluating a patient with metabolic acidosis is to measure serum electrolytes and calculate the anion gap. A formula for the anion gap using serum electrolyte concentrations is:

$$\text{Anion gap} = (Na^+ + K^+) - (Cl^- + HCO_3^-)$$

A "normal" anion gap is 10 to 14 mEq/L. The causes of metabolic acidosis with elevated and normal anion gaps are presented in Table 17.12.

Elevated Anion Gap	Normal Anion Gap	Normal–Hyperkalemic Acidosis
Renal failure	Renal tubular acidosis	Early renal failure
Ketoacidosis	Diarrhea	Hydronephrosis
Lactic acidosis	PostHypocapnic acidosis	Addition of HCl
	Carbonic anhydrase inhibitors	Sulfur toxicity
	Ureteral diversions	

Table 17.12 Causes of Metabolic Acidosis

The second step in evaluating a metabolic acidosis often is assessment of the adequacy of the patient's ventilatory response. The normal mechanism of compensation for a decreased serum bicarbonate is hyperventilation, which lowers the P_{CO_2} and corrects the impact of the decreased bicarbonate on pH. The expected response to a primary metabolic acidosis is often estimated by the following equation (115):

$$\text{Expected } P_{CO_2} = 1.5\ (\text{measured } HCO_3^-) \pm 2$$

Patients who have metabolic acidosis and whose measured P_{CO_2} levels fall below those expected on the basis of this equation should be suspected of having a second disturbance (i.e., an additional respiratory alkalosis). In patients with a P_{CO_2} higher than this expected level, additional respiratory acidosis should be suspected as complicating their metabolic disturbance.

The treatment of metabolic acidosis depends on its severity. In most cases, identification and treatment of the underlying cause is the only direct therapy necessary. In patients who have profound disturbances and bicarbonate levels less than 10 or pH less than 7.2, especially if there is associated hypotension or if the underlying disease is expected to worsen, bicarbonate therapy should be considered. Bicarbonate therapy should be undertaken with caution because there is a theoretical risk of causing a transient worsening of the cerebrospinal fluid pH or of inducing fluid overload and rebound metabolic alkalosis. Some researchers have suggested the administration of exogenous bicarbonate may even worsen the outcome in lactic acidosis (116), although most clinicians would still consider this therapy in cases of severe acidemia.

***Metabolic alkalosis* can also occur in hospitalized patients. Perhaps most commonly, metabolic alkalosis is associated with volume contraction.** In such conditions, sodium reabsorption by the kidney is linked to bicarbonate resorption. Metabolic alkalosis does not resolve until the patient regains intravascular volume. To determine the primary precipitant of metabolic alkalosis and appropriate treatment, the clinician can use urinary chloride measurements to divide patients into two groups (provided the patient has not received recent diuretic therapy). Those alkalotic patients with very low urinary chlorides have received nasogastric drainage, diuretic therapy, vomited, or have lingering alkalosis after hypercapnic lung failure. These chloride-responsive patients are treated with normal saline solution. Patients with metabolic alkalosis but higher urinary chloride concentrations do not respond to *sodium chloride* and must be managed by treatment of the underlying disease. Table 17.13 lists the causes of metabolic alkalosis.

A. Sodium chloride responsive (urine chloride <10 mmol/L)
1. Gastrointestinal disorders Vomiting Gastric drainage Chloride diarrhea
2. Diuretic therapy
3. Correction of chronic hypercapnia
B. Sodium chloride resistant (urine chloride >20 mmol/L)
1. Profound potassium depletion
C. Unclassified
1. Alkali administration
2. Milk-alkali syndrome
3. Massive blood or plasma transfusion
4. Nonparathyroid hypercalcemia
5. Glucose ingestion after starvation
6. Large doses of carbenicillin or penicillin

Reproduced and adapted from Schrier RW, ed. *Renal and electrolyte disorders*. 2nd ed. Boston: Little, Brown, 1980:146.

Table 17.13 Differential Diagnosis ot Metabolic Alkalosis in Gynecologic Oncology Patients

Maintenance Fluids

Management of water and electrolyte therapy is an important component in the care of these patients, particularly those who are not taking hydration or nourishment orally. In the average adult who is taking fluids orally, the average daily loss of water is approximately 3 L (2 L as urine and 1 L as insensible losses from perspiration, respiration, and feces). The condition of critically ill patients may be complicated by additional ongoing losses, derangements in renal function, increased insensible losses, and disturbances in free water metabolism induced by the underlying disease. Successful management of those patients requires frequent monitoring of volume status and serum electrolytes. Predictable losses of fluids and electrolytes must be replaced, particularly those from nasogastric suctioning and the increased insensible losses associated with fever and diarrhea (114).

Several simple guidelines can be kept in mind when managing fluid replacement in the hospitalized patient. **In a patient with no preexisting renal disease and no disorder of water or electrolyte metabolism, a reasonable maintenance fluid regimen is 3 L daily of a half-normal saline solution with 20 mEq of potassium chloride in each liter. In the presence of significant renal impairment (glomerular filtration rate <25 mL/minute), potassium therapy should not be given routinely, replacement being based on serial determinations of serum potassium.** In patients suspected of having a defect in free water excretion (see later), it is prudent to decrease the free water content of the initial maintenance fluids (typically by giving normal saline at half the rate). Gastric fluid is composed of hypotonic saline solution (one-fourth to one-half normal saline) with 5 to 10 mEq/L of potassium. Gastric fluid losses should be replaced with replacement fluids in addition to the maintenance prescription.

Hyponatremia and Hypernatremia

Hyponatremia is a common disorder in gynecologic oncology patients. Serum sodium concentration reflects total body water content, not total body sodium content (which reflects extracellular volume). **Hyponatremia represents relative water excess.** These disorders are best grouped into three different categories:

1. ***Hyponatremia associated with a diminished total body sodium content and hence extracellular volume depletion.*** In these patients, hyponatremia arises as the body sacrifices osmotic homeostasis to defend volume status. Hypovolemic patients block free water excretion by increasing antidiuretic hormone secretion. All forms of intravascular volume depletion in patients with normal renal function predispose to this form of hyponatremia, especially when losses have been replaced with hypotonic fluids. The urinary sodium level is low, and signs of volume depletion are frequently present.
2. ***Hyponatremia with normal or slightly expanded extracellular volumes.*** This is seen in patients with the syndrome of inappropriate antidiuretic hormone secretion and patients with hypothyroidism. Urinary sodium levels reflect free water and sodium intake and can be high or low.
3. ***Hyponatremia with increased total-body sodium and increased extracellular volume.*** The hallmark of these disorders is edema, and urinary sodium levels are high, consistent with intravascular volume excess. Patients with this category of hyponatremia usually have nephrotic syndrome, cirrhotic liver disease, or congestive heart failure.

The treatment of hyponatremia is tailored to its pathophysiology. **Patients with diminished extracellular volume are treated with infusion of normal saline solution. Patients with normal or increased extracellular volume can be managed initially with free water restriction.** Those with persisting or worsening hyponatremia and adequate extracellular volume can be managed acutely with *furosemide* to induce a hypotonic diuresis, and then with replacement of urine output with normal saline infusion. Therapy with hypertonic saline is rarely necessary, and reserved for patients with profound hyponatremia typically associated with seizures and/or markedly diminished mental status. An algorithm detailing an approach to the patient with hyponatremia is presented in Fig. 17.7.

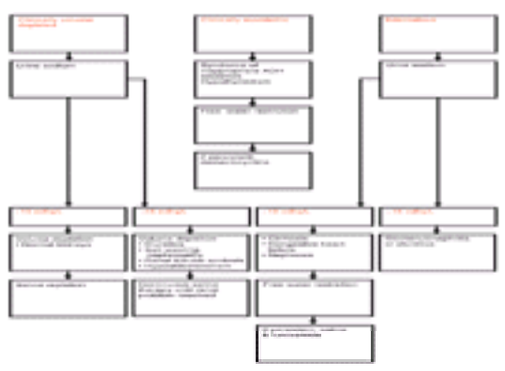


Figure 17.7 Evaluation of hyponatremia. ADH, antidiuretic hormone.

Hypernatremia, less commonly encountered in hospitalized patients, represents relative total-body water deficit. Usually it is the result of inadequate water replacement in a patient unable to take fluids spontaneously. This might be exaggerated or precipitated by failure of the kidneys adequately to reabsorb water (concentrate urine), a condition termed *diabetes insipidus*. Hypercalcemia (see next section) can occur in patients with malignancies and directly affects the kidney's ability to concentrate. Hyperglycemia can also worsen water losses by causing an osmotic diuresis. Treatment of hypernaturemia is directed at providing adequate hypotonic fluids (often as “free water” or fluids with very minimal solute), improving hypercalcemia and hyperglycemia. Rare patients may have disorders of antidiuretic hormone manufacture and secretion at the hypothalamus and posterior pituitary (central diabetes insipidus) and must receive exogenous hormone to maintain water balance.

Hypokalemia and Hyperkalemia

Disturbances in serum potassium concentration are common and important because of the pivotal role played by this ion in maintaining transmembrane potentials of the heart. Because 98% of total-body potassium is intracellular, small changes in serum potassium concentration may reflect very large excesses or deficits in total-body potassium content. For instance, a decrease in the plasma potassium concentration to 3 mEq/L can reflect a 100- to 200-mEq deficit in total-body potassium content; a decrease to 2 mEq/L can reflect a total-body deficit of 300 to 500 mEq of potassium.

Changes in hydrogen ion concentration can have an impact on the distribution of potassium between the intracellular and extracellular spaces. In acidemic patients, there is a shift in potassium from intracellular to extracellular sites. In a patient who is acidemic and hypokalemic, the plasma potassium concentration is not appropriately diminished, and the total-body potassium deficit will be under estimated.

Possible causes of hypokalemia include decreased dietary intake or insufficient replacement in maintenance fluids, often worsened by diarrhea, nasogastric suction, or diuretic therapy. Hypokalemia can present as weakness, ileus, and muscular cramps. Of most concern, hypokalemia increases myocardial irritability and can precipitate dangerous arrhythmias. Treatment involves reversal of the underlying cause and repletion of the potassium deficit. Potassium is replaced relatively slowly in most circumstance to allow cell membranes to equilibrate. **In general, patients should not receive more than 10 mEq/hour intravenously.** Patients undergoing potassium therapy in the presence of renal failure have a diminished capacity to excrete potassium, and therefore added caution is needed to avoid the equal dangers of hyperkalemia (see later).

Common causes of elevated serum potassium include renal insufficiency and decreased ability to excrete daily potassium load, cellular breakdown (including hemolysis) and increased potassium release into extracellular fluids, and redistribution from the intracellular to the extracellular compartment associated with acidemia. Occasionally, a high measured serum potassium results from hemolysis of the drawn blood sample in the test tube and does not accurately reflect serum concentration.

Patients with an elevated serum potassium typically have no symptoms. The condition is usually noted on screening laboratory tests or when changes are noted on an ECG. **Although variable, ECG changes associated with elevated serum potassium include peaked T waves, prolonged PR interval, and widening of the QRS complex.** These changes often herald dangerous serum potassium levels that need correction before the advent of cardiac arrest.

The initial approach to hyperkalemia is to identify and remove the precipitating cause and rapidly assess any ECG changes. In patients with mild hyperkalemia (serum K^+ <6 mEq/L) and minimal ECG changes, treatment of the underlying cause and careful monitoring of the serum potassium levels may be the only therapy necessary. **In patients with potassium levels greater than 6.5 mEq/L and evidence of QRS widening, rapid steps should be taken to decrease serum potassium levels with the use of potassium exchange resins and a loop diuretic such as *furosemide.*** If there is associated renal insufficiency, arrangements for dialysis are indicated. In patients with prolonged QRS duration approaching sine- wave configuration, or in patients who are hypotensive, the following treatments can “temporize” until more definitive treatment is arranged: calcium gluconate to reverse the adverse effects of hyperkalemia on the myocardial cell membranes, intravenous glucose and *insulin* (one unit of *insulin* for each gram of glucose in an ampule of glucose), and sodium bicarbonate.

Hypercalcemia

Hypercalcemia is associated with malignant disease and deserves mention. There are several mechanisms for the development of this disorder, the most common in gynecologic oncology patients being increased osteoclastic bone resorption. It is believed to result from tumor secretion of humoral factors that stimulate this activity. **Clear cell and small cell tumors of the ovary are commonly associated with this syndrome.**

The clinical presentation of hypercalcemia includes lethargy, confusion, psychiatric disturbances, polyuria (caused by a concentrating defect in the kidney; see earlier), constipation, and occasionally abdominal pain and nausea. Acute management includes hydration with normal saline and administration of a loop diuretic to increase urinary calcium excretion. Subsequent treatment is targeted to the underlying cause (treatment of the tumor), and also may include the use of bisphosphonates or *calcitonin* to control the elevated calcium level.

Nutrition

Patients who cannot eat for several days should be considered for nutritional support (beyond the minimal calories available in glucose-based maintenance fluids). Although the criteria for this intervention are not well defined, and clinical trials have shown variable results, most clinicians would consider this intervention after several days without adequate calories and several more anticipated. Enteral feeding is preferred because it may protect patients from gastrointestinal bleeding and infectious complications (117). **Parenteral feeding usually requires central line placement and carries additional risks. One large trial in postsurgical patients has shown these risks are outweighed by benefits only when the patients required parenteral feeding for longer than 14 days** (118). Various enteral and parenteral feeding formulas are available, and adjustments in constituents are often needed to avoid many of the fluid and electrolyte problems described previously.

Blood Replacement

Red Blood Cells Red blood cells can be transfused in the form of *whole blood*, or *packed red blood cells*. Whole blood contains red cells as well as platelets and plasma. Packed red blood cells are red cell concentrates that are prepared by removal of most platelets and all but approximately 100 mL of plasma from a unit of whole blood. In addition, red cells can be washed to remove leukocytes and contaminating plasma proteins for transfusion to selected patients who have had febrile reactions to them.

With the possible exception of the patient with massive exsanguination, there is little advantage to transfusion of whole blood and, as a practical rule, packed red blood cells should be used when red cell therapy is indicated. The indications for transfusion of red blood cells include:

1. A decreasing hematocrit value in a patient who, because of bone marrow failure, is unlikely to begin producing red blood cells in the near future.
2. Anemia in a patient with such symptoms as shortness of breath or chest pain. In general, patients have no symptoms if hemoglobin levels are above 10 g/dL.

One recent study suggested that transfusion is necessary only when the hemoglobin level is 7.0 g/dL or less in patients who are not actively bleeding (119). Although controversial, a restrictive strategy of red cell transfusion may be at least as effective and possibly superior to a more liberal transfusion policy in critically ill patients, with the possible exception of patients with acute **MI** and unstable angina.

Risks of red cell therapy include transfusion hepatitis and acquired immunodeficiency syndrome, as well as acute hemolytic reactions.

Acute Hemolytic Transfusion Reaction This reaction is life-threatening because of associated hypotension, disseminated intravascular coagulation (DIC), and renal failure. It is manifested by fever, chest pain, back pain, hypotension, and red urine. When a patient undergoing a red cell transfusion has any sign or symptom suggestive of a hemolytic transfusion reaction, the transfusion should be stopped immediately and the remaining aliquot of blood sent to the blood bank, along with a sample of the patient's blood for culture and repeat cross-matching. A screening for DIC, a urinalysis for hemoglobin, and a blood sample for bilirubin also should be obtained. In patients with symptoms of a hemolytic transfusion reaction who, on analysis, show no evidence of hemolysis, a hypersensitivity reaction to transfused leukocytes or plasma proteins contaminating the red cells should be suspected. The incidence of hemolytic transfusion reactions can be minimized by careful attention to clerical information, ensuring that the patient is receiving blood cross-matched to her blood sample, and careful cross-matching in the blood bank.

Platelets

Platelet concentrates are prepared by removal of platelets from whole-blood fractions. Platelets can be stored for 5 days at 22°C, and each 50-mL platelet unit contains approximately 6×10^{10} platelets.

Platelet transfusions are indicated in patients with:

1. Platelet counts less than 50,000/mL^3 who show evidence of bleeding
2. Platelet counts less than 10,000/mL^3 as prophylaxis against acute bleeding

Each unit of platelets should be expected to raise the platelet count approximately 5,000 to 10,000/mL^3. In general, prophylactic platelet transfusions are indicated only in patients whose platelet count is expected to recover in the future because platelets express human leukocyte antigens and hence induce antibodies in the recipient. After prolonged platelet therapy, most patients become resistant to platelet transfusions, presumably because of immune destruction of all transfused platelets.

Plasma Fractions

Several plasma fractions are available for transfusion.

Fresh Frozen Plasma All coagulation factors (including at least 50% of factors V and VIII present in the original unit of blood) are contained in fresh frozen plasma, and it is an adequate source of all coagulation factors for the treatment of mild coagulation factor deficiencies.

Cryoprecipitate Cryoprecipitate is produced by freezing of plasma, followed by thawing, and produces a precipitate rich in factor VIII and fibrinogen. This cryoprecipitate fraction contains approximately 250 mg of fibrinogen per unit and 80 clotting units of factor VIII. When cryoprecipitate is used in the treatment of patients with hemophilia, the factor VIII level rises by approximately 2% for each cryoprecipitate unit transfused in the average adult patient.

Factor VIII and Factor IX Concentrates Factor VIII concentrate for the treatment of classic hemophilia and factor IX concentrate for the treatment of hemophilia B are available. Although the factor VIII product contains only factor VIII, factor IX concentrate also contains factors II, VII, and X in high concentrations, in addition to containing 500 clotting units of factor IX. Factor IX concentrate has been associated with thrombosis and DIC in patients with liver disease, and this preparation is contraindicated in such patients.

Clotting Disorders

Massive Blood Transfusion

Several problems occur in patients who require massive transfusion, including the following:

1. Replacement with red cell preparations alone can cause *dilutional thrombocytopenia* and a "*washout*" *of protein clotting factors*. The net result is an increased risk of generalized microvascular bleeding (120). This has led to the recommendation that platelets, and occasionally fresh frozen plasma, be administered with every 6 to 12 units of red cell products in patients undergoing massive transfusions. However, a randomized, clinical trial of prophylactic platelet transfusions and fresh frozen plasma administration in this setting failed to show benefit from routine use of these supplements (121). **A prudent approach to massive transfusion would be to follow carefully the patient's platelet count and clotting parameters. If abnormalities are noted, appropriate supplements of clotting factors or platelets should be administered, provided DIC has been excluded.**
2. Several events take place during the storage of red blood cells: decreased oxygen affinity, increased osmotic fragility, decreased deformability, and decreased viability. Most important of these "storage lesions" is decreased oxygen affinity. In a patient who has had massive transfusions and whose blood essentially consists only of transfused blood, there is a theoretical problem with oxygen delivery by the transfused blood (122). **Although randomized, clinical trials are lacking, a prudent approach is to opt for the use of fresh blood or blood that has been stored for less than 1 week in patients undergoing transfusions of more than 10 units of red blood cells.**
3. **Widespread bleeding from mucous membranes, sites of blood drawing, or intravenous catheter sites is usually secondary to DIC or washout coagulopathy associated with massive transfusions.** Washout coagulopathy resolves when transfusion therapy is diminished; in the presence of bleeding, it can be treated with replacement of appropriate factors.

Disseminated Intravascular Coagulation

Disseminated intravascular coagulation is a syndrome that complicates the course of a variety of disease states and is characterized by the pathologic activation of the coagulation cascade and the fibrinolytic system. **In gynecologic oncology patients, it is usually seen in association with the following conditions:**

1. **Malignancy *per se*, especially mucin-producing adenocarcinomas**
2. **Sepsis**
3. **Acute vasculitis**
4. **Acute and chronic liver disease**
5. **Hemolytic transfusion reactions**

In its acute form, DIC appears rapidly in the critically ill patient and is manifested by bleeding from multiple sites, including venipunctures, surgical wounds, gingiva, gastrointestinal tract, and skin. Purpura and hemorrhagic bullae may occur (123). Thrombosis is uncommon. Mortality rates exceed 80%.

Direct demonstration of DIC requires demonstration of intravascular fibrin deposition. The laboratory diagnosis of DIC depends on indirect evidence of circulating thrombin and plasmin activity (124). Useful laboratory tests can be divided into screening and confirmatory tests (125). **Screening tests include:**

1. ***Platelet count*,** which is decreased in 90% of cases.
2. ***Prothrombin time*,** which is significantly prolonged in 90% of cases.
3. ***Fibrinogen*,** which is less than 150 mg in 70% of cases.

   If results of all three of the aforementioned tests are abnormal in the absence of severe liver disease, this triad is diagnostic of DIC. **If one or two screening tests are positive, confirmatory plasma tests are required. These include:**
4. ***Fibrin degradation products*,** which exceed 5 mg/mL in 95% of patients with DIC but are also positive in many postoperative patients. Plasma levels greater than 40 mg/mL are quite specific for DIC.
5. ***Protamine sulfate*,** which screens for the presence of circulating fibrin monomers and is very sensitive for diagnosing DIC, but somewhat nonspecific.
6. ***Factor VIII assay*,** which is decreased in DIC but not in liver disease.

The therapy of DIC is controversial. Because most patients with acute DIC die of their underlying disease, the primary treatment is aimed at controlling the underlying cause. **Treatment should include:**

1. **Empiric antibiotic therapy,** even in patients who are not febrile and in whom another cause of DIC can be found
2. **Treatment of other conditions adversely affecting coagulation,** such as vitamin K deficiency
3. **Replacement with appropriate hemostatic factors** in patients with active bleeding
4. **Consideration of some of the controversial options,** such as anticoagulation, factor replacement, *epsilon aminocaproic acid* with *heparin*, and antiplatelet drugs

The diagnosis of DIC is not *ipso facto* an indication that the disorder should be treated aggressively. Treatment decisions must be based on the individual clinical situation. *Heparin* is of clear benefit only in patients with thrombotic or thromboembolic complications.

Chronic Disseminated Intravascular Coagulation Chronic DIC follows a variable clinical course in a patient who is chronically ill over a period of months, with thrombotic complications much more common than bleeding complications. This problem is seen occasionally in gynecologic oncology patients because chronic DIC is frequently associated with adenocarcinomas (particularly those containing mucin), as well as in patients with cirrhosis or vascular abnormalities.

Symptoms are significantly relieved in 60% of the patients treated with *heparin* (126), but may recrudesce on discontinuation of the *heparin* therapy. *Warfarin* is not as effective as *heparin*. Hence, in patients with thrombotic complications from underlying adenocarcinomas, long-term *heparin* therapy is frequently necessary (127). This may include self-injection of *heparin* at home.

Thromboembolism

Detection: Deep Venous Thrombosis

Clinical signs of deep venous thrombosis are notoriously unreliable, and detection of thromboembolic disease once it occurs is an ongoing problem in acute care medicine. Most methods are more specific than sensitive, and gold standard testing is often difficult to perform. **Venous thrombosis of the lower extremity may present as a swollen, painful leg, although these clinical signs are very unreliable.** Lower extremity venous clot is now typically screened with compression ultrasonography of the femoral, popliteal, and calf vein trifurcation. This method is greater than 90% sensitive for proximal thrombosis, but much less sensitive for calf thrombosis. Clinicians should perform serial testing with this method or use contrast venography (gold standard test) if clinical suspicion remains high (128).

Detection of Pulmonary Embolus

Pulmonary embolism is often a life-threatening emergency. Presenting symptoms can include pleuritic chest pain, shortness of breath, cough with or without hemoptysis, and in the case of a very large embolus, syncope and hypotension. Patients are often tachycardic and hypoxic, the ECG may show evidence of right heart strain, and the chest radiograph may show an infarct with effusion. Unfortunately, the same constellation of symptoms and signs may be present in other conditions such as pneumonia and myocardial ischemia. **Most centers attempt to diagnose pulmonary embolism using ventilation–perfusion scanning. Unfortunately, a large study has shown this method lacks strong positive or negative predictive values in many clinical settings** (129). An entirely negative test is helpful in excluding a pulmonary embolus (risk of pulmonary embolism <1%), and a classic positive test obviates further testing, but unfortunately the test results are more typically intermediate. Combining results of the ventilation–perfusion scan with pretest clinical probability can improve its utility if clinical suspicion correlates with the scan results. Unfortunately, most testing is performed with an intermediate level of suspicion, and the results in hospitalized patients of ventilation–perfusion testing are often nondiagnostic. Studies suggest the use of a serum marker for coagulation chemistry, D-dimer concentration, might help rule out thromboembolic disease (130). Many postoperative patients, however, have ongoing coagulation activity and D-dimer serum positivity related to their surgery. Use of computed tomographic scanning of the chest may be helpful in diagnosing pulmonary embolism, although large, prospective, controlled trials of this method have not yet been performed (131). The reference standard for the diagnosis of pulmonary embolism remains direct angiography of the pulmonary arteries (132).

Treatment

Once documented, deep venous thrombosis or pulmonary embolism requires immediate treatment to decrease the risk of complications (pulmonary embolism or recurrent embolism). Patients who do not have an overriding contraindication to anticoagulation should be treated immediately with *heparin*, 5,000 units by intravenous bolus, followed by continuous *heparin* infusion of 10 to 15 U/kg/hour. The rate of *heparin* infusion customarily is adjusted to achieve an aPTT approximately two to three times that of the control value. It is important to wait at least 6 hours after the initial *heparin* bolus before obtaining the first aPTT because levels obtained earlier invariably are above the final steady-state level. Oral ***warfarin (Coumadin)* can be started when *heparin* has achieved a therapeutic level, often within 24 to 48 hours;** this is done to prevent the rare cases of *warfarin skin necrosis syndrome* at the initiation of *warfarin* therapy. The *coumadin* oral dosage is titrated to an international normalized ratio (INR) of 2.0 to 3.0. The optimal duration of oral anticoagulation for deep venous thrombosis remains controversial, but in general these medications are continued for at least 3 to 6 months. More recently, several trials have shown treatment with *low molecular weight heparin* is equal to, if not better than treatment with standard *heparin* (133).

Thrombolytic therapy should be considered in cases of pulmonary embolism with hypotension (134). If patients have active bleeding or a high risk of bleeding, or if they can not receive or are already receiving adequate anticoagulation, a filter should be inserted in the inferior vena cava to prevent recurrent pulmonary emboli.

Infection

In general, infections in patients with gynecologic malignancies should be managed as in all hospitalized patients, that is, with antibiotics chosen initially on the basis of possible infecting organisms and changed if necessary when the results of culture and sensitivity testing are known (135). Clinicians should be particularly alert to possible central venous catheter infections because many oncology patients require these devices for treatment. Central venous catheter infection rates range up to 5% depending on the type of catheter inserted (136).

Fever in the Neutropenic Patient

Of particular concern in oncologic treatment is fever in the neutropenic patient. When the absolute granulocyte count falls below 1,000/mm^3, the incidence of infection rises, and infected patients frequently decompensate rapidly. Hence, **it has become a maxim of oncologic care that febrile neutropenic patients should be treated immediately with broad-spectrum intravenous antibiotics, despite the absence of focal signs of infection or a positive culture result.** Frequently encountered pathogens in the neutropenic patient include *Staphylococcus aureus* and gram-negative enteric organisms such as *Escherichia coli, Klebsiella*, and *Pseudomonas*.

There are many acceptable combinations of antibiotics to achieve the goal of covering likely pathogens (typically a broad-spectrum semisynthetic *penicillin*, sometimes combined with an aminoglycoside) (137). There is evidence that in hospitalized, low-risk patients who have fever and neutropenia during cancer chemotherapy, empiric therapy with oral *ciprofloxacin* and *amoxicillin-clavulanate* is a safe and effective method of preventing infection (138). This approach is as effective as intravenous therapy, and is therefore the preferred approach to the management of these patients (139). Meticulous daily follow-up and adjustment of antibiotic coverage is more important than the precise initial combination chosen.

Use of growth factor rescue for febrile neutropenia has been studied, and several studies show the use of *granulocyte colony-stimulating factor (G-CSF)* shortens the duration of neutropenia (140,141,142,143 and 144). ***G-CSF*** is now commonly prescribed with chemotherapeutic regimens.

Fungemia

Fungemia is a life-threatening postoperative complication of surgery and severe medical illness. The typical patient at risk is receiving multiple antibiotics and hyperalimentation and has intravenous access lines and a Foley catheter (145,146). Additional important risk factors are cancer, chemotherapy, corticosteroids, and hyperglycemia. The clinical presentation of disseminated disease is identical to that of gram-negative sepsis. These patients may have signs of local fungal disease, such as oral thrush. The principal organisms found are *Candida* species, usually *Candida albicans*. The reported mortality rate is 40% to 50%. The treatment of choice for severe disseminated disease is *amphotericin B*. Clinical studies are underway to determine the role of *fluconazole* and other oral antifungal agents in the prophylaxis of patients at risk of fungemia. Patients with localized fungal infections should be aggressively treated with topical agents.

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18 Nutritional Therapy

David Heber

The diagnosis and management of the nutritional problems of the gynecologic oncology patient must not be overlooked in the presence of the more pressing medical and surgical concerns. Awareness of the methods for classification of malnutrition and appropriate treatment may improve the patient's ability to undergo definitive oncologic therapy, including surgery, radiation, or chemotherapy, and may improve the patient's quality of life.

Malnutrition

In hospitalized patients on general medical and surgical wards, the prevalence of malnutrition is 30% to 50% (1,2 and 3).

Risk Factors

Predisposing conditions frequently found in malnourished hospitalized patients include:

1. **Heart failure**
2. **Chronic obstructive pulmonary disease**
3. **Infection**
4. **Gastrointestinal (GI) disorders**
5. **Psychiatric disorders**
6. **Renal insufficiency**
7. **Malignancy**

It is typical for undernourished patients to have more than one predisposing condition (3).

These patients commonly have vitamin and mineral deficiencies, particularly of iron and vitamins A, D, E, and B_{12}. Decreased stores of these vitamins can be detected in early malnutrition. Because vitamins are stored in small amounts, the provision of only dextrose and water intravenously leads to their rapid depletion, abnormal enzyme function, and clinical signs of vitamin deficiency.

Normal Body Metabolism

Each day a variety of foods are ingested to provide the energy needed to maintain life. According to the *first law of thermodynamics*, the energy ingested must equal the energy expended or stored in the body at equilibrium. Although the quantity of energy intake and the amount expended and stored in any 24-hour period do not correspond exactly, body weight eventually reflects the balance between energy intake and energy expenditure.

Calorie

The unit of energy exchange is the calorie, which is the amount of heat required to raise the temperature of 1 mL of water 1°C at 1 atmosphere of pressure.

Dietary Calorie

The dietary calorie equals 1,000 calories. Thus, 1,500 dietary calories are equal to a 1,500-kilocalorie diet. This notation is used to examine body stores of energy and the quantity of food ingested.

Body Stores

Although the patient ingests a variety of foods, the body breaks them down into monosaccharides, amino acids, fatty acids, and glycerol. These are then redistributed to body stores or metabolized for energy.

The body stores of energy are very different from the composition of the diet (Fig.18.1). **The average diet has from 30% to 50% fat calories, 40% to 60% carbohydrate calories, and 15% to 20% protein calories.** The body contains only 1,200 carbohydrate calories as stored glycogen in muscle and liver, whereas it contains 130,000 to 160,000 calories as fat. The body also contains approximately 54,000 calories as protein in muscle and organs, but only 30% to 50% of this is available to be burned for energy. Protein is essential to life, and greater than 50% depletion of total body protein is incompatible with life (4).

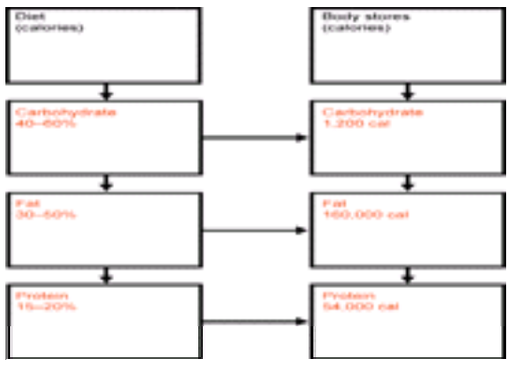

Figure 18.1 Body stores of energy versus dietary calories.

Metabolism During Starvation

During starvation, the body adapts to spare the vital protein stores. *The carbohydrate stores* of the body are depleted within 3 days of total starvation at rest or more rapidly if the body's energy requirements are elevated by the metabolic effects of certain illnesses. Many organs use glucose in large amounts, obligating the breakdown of 75 g/day of muscle early in starvation (5). If the muscle were to continue to be broken down at this rate, starvation would lead to death in 45 to 60 days. Over a period of 6 weeks, however, the body adapts from the carbohydrate economy of the fed state to the fat fuel economy of starvation (Fig. 18.2). In this adaptation, peripheral tissues and organs use *ketone bodies*, a breakdown product of fat, in place of glucose. Because the body contains fat equivalent to 160,000 calories, survival can now be extended to 140 to 160 days. Some muscle breakdown continues, limiting survival, because the brain and the red blood cells continue to require enough glucose to cause the breakdown of 20 g/day of muscle.

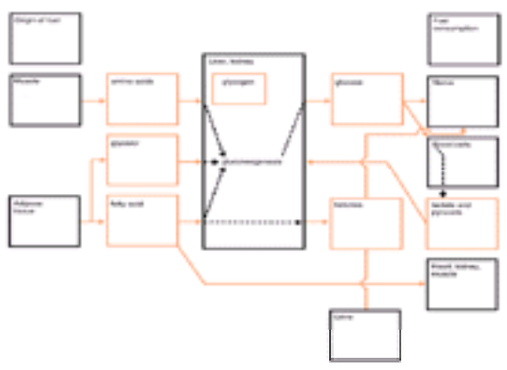

Figure 18.2 The metabolic adaptation to starvation. (Redrawn from Cahill GF, Owen OE. Some observations on carbohydrate metabolism in man. In: Dickens F, Randle PJ, Whelan WJ, eds. Carbohydrate metabolism and its disorders. New York: Academic Press, 1968:497, with permission.)

Clinical Features

Regardless of the metabolic features of malnutrition, weight loss is usually the presenting sign. To detect this sign, it is essential to know the patient's usual weight, as well as her ideal weight for height.

Ideal Body Weight

For the purposes of screening for malnutrition in gynecologic patients, a practical formula to use for determining the ideal body weight is the following:

Ideal weight = 100 lb for 5 ft + 5 lb/inch > 5 ft

For example, a woman whose height is 5 feet 4 inches would have an ideal body weight of 120 pounds. For many common cancers, loss of as little as 6% of usual body weight can have significant prognostic effects on survival (6). It is important to question patients about usual body weight, because some patients can be 70% of ideal body weight all their lives as a result of differences in frame size or habits such as chronic smoking, which affect body weight.

Weight Loss

Weight loss can result from loss of body fat, body protein, or body water. Each liter of body water lost represents a weight loss of 2.2 pounds, but this weight loss can be corrected rapidly with rehydration. The degree to which losses of body protein or body fat dominate the clinical picture is a reflection of the body's ability to adapt to a *fat fuel economy* in the face of inadequate nutrition (7). **There are three basic types of malnutrition: *kwashiorkor, marasmus, and a combination of the two, cachexia*** (Fig. 18.3).

Figure 18.3 Classification of malnutrition.

Kwashiorkor This form of malnutrition is variously termed protein calorie malnutrition, hypoalbuminemic malnutrition, protein energy malnutrition, or kwashiorkor-like malnutrition of the adult. If malnutrition is rapid and occurs in the face of disease factors that affect nutrition, a rapid depletion of protein stores can occur out of proportion to the loss of body weight. *Kwashiorkor* refers to a tropical pediatric disease and means *separation from the breast* in the African language, Swahili. Children are removed from their natural mother at 1 year of age and given to the care of an aunt or other adoptive mother. These children are then fed a diet consisting of cassava fruit, which is high in carbohydrates but contains no protein or fat, leading to a rapid depletion of body protein stores with hypoalbuminemia, edema, hypopigmentation, and an enlarged, fatty liver.

In hospitalized patients, the major signs of protein depletion are:

1. **Decrease in serum albumin** to less than 3.5 mg/dL
2. **Decrease in absolute lymphocyte count** to less than 1,500/mm^3
3. **Decrease in serum transferrin** to less than 150 mg/dL
4. **Loss of reactivity to common skin test antigens**

It is possible for this form of malnutrition to occur in the absence of weight loss if the hypoalbuminemia leads to ascites or edema.

Marasmus The other major form of malnutrition in adults is called marasmus or chronic inanition. Primary malnutrition resulting from anorexia or dietary inadequacy usually is seen with this form of malnutrition. It is characterized by a depletion of fat stores and the obvious appearance of malnutrition with visible loss of muscle and fat in the arms and legs. Although weight loss is often significant in these thin patients, protein stores can be remarkably preserved. It is not uncommon for the patient to have normal serum albumin and transferrin levels, a normal lymphocyte count, and normal skin test responses.

Cachexia When the two major forms of malnutrition occur together in patients with advanced malnutrition, the condition is called cachexia. In this advanced condition, there is depletion of body fat stores and body protein stores, which produces visible emaciation with loss of body muscle and fat as well as decreased circulating serum proteins. Cachexia is a life-threatening condition and has also been termed *combined marasmic-kwashiorkor* or mixed-form malnutrition of the adult.

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In tropical environments and other areas of endemic starvation, the most common cause of death is simple, uncomplicated pneumococcal pneumonia (7). Although the exact contribution of malnutrition to mortality in hospitalized gynecologic oncology patients is often difficult to quantify, immune impairment and an increased susceptibility to infections, poor wound healing, and cardiorespiratory impairment are all important negative effects of malnutrition on patient survival. These functions relate to the overall status of body proteins in vital organs, circulating cells, and serum.

Diagnosis

Serum levels of circulating proteins can be decreased and reflect impaired function of the liver and other organs, even in the absence of marked depletion of visceral and muscle protein (8). This usually occurs in the setting of excessive metabolic demands caused by specific illnesses that impair the body's ability to conserve protein.

Similarly, protein and fat stores can be depleted markedly while circulating proteins remain in the normal range. This occurs with anorexia and primary malnutrition in otherwise normal adults, in whom a gradual adaptation to starvation occurs.

Anthropometry, in which body stores are estimated by direct measurements, and *biochemical markers* that assess circulating proteins, must be used in concert to determine the specific type of malnutrition in any given patient (Table 18.1).

	Marasmus	Kwashiorkor	Cachexia
Albumin	Normal	↓	↓
Transferrin	Normal	↓	↓
White blood cell count	Normal	↓	↓
Skin tests	Normal	Negative	Negative
Body weight	↓	Normal	↓
Body fat	↓	Normal	↓

Table 18.1 Physical/Biochemical Markers of Malnutrition

Anthropometric techniques include the measurement of body weight and height in adults. The simple formula presented previously is used to calculate the percentage of ideal weight for height. From the history it is also possible to obtain the percentage of usual weight. The fat stores can be measured by assessing *skin-fold thickness.* The most commonly used skin fold in practice is the triceps. For this measurement, the patient sits with the right arm hanging freely at the side. For bedridden patients, the right arm is flexed at the shoulder while the forearm crosses the chest (9). The midpoint between the acromion and the olecranon posteriorly over the triceps muscle is marked. The skin and subcutaneous tissue at the midpoint are then pinched and pressure-regulated calipers (10) are applied for 3 seconds before a reading is taken. The calipers are designed to deliver a pressure of 10 g/mm^2 regardless of the fold thickness and can be used to compare the same patient's progress over time as well as to assess the severity of malnutrition.

Protein Store Assessment

Protein stores can be assessed by assaying a number of circulating proteins, most of which are secreted by the liver (11,12). Their synthesis and secretion are inhibited rapidly in the presence of protein malnutrition, and they decrease to a variable extent in the circulation according to their metabolic half-lives. The most widely used markers are albumin and transferrin. Each of these proteins has advantages and disadvantages (11).

Albumin Albumin has a long half-life, and significant decreases may not occur for up to 1 month after the onset of starvation. Albumin may be decreased by rapid loss of serum proteins (e.g., excessive losses from the GI tract). Restoration of the serum albumin to normal levels by nutritional means is slow and often lags behind clear improvement in nutritional status by other criteria.

Transferrin Transferrin is synthesized in the liver and other sites, where it can act as a growth-promoting peptide. In the liver, synthesis is modulated by the iron stores in the hepatocytes as well as by the overall protein status. The half-life of the protein is only 8 to 10 days, and the body pool is only 5 g. The synthetic rate is the major factor determining serum levels, and serum transferrin increases within 10 to 14 days of nutritional repletion. The problems with the interpretation of transferrin levels are that degradation rates increase during illness, and iron deficiency falsely elevates the levels.

For these reasons, both transferrin and albumin must be taken into consideration, together with the anthropometric determinations of body weight and triceps skin-fold thickness.

Retinol- and Thyroxine-Binding Proteins Retinol-binding protein and thyroxine-binding prealbumin also are synthesized in the liver, with half-lives of 10 hours and 2 days, respectively. At present, these markers are not widely used clinically. Their levels drop acutely with metabolic stress, and retinol-binding protein is also filtered and broken down by the kidney. These factors complicate the interpretation of serum levels for diagnosis of malnutrition, but they can be used in a research setting to assess response to nutrition.

The serum half-lives of these circulating proteins are listed in Table 18.2.

Protein	Half-life
Albumin	3-4 wk
Transferrin	1 wk
Thyroxine-binding prealbumin	2 days
Retinol-binding protein	10 hr

Table 18.2 Serum Half-Life of Circulating Proteins Decreased in Malnutrition

Immune Function

The absolute lymphocyte count and delayed cutaneous hypersensitivity responses to skin test antigens are nonspecific markers of impaired immune function in malnourished patients (13) (Fig. 18.4). In areas of endemic starvation, malnourished patients are at increased risk of opportunistic infections in the hospital and ambulatory settings because of the following:

Figure 18.4 Immunologic alterations associated with malnutrition.

1. Depressed levels of complement components, including C3
2. Reduced amounts of secretory immunoglobulin A in external body secretions
3. Abnormal T-cell function
4. Impairment of nonspecific defenses, including decreased epithelial integrity, decreased mucus production, and decreased ciliary motility

The precise nutritional deficiency that leads to decreased immune function remains unknown.

Most patients with protein and caloric malnutrition have multiple deficiencies, and almost any single nutritional deficiency, if severe enough, can affect immune function (14). Correction of malnutrition improves immune function; this is especially true in the gynecologic oncology patient, whose immune function can be impaired by therapy as well as by the tumor itself.

Absolute Lymphocyte Count The absolute lymphocyte count is calculated by multiplying the percentage of lymphocytes by the total white blood cell count. The absolute lymphocyte count and skin tests are the most widely used immune markers of nutritional status. The normal lymphocyte count is greater than 2,000/ mm^3 in patients who are not receiving chemotherapy.

Most circulating lymphocytes are T cells, and involution of the tissues producing T cells occurs early in the course of malnutrition. The delayed hypersensitivity skin test response reflects three processes:

1. Processing of the antigen by macrophages resulting in the generation of both effector and memory T cells
2. Recognition of antigen rechallenge resulting in blast transformation, cellular proliferation, and generation of lymphokine-producing effector cells
3. Production of a local wheal and flare secondary to the actions of lymphokines and chemotactic factors at the skin site

Antigens that are frequently tested include purified protein derivative, streptokinase-streptodornase, mumps, *Candida, Trichophyton*, and coccidioidin. The prevalence of nonreactivity to skin test antigens is approximately 50% in patients whose serum albumin level is less than 3.0 g/dL, but it can be as high as 30% in patients whose serum albumin level exceeds 3.0 g/dL. Other problems with interpretation of skin tests include:

1. Only approximately 60% of healthy patients respond to most of the antigens, so that failure to respond to one or two antigens may not be predictive.
2. Primary illnesses, including sarcoidosis and lymphoma, as well as immunosuppressive drugs, produce anergy.

The assessment of malnutrition by means of clinical examination in combination with routinely available laboratory tests provides an accurate estimation in more than 70% of patients (15). Difficulties with each of these tests have kept the nutritional assessment from becoming part of the routine database for every hospitalized patient.

Impact of Disease

Many systemic illnesses, including cancer, predispose patients to malnutrition (Fig. 18.5). Although abnormalities of metabolism, digestion, absorption, and utilization of nutrients all contribute to malnutrition in such patients, decreased nutrient intake is still a universal finding in most malnourished patients, with the exception of those with uncomplicated hyperthyroidism.

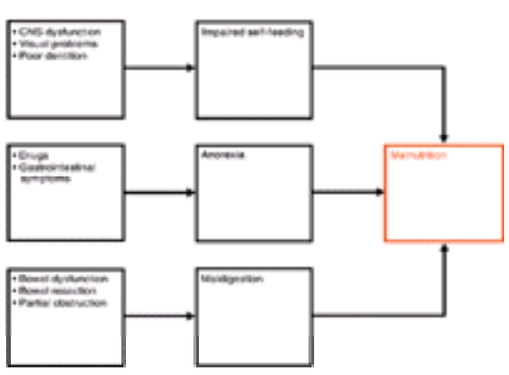

Figure 18.5 Impact of disease factors on nutrition.

Anorexia

Decreased appetite, or anorexia, is the major factor contributing to decreased intake in many disease processes. Although anorexia can be a feature of such diseases as cancer, it can also be a side effect of many drugs. These include antineoplastic drugs, which are most pertinent for the gynecologic oncology patient. A number of commonly used drugs (e.g., anticholinergics, antihistamines, *methyldopa*, sympathomimetics, *clonidine*, and tricyclic antidepressants) may cause a dry mouth. The latter can decrease sensation and food palatability. Another common type of anorexia is a learned aversion to food when it is known to cause adverse physical symptoms. GI diseases, including reflux esophagitis, gastritis, and peptic ulcer, frequently cause dyspepsia. Irritable bowel syndrome, food allergies, lactose intolerance, diverticula, and biliary disease can cause diarrhea or flatulence. All of these GI problems can cause patients to avoid foods altogether or to ingest an unbalanced diet. Improvements in the pharmacotherapy of nausea have lessened the anorexia associated with chemotherapy, and ***megestrol acetate*** **is available as an approved treatment for anorexia. This progestational steroid increases appetite through both central nervous system and peripheral mechanisms, analogous to the increased appetite that women note during the luteal phase of the menstrual cycle.**

Intestinal Dysfunction

Mechanical malfunction of the bowel is a particularly common problem among patients who have undergone abdominal radiation or extensive abdominal surgery. Postoperative or postirradiation adhesions can lead to partial or complete bowel obstruction. In patients with disseminated intraabdominal malignancy such as ovarian cancer, an *adynamic ileus or intestinal pseudoobstruction* can result in a nonfunctional GI tract. Impaired capacity for self-feeding can also markedly decrease food intake.

Metabolic Disturbances

Cancer specifically affects nutrient metabolism. Patients with metastatic and localized cancer have increased rates of whole-body glucose metabolism, whole-body protein breakdown, and insulin resistance (16,17). Improved nutrition often fails to correct such abnormalities, once severe malnutrition is present, despite continuous parenteral or enteral alimentation with adequate nutrients (17,18 and 19). Specific metabolic disturbances and their consequences are presented in Table 18.3.

Host Metabolic Abnormality	Consequence
Increased glucose production	Rapid weight loss, muscle breakdown
Increased lipid mobilization	Hypertriglyceridemia, rapid wasting
Insulin resistance	Hyperglycemia, hypertriglyceridemia
Hypoglycemia secondary to tumor humoral factors	Syncope, fatigue
Diarrheal syndromes due to tumor humoral factors	Electrolyte disturbances

Table 18.3 Metabolic Consequences of Cancer

Nutritional Support

Nutritional support is an adjunct to primary therapy for the gynecologic oncology patient. The aim is to prevent deterioration of nutritional status during planned primary therapy, such as radiation, surgery, and chemotherapy. Early initiation of nutritional support before any deterioration of nutritional status is desirable. This goal necessitates early evaluation, the proper choice of nutritional therapeutic modalities, and an accurate assessment of requirements.

Once a protein deficiency occurs, it is difficult to reverse, inasmuch as less than 5% of the protein is replaced per day, regardless of the amount of substrate provided. Vitamins and minerals are replaced more easily, but there is no substitute for adequate planning to meet caloric and protein requirements essential for nutritional maintenance of vital functions.

Caloric Requirements

The protein and caloric requirements can be estimated at 1 g/kg/day and 35 kcal/kg/day for healthy adults, respectively. If malnutrition exists or if the patient's metabolism is elevated by infection or other metabolic stresses, then 1.5 g/kg/day of protein and 45 kcal/kg/day should be supplied. More exact formulas are available for pediatric patients and patients at the extremes of height and weight.

Need for Support

There are two key aspects of the patient's nutritional status that affect decisions about nutritional support:

1. The degree of prior malnutrition at the time of assessment
2. The degree of hypermetabolism or metabolic abnormality expected to interfere with nutritional rehabilitation

If the degree of prior malnutrition is minimal and the patient has only mild hypermetabolism after elective surgery, a temporary form of nutritional support can be used. On the other hand, if the patient is going to require excess calories to restore preexisting severe malnutrition, forced intake of calories by an enteral or parenteral route must be used. The following guidelines can be used:

1. If a patient is to be without nutrition for a **period** of 7 days, some form of nutritional support should be used.
2. If nutritional support is to be continued for more than 2 weeks, a permanent entry port for enteral or parenteral nutritional support should be used and arrangements made for home enteral or parenteral nutrition.

Method of Support

The choice between *parenteral* and *enteral* therapy should be made on the basis of the availability and functional status of the GI tract (Fig. 18.6). **If the GI tract is functioning normally, the expense and complications of parenteral nutrition argue against its use.**

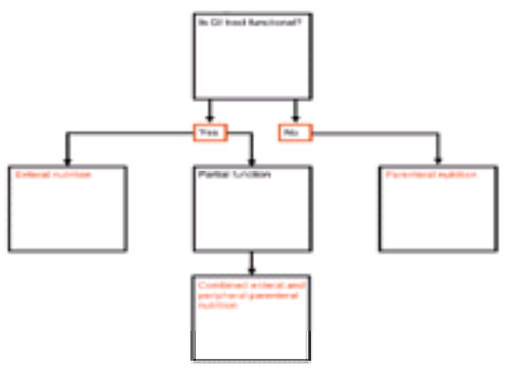

Figure 18.6 Parenteral versus enteral nutrition.

Enteral

If the GI tract is atrophied from prior malnutrition, a period of rehabilitation with special formula diets can be used to renourish the patient gradually so that routine formula diets can be used (20). The epithelium of the GI tract is directly nourished by the infused nutrients in the formula diet bathing these cells, and ultimately a complete formula diet can be used. **If the patient is already severely malnourished and hypermetabolic, careful consideration should be given to initiation of concurrent parenteral nutrition to provide calories and protein during the period of nutritional rehabilitation of the GI tract.**

When fewer calories than those required for total support are provided by the parenteral route, a peripheral vein can be used. The 10% glucose solution irritates the peripheral veins by causing a chemical phlebitis. This may limit the use of any single peripheral vein to a period of approximately 10 days. A large central vein is required for the 20% to 25% glucose solution plus added amino acids required for total parenteral nutrition (TPN). In patients receiving chemotherapy, peripheral veins are often sclerosed, and a central venous route for nutrition and medications must be used.

In view of the difficulties inherent in the use of parenteral nutritional support, every effort should be made to use the enteral route whenever possible. A *gastrostomy tube* or a *jejunostomy tube* can be easily placed early in the course of management without interfering with the patient's lifestyle. **The gastrostomy port can be used at night for enteral support therapy by continuous infusion of isotonic enteral supplements at a rate no greater than 100 kcal/hour.** The next day, the patient can cover the port with a dressing and go through her usual daily activities. This approach is often more acceptable to patients than a nasogastric tube, which is visible and irritating. In some patients, the gastrostomy port has the added advantage that the stomach can be used as a reservoir for bolus feeding, which is more convenient. In cases of abnormal gastric motility, esophageal reflux, or possible aspiration of gastric contents, continuous slow infusion of supplement should be used, or a tube should be passed beyond the pylorus into the jejunum.

Diarrhea is often a complication of enteral feeding and can be dealt with in the following ways:

1. **The rate of infusion can be decreased.** If the GI tract dysfunction is due to atrophy of the epithelial cells, a gradual increase in infusion rate is often tolerated, starting with an initial rate of 25 mL/hour and increasing by twofold increments every 48 hours.
2. **The type of enteral formula can be changed to an isosmolar formula.** Many of the high-calorie or high-nitrogen supplements are also hyperosmolar. Changing to an isotonic formula often decreases intestinal hypermotility.
3. **A number of specific medications can be used to decrease intestinal motility.** In the presence of partial obstruction, such medications must be used with caution.
4. **The level of enteral support can be decreased and temporarily combined with peripheral parenteral alimentation** until intestinal motility problems respond to the maneuvers discussed previously.

Parenteral

***Total parenteral nutrition* is the provision of all calories in an intravenous solution of dextrose, amino acids, and emulsified lipids. This form of therapy, although appearing more invasive and definitive, confers no special advantage to the malnourished patient with a functional GI tract.** In some patients receiving chemotherapy or radiation therapy, mucosal inflammation, nausea, and vomiting impair normal intake. In such patients, TPN may be needed as an adjunct to restore functional status and allow continuation of therapy. Patients with GI fistulas often require avoidance of enteral feeding.

Total parenteral nutrition is usually administered through a central venous catheter surgically placed in the subclavian vein, although there are other vessels that can be used when needed, as described in Chapter 19. The patient must be given special training in aseptic handling of the catheter site and use of the infusion equipment required. Many medical centers have special home parenteral nutritional support teams, whereas in other areas private firms provide this service. Potential medical problems for these patients depend to a great extent on the experience of the team providing home parenteral support. It is not uncommon for patients to require hospitalization for blood cultures and other studies to investigate a fever.

Combined Enteral–Parenteral Feeding

Sometimes combined parenteral and enteral nutritional therapy can be used to advantage. For example, parenteral nutrition can be used in postsurgical patients when the GI tract is functional but the total caloric requirement cannot be met by the enteral route.

Evaluation of Response to Nutritional Support

Because the goal of nutritional support is the attainment of an anabolic state or reduction of nitrogen losses, assessment of nitrogen balance is the most useful clinical tool to determine the effectiveness of therapy. **Nitrogen balance is defined as the difference between nitrogen intake and nitrogen excretion.**

One gram of nitrogen is equivalent to 6.25 g of protein. Hence, nitrogen intake can be determined by dividing protein intake, as determined from dietary records, by 6.25. Nitrogen excretion is defined as the urinary nitrogen excreted per 24 hours plus a fixed estimate of 4.0 g/24 hours for unmeasured nitrogen losses from cellular sloughing into the feces (1 g), losses from the skin (0.2 g), and nonurea nitrogen losses in the urine (2 g) (21). Because nitrogen balance is most usefully applied in a serial fashion in the same patient, the particular constants used to estimate unmeasured excretion are important only for comparison of published results.

At any given level of nitrogen intake, nitrogen balance improves with increased administration of nonprotein calories. The maximum benefit is achieved when the ratio of nonprotein calories to grams of nitrogen is 150:1 (22).

Proteins vary in their biologic value according to their mixture of essential and nonessential amino acids. Albumin has the ideal mixture of amino acids for optimal use of protein and is assigned a biologic value of 100. Casein is close to albumin in its biologic quality, whereas meat proteins, such as those found in steak or tuna, have a biologic value of 80. Corns and beans, each with biologic values of 40 or less, can be combined in a protein mixture with a biologic value of 80, because the amino acid mixtures of the two proteins are complementary. **The protein requirement for normal people is 0.55 g/kg for protein with a high biologic value, such as milk or albumin, but 0.8 g/kg for the mixture of proteins found in the average American diet** (23).

Effect of Nutritional Support on Prognosis Although it is easy to demonstrate the impact of renutrition on a patient with uncomplicated starvation or an inability to absorb calories because of a loss of intestinal tissue, it is much more difficult to demonstrate the beneficial effect of nutritional support in a patient with a chronic illness such as cancer (24). Often the course of the underlying illness masks the beneficial effects of nutritional therapy.

In patients with mild disease or elective surgery, malnutrition is relatively well tolerated from a clinical standpoint. In such cases, nutritional rehabilitation usually occurs without any special effort as the underlying medical or surgical condition runs its course. In patients with severe disease, nutrition is often relegated to the secondary list of problems as the progress of the primary illness dictates therapeutic decisions. In both of these instances, however, nutritional therapy may play a beneficial role in either preventing or retarding malnutrition in individual patients (25). On the other hand, an extensive meta-analysis of 53 published studies of parenteral and enteral nutrition showed that survival was improved in 6 studies, unchanged in 43, and worse in 2 (26). The judicious application of nutritional support for gynecologic oncology patients may lead to the prevention of progressive malnutrition as well as an improvement in the quality of life and prognosis.

Complications Complications can occur after either enteral or parenteral nutrition. Complications of enteral nutrition are either mechanical or metabolic, whereas complications of parenteral nutrition can be mechanical, infectious, or metabolic (27).

Mechanical problems **of enteral feeding include aspiration, especially in semiconscious patients or patients with abnormalities of swallowing.** This problem can be minimized by proper placement of the feeding tube and by determination of the volume of the residual gastric contents 8 hours after feeding to eliminate the possibility of gastric outlet obstruction or gastric atony. If these latter problems occur, the feeding tube can be placed into the jejunum. Proper placement should be ensured radiologically. Irritation of the oropharynx and the gastric mucosa can occur, especially with the use of larger-bore and less flexible feeding tubes. This problem can be minimized with the use of inert silicone rubber and polyurethane tubes.

Diarrhea **is the most common complication associated with tube feeding** (28). Carefully increasing the rate of administration helps avoid this problem. Prolonged starvation can lead to GI epithelial atrophy and maldigestion, which in turn can result in diarrhea. Diarrhea also can be due to the effects of other medications, colonic infections (e.g., *Clostridium difficile*), or overly rapid administration of hypertonic enteral formulations. Most enteral formulations are free of lactose, so that lactose intolerance is not likely to cause diarrhea.

Dehydration with hypernatremia can be a problem in the elderly, in whom inadequate fluid intake can occur during the administration of a hypertonic enteral formula. When high-carbohydrate enteral formulas are used, *glucosuria* can occur in some patients without a prior history of diabetes.

The complications of parenteral nutrition are often more serious than those associated with enteral nutrition (29). *Pneumothorax* and *subclavian venous thrombosis* are the most common catheter-related complications. Pneumothorax should occur in only 1% to 2% of catheter insertions, but this rate is higher when transthoracic puncture is used rather than open surgical placement, or when less experienced people insert the catheter (30). A chest radiograph to confirm proper catheter placement and to exclude a pneumothorax is essential. A pneumothorax usually resolves spontaneously, but a chest tube may be required in some cases. Thrombosis of the catheter in the central veins has been reported in 5% to 10% of patients receiving parenteral nutrition, especially with the hypercoagulable states of sepsis or cancer (31). In such patients, the catheter should be flushed with *heparin* solution (300 U/mL) to prevent this complication. **When thrombosis occurs, the catheter must be removed.** Peripheral venous nutrition must be used while a full course of *heparin* is given to treat the thrombosis. **Infections most commonly occur from skin contaminants, such as gram-positive organisms, but can include fungi and unusual bacteria,** especially if acquired during hospitalization. Infected catheters must be removed before the systemic treatment of catheter-related sepsis. In patients committed to lifelong parenteral nutrition, this decision must be made carefully because only eight external sites are available for central venous catheter placement.

Infections occur in 2% to 5% of central catheters placed for parenteral nutrition. When the patient is febrile and a peripheral source of infection is not found within 96 hours, the catheter should be removed and cultured for evidence of catheter-related infection. Infected catheters can be a source of life-threatening phlebitis. Blood-borne infections from sources other than the catheter can be treated with intravenous antibiotics without removal of the catheter, but the patient should be observed carefully because the catheter is a foreign body in the vascular system and can be seeded with bacteria.

In patients treated with broad-spectrum antibiotics, ***systemic candidiasis*** **can occur.** The eyegrounds should be examined for the presence of cotton-wool exudates that are pathognomonic of systemic candidiasis, and blood cultures should be sent for special fungal isolation procedures. If present, these infections require treatment with *amphotericin*, which has significant systemic side effects.

A variety of metabolic complications can occur during parenteral nutrition. The most common is overfeeding, which results in excess CO_2 production that can add to respiratory problems in patients with pulmonary disease (32). ***Hyperglycemia*** **can occur in some as a result of transient insulin resistance or relative insulin deficiency.** Both subcutaneous insulin and insulin added to the parenteral solutions can be used to treat this complication (33). ***Metabolic acidosis*****, which occurred** commonly when potassium and sodium were administered only as chloride salts, is less frequently a problem because acetate buffers have been used in parenteral solutions. ***Abnormalities of phosphate, potassium, calcium, and magnesium*** **can occur because of excessive or inadequate administration,** particularly in the presence of underlying disorders, such as renal failure or GI fistulas, which themselves predispose to electrolyte abnormalities (34,35). ***Deficiencies of trace minerals*** **such as zinc, copper, and chromium rarely occur** because these are now added routinely to parenteral solutions (36). ***Azotemia*** **can occur** in patients with renal failure or when there is excessive administration of amino acids relative to nonprotein calories, and this is simply treated by reduction of the amino acid load (37). ***Essential fatty acid deficiency*** **rarely occurs** because the use of intravenous lipid emulsions has become so common (38). In most cases, the metabolic complications associated with parenteral nutrition respond to careful fluid and electrolyte management with daily monitoring of input and output.

Multiple Organ Failure Syndrome Multiple organ failure syndrome can develop in the critically ill patient secondary to a decline in cellular oxygen consumption, leakage of intracellular enzymes, and cell death (39). A cascade of events leads to these terminal events, including at different times hypoperfusion/ hypoxia, immunodysfunction, endocrine dysfunction, acute starvation, and metabolic derangement. Early organ failure usually appears from 5 to 7 days after the initial insult but can occur as late as 21 days later.

The nutritional therapy provided to such patients has been called metabolic *support* to differentiate it from the nutritional support given to more stable patients with chronic anorexia and starvation. In nutritional support, the goals are simply to provide adequate calories and nutrients to restore nutritional deficiencies and to maintain protein synthesis, positive nitrogen balance, and lean body mass (40). **Metabolic support of the critically ill patient at risk of multiple organ failure syndrome is directed at partial caloric replacement, sustenance of important cellular**

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A breakdown in the physical and immunologic barriers of the GI tract can promote multiple organ failure syndrome. The GI tract is particularly susceptible to ischemic and reperfusion injury. Glutamine, a preferred fuel for the gut epithelium, may promote healing of the GI tract epithelium after an injury (42). In animal studies, an enteral formula containing glutamine has been shown to maintain muscle glutamine metabolism without stimulating tumor growth while also improving GI mucosal integrity and nitrogen balance (43,44). Research is under way on utilization of the physiologic properties of specific nutrients to prevent multiple organ failure syndrome. However, **the critical therapeutic difference between the multiple organ failure syndrome and chronic malnutrition is the need to avoid overfeeding by providing a hypocaloric protein-sparing nutritional regimen in the former.**

Calculation of Requirements

There are many methods of estimating basal energy requirements. The following are guidelines:

1. Obese patients maintain their body weight when given only 25 kcal/kg actual body weight per day.
2. Lean patients maintain their weight when given 35 kcal/kg/day.
3. In patients with malnutrition, there is a cost of anabolism that involves the calories necessary for new protein synthesis. For patients with very severe illnesses and in whom malnutrition may be combined with sepsis or trauma to elevate energy requirements, 45 kcal/kg/day may be required.

There are many other formulas for estimating energy requirements that take the patient's height into consideration. Taller patients have a higher resting energy expenditure at the same weight than shorter patients, because they have larger livers and other vital organs. In older people, metabolic rates tend to fall, in part because of a decrease in lean body mass. Although such equations are useful for clinical nutritional research, they are generally unnecessary for clinical management. A more practical set of guidelines is given in the following sections.

Estimation of Total Caloric Requirement

Severity of Illness	Daily Caloric Requirement
Mild	35 kcal/kg
Moderate	40 kcal/kg
Severe	45 kcal/kg

Estimation of Protein Requirement **Once the caloric requirement has been estimated, the protein requirement can be estimated at approximately 1.0 g/kg of usual or ideal body weight.**

Estimation of Nonprotein Calories **The nonprotein caloric requirement may be estimated by initially estimating the amount of nitrogen administered according to the following formula: 1 g nitrogen = 6.25 g protein. By** either the parenteral or the enteral route, 150 nonprotein calories must be provided for each gram of nitrogen administered. Therefore, estimation of nonprotein calories can be achieved as follows:

Nonprotein calories = [Protein requirement × 150] / 6.25

An alternative is simply to subtract the protein calories from the total number of calories.

Determination of Carbohydrate Requirement **It is usual to give approximately half the total calories as carbohydrates.** Most nutritional solutions are already premixed, and the precise formulas available vary in different hospitals.

Determination of Fat Requirement **The absolute fat requirement for essential fatty acids (i.e., linoleic acid and linolenic acid) is only 4% of the total calories.** However, the amount of fat usually administered either enterally or parenterally exceeds this amount. Indeed, the remainder of the calories necessary to fulfill the minimum total caloric requirement after the protein and carbohydrate calories have been calculated can be given as fat. In all cases, the number of calories given as fat is far less than 60% of the total calories, which is the maximum fat that should be given.

Sample Calculations

Sample calculations for both enteral and parenteral formulations are presented.

Enteral

A 50-year-old woman who weighs 45 kg has a usual body weight of 70 kg and is severely ill with sepsis and postsurgical stress. Her GI tract is functional, and enteral formulation must be prescribed. The following steps allow calculation of the specific requirements:

1. The total daily caloric requirement is estimated by multiplying the caloric requirement based on severity (in this case, 45 kcal/kg/day) by the patient's weight (i.e., 45 kg). Therefore, the caloric requirement is 45 kcal/kg × 45 kg 2,025 kcal.
2. The minimum protein requirement is determined by multiplying the ideal body weight by 1.0 g/kg (e.g., in this case 70 kg), and 1.0 g/kg = 70 kcal/g. because protein = 4 kcal/g, the protein caloric need is 280 kcal.
3. The estimation of nonprotein calories is determined by multiplying the protein requirement (70 g) by 150, and this figure is divided by 6.25. Therefore, the minimum nonprotein calories required = [**70 g × 150]/ 6.25 = 1,680 kcal.**
4. The determination of specific carbohydrate and fat needs is empiric; that is, if approximately one-half the total caloric need is given in carbohydrates (in this case, 1,010 kcal), the remainder of the calories may be given as fat. Therefore, fat calories = 2,025 - (1,010 + 280) = 735 kcal.
5. An enteral formula that approximates these caloric requirements should be used. A standard formula containing 1.0 kcal/mL, 15% protein, 34% fat, and 51% carbohydrate, would provide approximately 150 kcal of protein, 340 kcal of fat, and 510 kcal of carbohydrate for every liter of formula given to the patient. Therefore, this patient's caloric requirements would be met by giving her approximately 2 L of formula per day.

Parenteral

A 45 kg, 70-year-old woman has lost 15 kg as a result of postirradiation changes to the bowel. In view of her poor GI function, parenteral alimentation is appropriate. The estimation of her nutritional requirements is as follows:

1. The total daily caloric requirement is estimated by multiplying the caloric requirement based on severity by the patient's weight (i.e., 45 kcal/kg × 45 kg = 2,025 kcal).
2. The minimum protein requirement is determined by multiplying the usual body weight (60 kg) by 1.0 g/kg = 60 g. At 4 kcal/g, the protein caloric need is 240 kcal.
3. The nonprotein caloric requirement thus equals approximately 1,785 kcal, which should include approximately 775 kcal fat and 1,010 kcal carbohydrate.
4. A standard TPN formula containing 20% dextrose and 3.5% protein (e.g., Travasol), would provide 680 kcal of dextrose per liter and 35 g (140 kcal) of protein per liter. Therefore, 1.7 L of this formula would approximate the carbohydrate and protein needs of the patient. The parenteral solution is administered at a rate of 75 mL/hour.
5. A single unit of 10% intravenous fat emulsion provides 550 kcal/unit. Therefore, the usual amount of fat given would be provided by 1.4 units (or 700 mL). Because fat emulsions are available in single units, it is preferable to give this patient 2 units of fat emulsion per day.

In this typical example, the intravenous fat emulsion provides needed additional calories, allowing for the more complete utilization of the administered protein. An additional reason to provide fat emulsions parenterally is the need to provide essential fatty acids at a minimum level of 4% of total calories. For example, 4% × 80 kcal/day. This requirement can be met by one 550 kcal unit of intravenous fat emulsion per week. **In the absence of any fat administration, essential fatty acid deficiency develops in 4 to 6 weeks in most people, once endogenous stores of essential fatty acids are depleted**. Because the cost of lipid emulsions has decreased considerably, fat is being used as a parenteral caloric source in amounts exceeding those needed to meet the minimal essential fatty acid requirements, as outlined in the previous example.

Standard electrolytes per liter of solution are listed by most pharmacies, and they are designed together with acetate buffers to deliver a nonacid solution with a pH of between 5.3 and 6.8. In special fluid and electrolyte situations, the composition of the solution can be custom designed, but this significantly increases the cost of parenteral nutrition. The use of standard fluid and electrolyte solutions with supplements as necessary is preferable. Typical parenteral nutrition solutions are shown in Table 18.4.

Solution	Na^+ (mEq/L)	K^+ (mEq/L)	Mg^{2+} (mEq/L)	Acetate (mEq/L)	Cl^- (mEq/L)	Protein (g/L)	Calories/L (D 20%*)
FreAmine III 3%	35	24.5	5	44	40	29	800
Aminosyn 4.25%	70	66	10	142	98	85	850
Travasol 4.25%	70	60	10	105	70	89	850
Travasol 3.5%	35	15	5	54	35	37	800

*% admixed with the solution in 20% dextrose.

Table 18.4 Typical Parenteral Nutrition Solutions

Osmolarity and caloric content of the parenteral solution are related to the glucose concentration. For lipid preparations, the osmolarity and caloric content are also related to the percentage of lipid in the solution (Table 18.5).

Glucose Concentration (wt/vol)	Osmolarity (mOsmol/L)	Calories (kcal/dL)
5%	250	17
10%	500	34
20%	1,000	68
50%	2,500	170
70%	3,500	237
Lipid Concentration (wt/vol)		
10%	280	110
20%	340	200

Table 18.5 Osmolarity and Caloric Content of Glucose and Lipids in Parenteral Nutritional Solutions

Recommended vitamins that should be provided on a daily basis in parenteral solutions are listed in Table 18.6. These substances are available in preformulated ampules, and one ampule per day added directly to the parenteral solution meets all the requirements in most patients. In patients who are especially stressed (e.g., septic), 500 mg of vitamin C should be given. Patients receiving common medications such as *phenytoin (Dilantin)* may require additional specific vitamin supplements (e.g., vitamin D).

Vitamin	Daily Intravenous Dose
A	3,300 IU
D	200 IU
E	10 IU
B_1 (thiamin)	3.0 mg
B_2 (riboflavin)	3.6 mg
B_3 (pantothenic acid)	15.0 mg
B_5 (niacin)	40.0 mg
B_6 (pyridoxine)	4.0 mg
B_7 (biotin)	60.0 mg
B_9 (folic acid)	400.0 mg

patients who are especially stressed (e.g., septic), 500 mg of vitamin C should be given. Patients receiving common medications such as *phenytoin (Dilantin)* may require additional specific vitamin supplements (e.g., vitamin D).

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B_5 (pantothenic acid)	15.0 mg
B_3 (niacin)	40.0 mg
B_6 (pyridoxine)	4.0 mg
B_7 (biotin)	60.0 mg
B_9 (folic acid)	400.0 mg
B_{12} (cobalamin)	5.0 mg
C (ascorbic acid)	100.0 mg
K	5.0 mg/wk*

*Parenteral vitamin K supplementation is not included in the official recommendation because some patients are receiving anticoagulants.
From American Medical Association/Nutrition Advisory Group Guidelines. JPEN J Parenter Enteral Nutr 1979;3:258, with permission.

Table 18.6 Guidelines for Daily Adult Parenteral Vitamin Supplementation

Major mineral requirements are listed in Table 18.7. The daily requirement has a wide range that depends largely on the extent of GI and renal losses. In patients with abnormally high excretion, the losses must be replaced aggressively.

Electrolyte	Daily Requirement Range
Sodium	50–250 mEq
Potassium	30–200 mEq
Chloride	50–250 mEq
Magnesium	10–30 mEq
Calcium	10–20 mEq
Phosphorus	10–40 mmole

Modified from Alpers DH, Clouse RE, Stenson WF. Manual of nutritional therapeutics. Boston: Little, Brown, 1983:238.

Table 18.7 Range of Daily Requirements of Major Minerals and Electrolytes in Parenteral Solutions

Supplementation with zinc, copper, chromium, and selenium is essential in parenteral nutrition (Table 18.8). *Deficiency states* of these trace elements have been described in patients who have been receiving parenteral nutrition without supplementation. These patients respond to the specific replacement of deficient trace elements.

Trace Element	Requirement	Deficiency Syndrome
Iron	10–18 mg/day	Anemia
Copper*	30 μg/kg/day	Rare hemolysis
Zinc*	15 mg/day	Blepharitis, conjunctivitis, growth retardation, dermatitis, diarrhea
Selenium*	60–200 μg/day	Cardiomyopathy
Chromium*	20 μg/day	Glucose intolerance, hypercholesterolemia, hyperaminoacidemia
Manganese	3–5 mg/day	Dermatitis, hypocholesterolemia, hair color change, decreased hair and nail growth
Iodine	100 μg/day	Hypothyroidism
Fluoride	1.5–4.0 mg/day	Anemia, growth retardation
Molybdenum*	200–500 μg/day	Muscle cramps

*Required in total parenteral nutrition solutions.
†Not absolutely required but included in most formulations.
Adapted from Guidelines for essential trace-element preparations for parenteral use. A statement by an expert panel. AMA Department of Foods and Nutrition. JAMA 1979;241:2051–2054, with permission.

Table 18.8 Suggested Daily Adult Intravenous Requirements of Essential Trace Elements and Associated Deficiency Syndromes

Manganese has not been clearly established as an essential component of TPN solutions, but it has been included in some recommended regimens. Iodine is not normally supplemented because the transdermal absorption of iodine-containing solutions that are used to clean catheter sites permits intake of the required amount of iodine. In the presence of excessive GI losses (e.g., small bowel fistula), additional zinc should be given for replacement. It is recommended that 12.2 mg of additional zinc per liter of small bowel loss should be given.

In patients who are being given enteral supplementation, 2 L of formula per day includes all the recommended dietary allowance for vitamins, minerals, and trace elements.

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19 Surgical Techniques

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In the practice of gynecologic oncology, it is occasionally necessary to perform a number of surgical procedures that are not part of the standard training in general gynecology. These include selected operations on the intestinal and urologic tracts and plastic reconstructive operations, including the creation of a neovagina. In addition, central venous access is frequently required for hyperalimentation or chemotherapy. The surgical techniques for these nongynecologic procedures are presented.

Central Lines

Central venous access catheters are often necessary in the critically ill gynecologic oncology patient for either central venous pressure monitoring or centrally administered hyperalimentation or chemotherapy (1). The most frequently used veins are the subclavian and the jugular. Less frequently used are the brachial and the femoral veins.

Subclavian Venous Catheter

Infraclavicular Technique Although there are many different techniques for the insertion of a central venous catheter into the subclavian vein, the *infraclavicular technique* remains the most commonly used and the simplest. The subclavian vein lies immediately deep to the clavicle within the costoclavicular triangle, where the vein is more commonly approached from the right side (Fig. 19.1A). The *costoclavicular-scalene triangle* is bounded by the medial end of the clavicle anteriorly, the upper surface of the first rib posteriorly, and the anterior scalene muscle laterally (1). The anterior scalene muscle separates the subclavian vein anteriorly from the subclavian artery posteriorly. Just deep to the subclavian artery are the nerves of the brachial plexus. The subclavian vein is covered by the medial 5 cm of the clavicle. Just deep to the medial head of the clavicle, the right internal jugular vein joins the right subclavian vein to form the innominate vein, which then descends into the chest, where it joins the left innominate vein to form the superior vena cava in the retrosternal space.

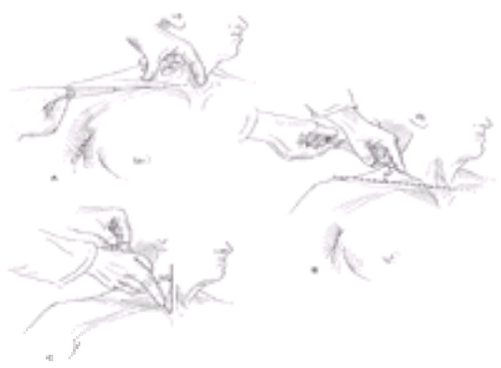


Figure 19.1 Central venous catheter insertion sites. The right subclavian and right internal jugular vein insertion sites are illustrated. The insertion sites for the subclavian venous catheter are the infraclavicular technique **(A)** and the supraclavicular technique **(B)**. The insertion site for the internal jugular vein is shown **(C)**. The needle is directed toward the suprasternal notch.

There are several other vital structures in the scalene triangle. The phrenic nerve courses anterior to the anterior scalene muscle and therefore lies immediately deep to the subclavian vein. If the deep wall of the vein is penetrated, the phrenic nerve can be injured. If the subclavian artery is penetrated, the brachial plexus, lying just deep to the vessel, can be injured. The right lymphatic duct and the thoracic duct on the left enter their respective subclavian veins near the junction with the internal jugular veins and therefore may be injured by a misplaced needle. **The most common injury is to the pleura, the apex of which is just beneath the subclavian vein at the junction of the internal jugular vein.**

The technique for infraclavicular insertion of a catheter into the right subclavian vein is as follows:

1. The patient is placed in the supine position, with the foot of the bed elevated approximately 1 foot so that the patient is in the Trendelenburg position. If possible, a bed that can be tilted into this position should be used. This position creates venous distention and increases the intraluminal pressure in the subclavian vein. The patient's head should be tilted away from the site of insertion so that the landmarks can be identified easily.
2. After careful skin preparation with *povidone-iodine* solution, the skin and subjacent tissues are anesthetized by means of *lidocaine* without *epinephrine.*
3. The site of insertion is located at the junction of the middle and medial thirds of the clavicle, approximately 1 cm below the bone's inferior margin.
4. Before insertion of the catheter needle, a probe needle is used to localize the subclavian vein and to identify the presence of dark venous blood. An 18-gauge needle attached to a 10-mL syringe filled with normal saline solution is used.
5. A 14-gauge *Intracath* needle is used to insert the catheter (Fig. 19.1A). The needle attached to the syringe is inserted into the skin with the bevel directed toward the heart. The needle should be held and directed parallel to the anterior chest wall.
6. After insertion through the skin, the needle is directed medially and advanced along the undersurface of the clavicle in the direction of the suprasternal notch.
7. The syringe is pulled gently to apply suction as the needle is inserted. **The patient should exhale during insertion to avoid an air embolus.**

5. A 14-gauge *Intracath* needle is used to insert the catheter (Fig. 19.1A). The needle attached to the syringe is inserted into the skin with the bevel directed toward the heart. The needle should be held and directed parallel to the anterior chest wall.
6. After insertion through the skin, the needle is directed medially and advanced along the undersurface of the clavicle in the direction of the suprasternal notch.
7. The syringe is pulled gently to apply suction as the needle is inserted. **The patient should exhale during insertion to avoid an air embolus.**
8. After a free flow of blood has been obtained, the needle is held carefully in place, the syringe is detached, and the central venous catheter is advanced inside the lumen of the needle. The catheter should advance freely, and there should be blood returning through the catheter. The catheter is advanced into the innominate vein and then into the superior vena cava. The catheter should be aspirated, and if blood is easily withdrawn, the needle is removed.
9. **While the needle is in place, the catheter should not be withdrawn because the tip can be sheared off and embolize.**
10. The end of the catheter is connected to an intravenous set and the catheter is sutured to the skin.
11. The position of the catheter is verified by a chest radiograph. It should be located in the superior vena cava, not in the right atrium or ventricle, which can result in trauma to the heart.

If central venous pressure readings are to be determined, the intravenous line is attached to a manometer and the base of the water column is positioned at the level of the right atrium, which is approximately 5 cm posterior to the fourth costochondral junction when the patient is in the supine position. The normal central venous pressure should be between 5 and 12 cm of water. Because the central venous pressure may not accurately reflect left ventricular function in patients with cardiac dysfunction, a flow-directed, balloon-tipped intracardiac catheter *(Swan-Ganz)* may have to be inserted in such patients. The use of this catheter is discussed in Chapter 17.

The complication rate for central venous catheter insertion through the subclavian route is approximately 1% to 2% (1). **Most serious complications are related to puncture of the pleura and lung or perforation and laceration of vessels, resulting in a pneumothorax or hemothorax.** Catheter-related infection is seen in approximately 0.5% of patients, and the catheter should be removed if this source of infection is suspected.

Supraclavicular Insertion An alternative route of insertion into the subclavian vein is the supraclavicular route (Fig. 19.1B). Some prefer this to the infraclavicular route, but the morbidity of insertion is comparable between the two methods, and the preference is related to the technique that is most comfortable for the operator.

The technique for insertion is identical to that of the infraclavicular route, except that the needle is inserted above the clavicle, approximately 5 cm lateral to the mid-sternal notch. The angle of insertion is approximately 30 degrees from a line drawn between the two shoulders and directed caudally. The needle is aimed at the suprasternal notch.

Jugular Venous Catheterization

Another alternative for central venous access is use of either the internal or external jugular vein. Jugular venous catheterization is frequently the method of choice when the catheter is inserted during surgery and is to be used primarily for acute monitoring. The advantage is that there is relatively easy access while the patient is anesthetized and draped for surgery, whereas the disadvantage is that it is more difficult to anchor the catheter because the neck is more mobile than the anterior chest wall. The location for the insertion site is illustrated in Fig. 19.1C.

The technique for insertion is as follows:

1. The patient is placed in the Trendelenburg position. With the patient's head turned away from the side of insertion, the needle is inserted just above the medial head of the clavicle between the medial and middle heads of the sternocleidomastoid muscle, where a small pocket is readily apparent and helps to localize the site for insertion.
2. The angle of insertion is approximately 20 to 30 degrees from the sagittal median of the patient, and the direction is toward the heart.
3. As with subclavian catheterization, the use of a probe needle helps to localize the appropriate vessel.
4. The technique of catheter placement is the same as described previously for the subclavian catheter. However, the length of catheter that must be inserted is less because the distance to the proper location in the superior vena cava is less.
5. The position of the line inserted during surgery is checked with a chest radiograph obtained in the recovery room if the catheter is to be left in place.

External jugular catheters may also be used in patients who are under general anesthesia. Some patients have relatively prominent external jugular veins, and they are very easily catheterized. The external jugular is not durable, however, and this route is not useful for central hyperalimentation. The complication rate for jugular venous catheterization is essentially the same as that for the subclavian route.

Semipermanent Lines

The placement of semipermanent lines is useful in patients who require prolonged access to the central venous system, such as those with a chronic intestinal obstruction or fistula who are to receive hyperalimentation after discharge from the hospital (2).

Broviac, Hickman, and Quinton Catheters The most common types of lines are catheters made of flexible, synthetic rubber (e.g., Broviac, Hickman, or Quinton catheters). The catheters are available in several sizes, although the adult type is used for most patients; the length is adapted by cutting the catheters as necessary. The catheters are available with either a single or double lumen. The single-lumen catheters usually are sufficient for parenteral nutrition, whereas the double-lumen ones may be necessary for patients requiring frequent bolus medication, such as intravenous pain or antibiotic medications (2).

The most common site for insertion of a semipermanent catheter is the right subclavian vein. The method of insertion is initially identical to the technique used for the insertion of a temporary catheter, but an insertion cannula, called a Cook introducer, can simplify and facilitate insertion of the catheter (Fig. 19.2). It is preferable to insert the catheter under fluoroscopic guidance.

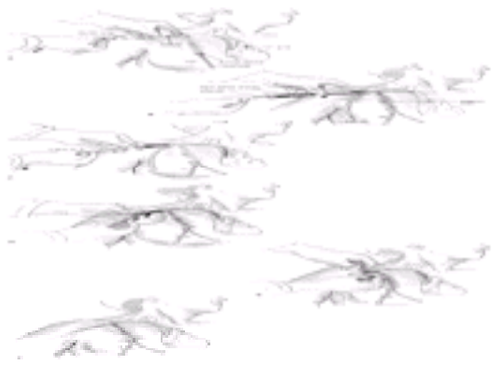


Figure 19.2 Semipermanent catheter insertion. The technique for insertion of the semipermanent (e.g., Hickman) catheter is illustrated. **A:** A needle is inserted into the right subclavian vein, a guide wire is inserted through the needle, and the needle is withdrawn. Note that the catheter is tunneled in the subcutaneous tissue, and this can be performed prior to or after venous insertion. **B:** The Cook introducer then is inserted over the guide wire. **C:** After the introducer with its outer sheath is in place in the right subclavian vein, the wire is withdrawn. *(continued)* **D:** The central catheter of the Cook introducer is withdrawn, and the free end of the semipermanent catheter is inserted through the outer sheath. **E:** The outer sheath of the Cook introducer is peeled away. **F:** The semipermanent catheter is situated under the skin of the right side of the chest, and the free end is exteriorized.

The technique is as follows:

1. After the patient has been properly positioned and the anterior chest and clavicular areas prepared, the subclavian vein is identified in the manner described previously.
2. A premade kit is available for the Cook introducer. An 18-gauge needle is used to introduce a guide wire into the subclavian vein, and the guide wire is passed into the superior vena cava under fluoroscopy (Fig. 19.2A).
3. The proper position of the guide wire is documented, and the Cook introducer is fed over the guide wire and advanced into the subclavian vein (Fig. 19.2B).
4. The introducer has an inner catheter and an outer sheath. After insertion of the entire apparatus, the central cannula is removed (Fig. 19.2C) and the semipermanent catheter is threaded through the outer sheath, which remains in the subclavian vein (Fig. 19.2D).
5. After the semipermanent catheter has been inserted, the outer sheath is peeled away, leaving the catheter in place (Fig. 19.2E).
6. The proximal end of the semipermanent catheter is tunneled under the skin of the anterior chest wall and exteriorized through a stab incision in the skin as illustrated (Figure 19.2A,Figure 19.2B,Figure 19.2C,Figure 19.2D, and Figure 19.2F). This can be done prior to or after placement of the subclavian line.
7. An intravenous line is connected to the catheter's adapter, and fluid is run into the line to establish its patency. The catheter is sutured into place.

Peripherally Inserted Central Catheter Lines Another type of semipermanent line is inserted through a peripheral access site, the *peripherally inserted central catheter (PICC) line.* The PICC line is inserted into the brachial vein in the antecubital fossa. The catheter is passed cephalad until it reaches the central subclavian vein. This line is suitable for the infusion of parenteral nutrition as well as chemotherapy.

This approach is less durable than the centrally inserted catheters and somewhat more cumbersome because of the location of the insertion site. Its main advantage, however, is that it can be easily inserted at the bedside. Furthermore, it can be placed by a certified nurse or an intravenous technician trained in the insertion technique. Alternatively, an implantable port can be inserted in the antecubital fossa by a physician.

Peritoneal Catheters

Peritoneal catheters are used in gynecologic oncology for the instillation of intraperitoneal chemotherapy. A commonly used catheter is the Tenckhoff peritoneal dialysis catheter, which is designed to minimize the risk of infection even though it is left in place many months (3). Alternatively, a Hickman venous access catheter can be used.

The catheter is implanted into the peritoneal cavity lateral to the midline laparotomy incision (Fig. 19.3). The catheter is tunneled in the subcutaneous tissue and brought out through a stab incision lateral to the fascial incision. The tip of the catheter in the peritoneal cavity is directed toward the pelvic cul-de-sac.

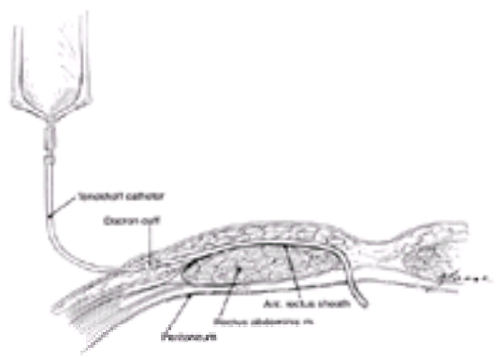


Figure 19.3 Tenckhoff peritoneal catheter. Placement of the Tenckhoff catheter into the peritoneal cavity is illustrated.

An alternative peritoneal access catheter is the Port-A-Cath (Bard, Salt Lake City, Utah), which is a completely implantable device. The implantable port is attached directly to a peritoneal access Tenckhoff or Hickman catheter. The port is inserted into the subcutaneous tissue and positioned in the left or right lower quadrant of the anterior abdomen for ready access (Fig. 19.4). The port is entered percutaneously with a 21-gauge needle.

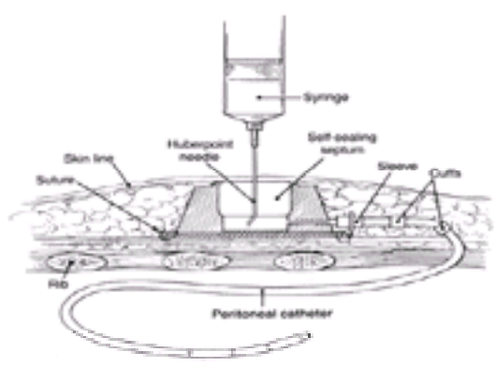


Figure 19.4 Port-A-Cath peritoneal catheter. The totally implantable peritoneal access catheter is tunneled through the subcutaneous tissues into the peritoneal cavity.

The most common problem associated with these catheters is blockage, and there is no effective way to prevent some deposition of fibrin around the catheter. Occasionally, this produces a “ball valve” effect, that is, fluid flows in but cannot flow out. Minor infections can be treated with antibiotics, and low-grade peritonitis can be treated by the instillation of antibiotics directly through the catheter. For persistent and severe infections, the peritoneal catheter may require removal.

Incisions

Particularly important in the operative plan for any patient is the determination of the type of incision to be made. The surgeon should have a general philosophy and *modus operandi* when planning the surgical procedure. There are certain incisions that are more appropriate in patients who are undergoing surgery for cancer rather than for benign conditions. In addition, special guidelines for the closure of incisions should be followed.

Vertical Incisions

Abdominal incisions used in the gynecologic oncology patient are most commonly vertical. Transverse incisions are also appropriate in certain circumstances. The indications and techniques for these incisions and their modifications are discussed.

Patients with suspected malignancies of the ovary or fallopian tube are best explored through a vertical abdominal incision. With a vertical incision, the patient's disease can be staged properly. Also, this approach permits the removal of any upper abdominal metastases, which cannot always be appreciated before surgery. The most likely site of resectable upper abdominal disease is the omentum. For an omentectomy, access to the region of the splenic and hepatic flexures is required.

A vertical incision is also necessary in patients being explored for intestinal obstruction or fistulas. The performance of a paraaortic lymphadenectomy is facilitated by a vertical incision. Patients being explored for recurrent malignancies or possible pelvic exenteration also require a vertical abdominal incision.

The most commonly used vertical incision is in the midline. This incision has the advantage of being easy to perform; it can be accomplished quickly, because the midline is the least vascular area of the abdominal wall, and the smallest depth of tissue must be divided. The principal blood supply to the anterior abdominal wall is from the inferior epigastric vessels, which are located laterally in the rectus sheath posterior to the rectus abdominis muscles, and these vessels are avoided by the midline incision.

The principal problem associated with the midline incision is that it has the highest rate of wound dehiscence compared with all other incisions. The wound disruption rate is approximately 0.1% to 0.65% (4,5 and 6), although this rate may be higher in patients with cancer, particularly those with ascites and malnutrition or those needing postoperative radiation. Dehiscence rates as high as 2% to 3% have been reported in obese, diabetic patients with cancer (4). Most wound dehiscences are associated with wound infection or poor closure technique.

Transverse Incisions

In patients with a probable benign condition who are undergoing abdominal exploration for the first time, a lower transverse abdominal incision is frequently used. The advantage of this incision is that it is more cosmetic, is usually less painful, and is associated with fewer incisional hernias. The disadvantage is the relative problem of upper abdominal exposure and the more frequent occurrence of wound hematomas.

If exposure to the upper abdomen is required, the surgeon has several choices. The incision can be modified by division of the rectus abdominis muscles in a transverse direction at the level of the incision (i.e., a *Maylard incision*), or the rectus abdominis muscles may be detached from the symphysis pubis (i.e., the *Cherney incision*). After division or mobilization of the rectus muscles, the inferior epigastric vessels are ligated bilaterally and, if necessary, the incision is further extended laterally by incising (with the diathermy) the "strap" muscles of the anterior abdominal wall. The conversion of the incision to a Maylard or a Cherney incision always provides considerably more exposure in the pelvis and low paraaortic area.

If better access to the upper abdomen is required, the incision can be modified further by extending the incision cephalad to form a **"J,"** a reverse **"J,"** or a "hockey stick" incision. In general, any of these techniques is preferable to the making of a second incision, that is, a midline incision coincident with the transverse incision, a so-called **"T"** incision. The principal difficulty with the latter approach is the weakness of the incision at the point of intersection of the two incisions.

In patients undergoing radical hysterectomy and pelvic lymphadenectomy for early-stage cervical cancer, a lower abdominal transverse incision is acceptable.

Incisional Closure

Of primary importance is the technique of incisional closure (4,5,6,7,8,9,10,11,12 and 13). The closure can be accomplished by closing the peritoneum, fascia, subcutaneous tissue, and skin individually, or a bulk closure can be performed that incorporates the peritoneum and the fascia together. This bulk closure or internal retention suture, the Smead-Jones closure, is the strongest closure technique (6). Mass closure with a continuous, single strand of polyglyconate monofilament absorbable suture *(Maxon)* or polydioxanone *(PDS)* has been shown to be an effective, safe alternative to the use of interrupted sutures, even in vertical midline incisions (4,6,7,8,9 and 10).

Internal Retention Suture

The Smead-Jones or internal retention technique uses interrupted sutures that are placed as illustrated in Fig. 19.5. The sutures are placed in a far-far, near-near distribution, which is a modified figure-of-eight. The first suture is placed through the anterior fascia, rectus muscle, posterior fascia, and peritoneum and the second through the anterior fascial layer only. The key is to place the sutures at least 1.5 to 2 cm from the fascial edge and not more than 1 cm apart (6). The disruption rate of midline incisions with this technique was only 0.1% in this series of patients undergoing operations for cancer, compared with 0.4% for a closure by the traditional layer-by-layer technique.

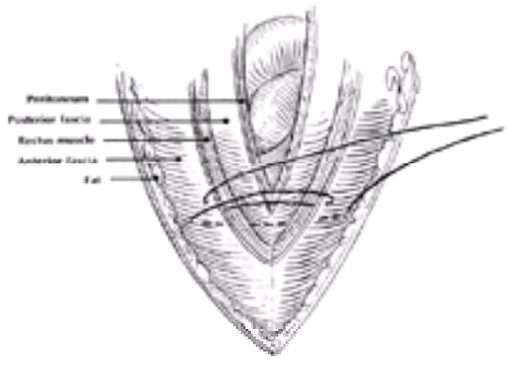


Figure 19.5 Internal retention abdominal closure. The Smead-Jones far-far, near-near closure.

Suture Material

The choice of suture should be dictated by the circumstances (4,5,6,7,8,9,10,11,12 and 13). If there is evidence of significant infection, as with an abscess or an intestinal injury, a monofilament, nonabsorbable suture is most appropriate. The most frequently used substances are nylon sutures, such as *Prolene.*

For vertical incisions, an absorbable, long-lasting synthetic suture offers the best combination of strength, durability, and ease of use. Most suitable is either *Maxon* or *PDS*. Braided, polyglycolic acid suture, such as *Vicryl* or *Dexon*, is suitable for transverse incisions. A grade 0 or 1 suture is necessary to provide a suitably strong closure. The tissue reactivity of these synthetic materials is less than that of chromic catgut. Nonabsorbable polyfilament materials such as cotton and silk are not used for incisional closure because of the higher potential for stitch abscess formation.

External Retention Suture

External retention sutures can be used to prevent evisceration in patients who are at high risk of this potentially catastrophic occurrence. The routine use of internal retention sutures has reduced the need for the external retention sutures. However, in patients who are morbidly obese, have a major wound infection, or whose incisions have eviscerated in the past, the addition of external retention sutures may be indicated. These sutures are placed in a manner similar to that of internal retention sutures (i.e., far-far, near-near), with the far sutures also placed through the skin so that the retention sutures are knotted externally. The preferable suture material for this closure is nylon. The external retention sutures are inserted through a rubber bolster that helps to protect the skin from injury from the suture. Sutures are placed at approximately 2- to 3-cm intervals, and interrupted fascial sutures are placed between them.

Skin Closure

Primary Closure Skin closure of vertical incisions in patients with cancer usually should be interrupted, either with nylon or metal skin clips. Subcuticular closures are not appropriate in most circumstances for vertical incisions, but they are quite cosmetic and acceptable for small transverse incisions where the risk of wound infection is low.

Secondary Closure A delayed or secondary skin closure is useful in patients whose incisions are infected, such as after the drainage of an intraabdominal abscess or repair of an intestinal fistula. This is achieved by placement of interrupted mattress sutures in the skin, which are not tied, so that the skin remains unapproximated. Thus the skin can be closed later, usually after 3 to 4 days, when the infection is under control.

Intestinal Operations

Preoperative Intestinal Preparation

If bowel resection is planned or contemplated, a thorough mechanical and antibiotic bowel preparation should be undertaken before surgery. If the intestine is prepared properly, the segment is well vascularized, and there is no sepsis, prior irradiation, or evidence of tumor at the site of anastomosis, colonic reanastomosis can be accomplished without leakage in 98% of cases (11). More proximal resection of the small intestine can be performed without a bowel preparation because this portion of the intestine does not contain bacteria.

An effective protocol for bowel preparation is presented in Table 19.1. In a prospective, randomized, double-blinded study, the rate of serious complications, mostly infection, associated with colonic resection were reduced from 43% in the unprepared group to 9% in the prepared patients (14).

Preoperative day 2
Clear-liquid diet
Tap water or Fleet enema at night (optional)
Preoperative day 1
Clear-liquid diet
2 L Go-LYTELY® (polyethylene glycon) or 1 bottle mineral oil at 8 a.m.
Oral neomycin, 1 g every 4 hr for three doses (4, 8, 12 p.m.)
Oral erythromycin base, 1 g every 4 hr for three doses
Tap water or Fleet enemas until no solid stool at night
Operation day
Fleet enemas until clear

®Braintree Laboratories Inc., Braintree, Massachusetts.

Table 19.1 Bowel Preparation

Before laparotomy for small intestinal obstruction caused by ovarian cancer, it is useful to insert a long gastrointestinal tube (e.g., a Cantor tube) at least 48 hours before surgery (6). The advantage, in an abdomen where multiple adhesions are present, is that the tube can decompress the bowel, help localize the site of obstruction, and differentiate between proximal and distal loops of small bowel. The long tube is particularly useful in patients who have been previously irradiated or who are undergoing exploration for an intestinal fistula. The injection of radiocontrast medium through the tube may help to identify the site of obstruction, although multiple obstructions are common in patients with disseminated ovarian cancer.

Minor Intestinal Operations

The most common intestinal operations are lysis of adhesions, repair of an enterotomy, and creation of an intestinal stoma.

Repair of Enterotomy

Intestinal enterotomy is a common inadvertent occurrence in abdominal surgery, and it can occur in the most experienced hands. Factors that predispose to serosal and mucosal injury include extensive adhesions, intraabdominal carcinomatosis, radiation therapy, chemotherapy, prior abdominal surgery, and peritonitis.

An enterotomy usually does not cause any problems, provided it is identified and repaired. Any defect should be repaired when it occurs or marked with a long stitch so that it will not be overlooked later. At the completion of any intraabdominal exploration necessitating significant lysis of adhesions, the surgeon must “run the bowel,” carefully inspecting it to exclude either a serosal injury or an enterotomy.

Serosal defects through which the intestinal mucosa can be seen must be repaired. Less complete defects must be repaired in all patients who have had radiation treatment to the abdomen. When in doubt, the defect should be repaired to minimize the risk of intestinal breakdown, peritonitis, abscess, and fistula.

When there is an enterotomy, the repair should be made with interrupted 3-0 or 4-0 sutures on a gastrointestinal needle, placed at 2- to 3-mm intervals along the defect. The suture material most commonly used for this purpose is silk, although a suitable alternative is *Vicryl* or *Dexon.* **The direction of closure should be perpendicular to the lumen of the bowel to minimize the potential for luminal stricture** (Fig. 19.6).

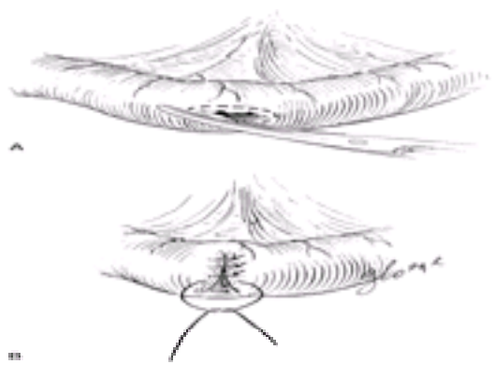


Figure 19.6 Closure of an intestinal enterotomy. A: The edges of the enterotomy are trimmed. **B:** The enterotomy is closed perpendicular to the lumen in two layers.

With small defects (i.e., <5 to 6 mm), the closure can be accomplished with a single layer of sutures passed through both the serosa and the mucosa. However, it is preferable to close more extensive defects in two layers, an inner full-thickness layer covered with an outer seromuscular layer. Care should be taken to approximate the tissues carefully without cutting through the fragile serosa.

Gastrostomy

A gastrostomy may be necessary in patients with chronic intestinal obstruction, usually from terminal ovarian cancer. It is particularly useful in those who require prolonged intestinal intubation and in whom the underlying intestinal blockage cannot be relieved adequately. This procedure may permit the removal of an uncomfortable nasogastric tube that is irritating to the nasopharynx. The two most common procedures are the Stamm and the Witzel gastrostomies (15).

Stamm Gastrostomy The simplest technique is the Stamm gastrostomy, in which a small incision is made in the inferior anterior gastric wall. A Foley catheter with a 30-mL balloon is brought into the peritoneal cavity through a separate stab incision in the left upper outer quadrant of the abdomen. Two or three successive pursestring sutures, with 2-0 absorbable suture material, are used to invert the stomach around the tube. Interrupted 2-0 silk sutures are placed in the serosa, and the same material is used to suture the serosa to the peritoneum, approximating the gastric wall to the anterior abdominal wall in an effort to prevent leakage.

Witzel Gastrostomy The Witzel technique is similar, but the catheter is tunneled within the gastric wall for several centimeters with Lembert sutures of 2-0 silk. This technique results in a serosal tunnel that may further reduce the risk of leakage. The most important step in preventing gastrostomy leakage is approximation of the gastric serosa to the anterior abdominal wall.

Percutaneous Gastrostomy Another technique for gastrostomy in patients not otherwise undergoing laparotomy is the percutaneous placement of a catheter into the stomach. This method involves the initial passage of a gastroscope. The site for catheter insertion is illuminated by a fiberoptic light source through the gastroscope, and the catheter is introduced into the stomach percutaneously.

Baker Tube Placement

The Baker tube is an 18-Fr tube that is 270 cm long and has attached to the tip a 5-mL bag that can be filled with saline solution (16). The tube is placed at the time of a laparotomy; it is placed by means of a jejunotomy and advanced through the bowel by milking of the balloon through the lumen until it has passed through the site of chronic obstruction or intestinal damage. The proximal end of the tube is exteriorized through a stab incision in the anterior abdominal wall and connected to a drainage container. It splints the bowel into a position of function, thereby minimizing the likelihood of recurrent obstruction.

The placement of a Baker tube may be useful in patients who have had abdominal radiation therapy and have developed a chronic obstruction of the small bowel.

Cecostomy

The performance of a cecostomy may be useful in the occasional patient who has an obstruction of the colon and a grossly dilated cecum and in whom a simple palliative measure to relieve the obstruction is indicated. A more definitive procedure for relief of the obstruction may be appropriate when the patient's condition is more stable.

The cecostomy is performed by placement of a Foley catheter into the dilated portion of the cecum. The tube is sutured into place by the technique used for a Stamm gastrostomy. The tube is exteriorized through a stab incision in the right lower quadrant of the abdomen and attached to gravity drainage.

Colostomy

Colostomies may be temporary or permanent. A temporary colostomy may be indicated for protection of a colonic reanastomosis in patients who have had prior radiation therapy or to palliate severe radiation proctitis and bleeding. It is indicated also in patients who have a large bowel fistula (e.g., rectovaginal fistula) to allow the inflammation to subside before definitive repair. A permanent colostomy is indicated in patients who have an irreparable fistula or a colonic obstruction from a pelvic tumor that cannot be resected. Permanent colostomy is also indicated in patients undergoing total pelvic exenteration, unless the distal rectum can be preserved and the colon reanastomosed, and in those who require anoproctectomy because of advanced vulvar cancer.

The site of the colostomy should be selected so that the stomal appliance and bag can be applied to the skin of the anterior abdominal wall without difficulty. The best site is approximately midway between the umbilicus and the anterior iliac crest. The most distal site possible should be used in the large intestine. After selection of the stomal site, a circular skin incision is made to accommodate two fingers. The subcutaneous tissue is removed and the fascia of the rectus sheath is incised similarly (Fig. 19.7). The end of the colon is brought through the stoma and sutured to fascia with interrupted 2-0 silk, and the stoma is everted to the skin to form a “rosebud” with the use of interrupted 2-0 or 3-0 absorbable braided suture.

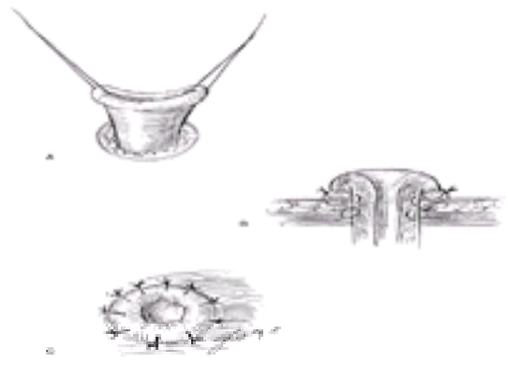


Figure 19.7 Formation of a colostomy. A: The end of the colon is brought through the abdominal wall. **B:** It is sutured to the fascia and skin. **C:** The “rosebud”stoma is formed.

Temporary

For patients who require temporary diversion, a transverse or sigmoid colostomy is usually created. The most distal portion of the colon should be used to allow the most formed stool possible. A loop colostomy is usually created: a loop of the colon is brought out through an appropriately placed separate incision in the abdominal wall. The loop is maintained by suturing it to the fascia beneath it. It can be reinforced with a rod of glass or plastic passed through a hole in the mesentery. The stoma can be opened immediately by means of an incision along the taenia coli in the longitudinal direction. Alternatively, the loop may be “matured” 1 to 2 days later to minimize the risk of sepsis if the bowel is unprepared.

The colon can be brought out as an *end* colostomy, which requires transection of the colon. This can be readily accomplished by means of a gastrointestinal anastomosis (GIA) stapler, which closes and transects the colon simultaneously. The distal end is sutured to the fascia and the proximal end is brought out as the colostomy. If the distal colon must also be diverted (because of distal obstruction), either a *double-barrel* or a *loop* colostomy can be created.

Permanent

A permanent colostomy is an end or terminal colostomy, performed as far distally as possible to allow the maximum amount of fluid reabsorption. The distal loop of the transected colon may be oversewn to create a *Hartman's pouch* if there is no distal obstruction. **In patients in whom there is complete distal obstruction, a mucous fistula should be created.**

Enterostomy

If the colon is surgically inaccessible because of extensive carcinomatosis or radiation-induced adhesions, it may become necessary to palliate the bowel obstruction by the creation of a small intestinal stoma. Because the small bowel contents are loose and irritating compared with colonic contents, an ileostomy or a jejunostomy should be undertaken only when absolutely necessary.

Intestinal Resection and Reanastomosis

After a segment of bowel, along with its wedge-shaped section of mesentery, has been resected, a reanastomosis may be performed (17,18,19,20,21,22,23,24 and 25). The most commonly used technique for reanastomosis is the *end-to-end* anastomosis, which is performed as either an open two-layered closure or a closed one-layered anastomosis. An *end-to-side* anastomosis may be used to create a J-pouch, that is, a segment of bowel created to improve low colonic continence (20,21,22,23 and 24). A *side-to-side* anastomosis may be useful to increase the size of the lumen at the site of anastomosis. Increasingly, the use of surgical stapling devices has permitted more rapid performance of the reanastomosis, which is particularly useful when more than one resection is being carried out or when the duration of the procedure is of major concern.

Hand-Sewn Anastomosis

End-to-End Enteroenterostomy

When the reanastomosis is to be hand sewn, the proximal and distal ends are clamped with Bainbridge clamps (Fig. 19.8A) and the posterior interrupted, seromuscular *Lembert* stitches are placed with 3-0 silk or *Vicryl* (Fig. 19.8B). The clamps are removed, the devitalized ends are trimmed, and an inner, continuous, full-thickness layer of 3-0 chromic catgut or *Vicryl* is placed to complete the posterior portion of the anastomosis. After the corner is reached, the needle is brought through the wall to the outside, and the continuous layer is completed anteriorly with a *Connell* stitch (outside-in, inside-out) to complete the inner layer (Fig. 19.8C). The anterior seromuscular layer is then placed with interrupted 3-0 silk or *Vicryl* sutures (Fig. 19.8D). The defect in the intestinal mesentery is repaired.

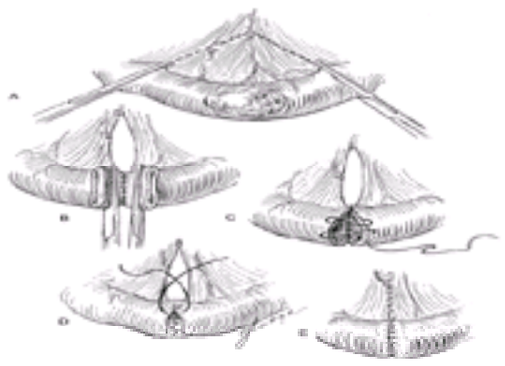


Figure 19.8 Hand-sewn end-to-end enteroenterostomy. A: The tumor and bowel are resected along with the mesentery. **B:** The posterior seromuscular layer is sutured. **C:** The Connell stitch is placed. **D:** The anterior seromuscular layer is placed. **E:** The completed anastomosis.

A single-layered closed technique is occasionally used for colonic reanastomosis in obstructed, unprepared bowel in an effort to minimize peritoneal contamination. In these circumstances, however, the use of the surgical staplers is now recommended (15).

Side-to-Side Enteroenterostomy

The side-to-side anastomosis is particularly useful in patients who are undergoing intestinal bypass rather than resection to palliate bowel obstruction, such as in patients with unresectable or recurrent tumor. The loops of intestine are aligned side-to-side, and linen-shod clamps are applied to prevent spillage of intestinal contents. A posterior row of 3-0 silk or *Vicryl* is placed with interrupted Lembert sutures, and the lumina are created. An inner layer of continuous, full-thickness 3-0 chromic catgut or *Vicryl* sutures is placed and continued anteriorly to complete the layer with a Connell stitch. The anastomosis is completed by placement of an anterior seromuscular layer with the use of interrupted 3-0 silk or *Vicryl* sutures.

Intestinal Staplers

The principal advantage of the gastrointestinal staplers is the speed with which they can be used. **There is no increase in the complication rate with the use of staplers compared with hand-sewn anastomoses** (15,16,17,18 and 19). The staplers are especially useful in facilitating reanastomosis after low resection of the rectosigmoid colon, because a hand-sewn anastomosis is technically difficult when performed deep in the pelvis. **A disadvantage of the staplers is their increased cost, and staplers are difficult to use when the intestinal tissues are very edematous.**

Types of Stapling Devices

The staplers are available in either reusable metal devices or in single-use disposable devices (Fig. 19.9).

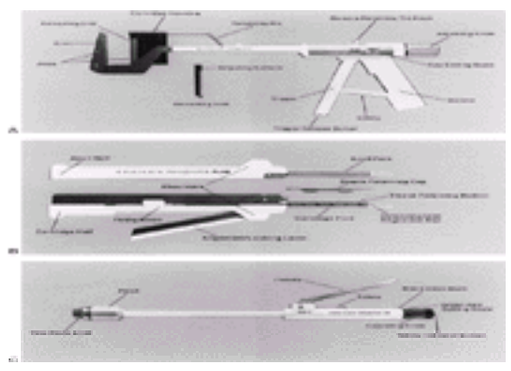


Figure 19.9 Stapling devices for intestinal anastomosis. Single-use staplers include the thoracoabdominal (TA) **(A),** the gastrointestinal anastomosis (GIA) **(B),** and the end-to-end anastomosis (EEA) **(C).**

Thoracoabdominal Stapler The thoracoabdominal (TA) stapler comes in several sizes, the TA-30, TA-55, TA-60, and TA-90, corresponding to the length in millimeters of the row of staples. Individual staples are either 3.5 or 4.8 mm long. The TA closes the lumen in an everting fashion. The Roticulator-55 (Ethicon, Cincinnati, Ohio) is a TA device with a roticulating end that can be adjusted for placement into narrow areas (e.g., the deep pelvis).

Gastrointestinal Anastomosis Stapler The GIA device places two double rows of staples and then cuts the tissue between the two rows.

End-to-End Anastomosis Stapler The end-to-end anastomosis (EEA) stapler is used primarily to approximate two ends of the colon, especially to facilitate the reanastomosis of the lower colon after pelvic exenteration or resection of pelvic disease in patients with ovarian cancer. The stapler places a double row of staples, approximates the two ends of the intestine, and cuts the devitalized tissue inside the staple line. It is available in diameters of 21, 25, 28, 31, and 35 mm, and a metal sizing device is used to measure the diameter of the intestinal lumen (25).

Intraluminal Stapler The intraluminal stapler (ILS) is a disposable EEA stapler that has a detachable anvil. This removable feature can facilitate the placement of the anvil into a portion of one intestine that is difficult to mobilize. The anvil can be reattached to the rod of the ILS device after it has been placed in the anastomosis.

Stapling Technique

Functional End-to-End Enteroenterostomy Anastomosis This operation is illustrated in Fig. 19.10. The GIA stapler is used to staple and divide each end of the bowel segment to be resected. The antimesenteric borders of the bowel loops are approximated and the corners are resected. A fork of the GIA device is inserted into each bowel lumen, and after alignment, the stapler is fired. The defect where the stapler was introduced then is closed with a TA stapler.

Functional End-to-End Enteroenterostomy Anastomosis This operation is illustrated in Fig. 19.10. The GIA stapler is used to staple and divide each end of the bowel segment to be resected. The antimesenteric borders of the bowel loops are approximated and the corners are resected. A fork of the GIA device is inserted into each bowel lumen, and after alignment, the stapler is fired. The defect where the stapler was introduced then is closed with a TA stapler.

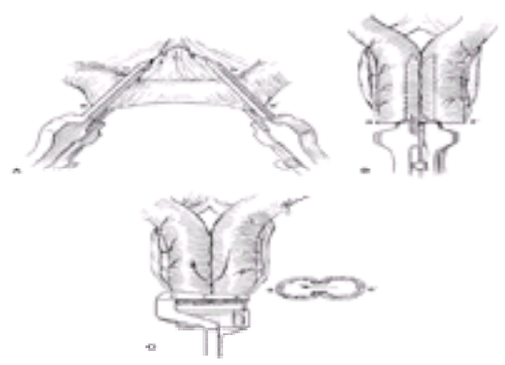


Figure 19.10 Functional end-to-end anastomosis using the stapling technique. A: The gastrointestinal anastomosis (GIA) stapler is used to resect the intestine. **B:** The sides of the transected intestine are placed side to side, and each antimesenteric corner is incised to create two holes into which the two forks of a second GIA stapler are placed. The GIA stapler is fired to create the new intestinal lumen. **C:** The thoracoabdominal (TA) stapler is placed over the end and fired to close the remaining defect. Note the cross section at a-a'.

Side-to-Side Enteroenterostomy Anastomosis When a bypass enteroenterostomy is performed, the two loops of bowel to be anastomosed side to side are aligned, an enterotomy is created in each loop, and a fork of the GIA stapler is slid into each lumen, fired, and removed. This creates the lumen between the two bowel segments, and the enterotomy that is left when the instrument is withdrawn is then approximated with a TA stapler.

Low Colonic End-to-End Anastomosis A low colonic resection is performed by isolating and removing the portion of the rectosigmoid colon involved with disease. The EEA stapler is inserted through the anus and advanced to the site of the anastomosis. The instrument is opened to allow the anvil to accommodate the proximal colon, which is mobilized and tied over the distal end of the EEA. The distal colon is likewise tied over the EEA with a pursestring suture (Fig. 19.11). The EEA is then closed, approximating the two ends of the colon, and the instrument is fired and removed. A reinforcing layer of interrupted 3-0 silk or *Vicryl* Lembert sutures is placed anteriorly. The anastomosis is palpated to confirm that it is intact. Also, the pelvis can be filled with saline solution, and air can be insufflated through the rectum to search for bubbles, which would indicate a defect in the anastomosis (25).

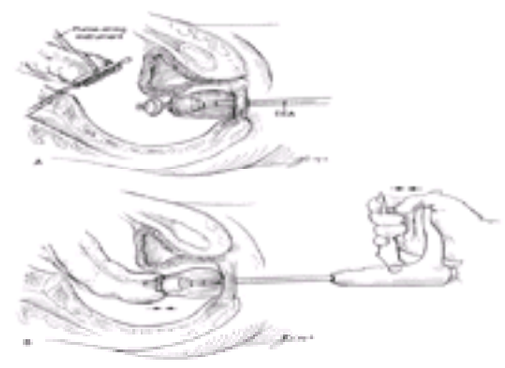


Figure 19.11 Low colonic end-to-end anastomosis using the end-to-end anastomosis (EEA) stapler. A: After resection of the rectosigmoid colon, the distal end of the descending colon is mobilized and a pursestring suture is placed by hand or with a special instrument (illustrated). A pursestring suture is also placed around the rectal stump. The open end of the EEA stapler is inserted through the anus and the rectal pursestring is tied around the instrument. The end of the descending colon is placed over the end of the EEA and the second pursestring is tied. **B:** The EEA device is closed and fired.

Low Colonic End-to-Side Anastomosis (J-Pouch) An alternative end-to-side (functional end-to-end) low colonic anastomosis can be performed with the use of one of the newer disposable stapling devices that has a removable distal one-piece anvil, the *intraluminal stapler.* In this manner, a J-pouch can be created, which has the potential to improve the continence of patients (Fig. 19.12). **Studies comparing the colonic J-pouch to the direct end-to-end anastomosis have suggested that there is a lower leak rate, better continence rate, fewer stools per day, and better control of urgency and flatus** (20,21,22,23 and 24). **The problem with this approach is that some patients have more difficulty emptying the pouch, a problem that can be minimized by limiting the size of the pouch to approximately 5 cm in length** (24).

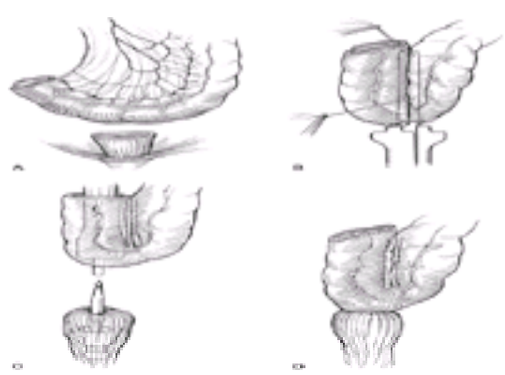


Figure 19.12 Low colonic end-to-side anastomosis to create a J-pouch. A: The end-to-side anastomosis allows the mesocolon to be preserved and to cover the sacral hollow. **B:** The terminal end of the colon has the J-pouch created by stapling a loop side-to-side using a gastrointestinal anastomosis (GIA) stapler. **C:** The end-to-end anastomosis (EEA) stapler is then inserted into the rectal stump to perform the anastomosis end-to-side to the pouch. **D:** The end of the pouch is stapled closed with a GIA or thoracoabdominal (TA) stapler, and the EEA is then stapled to complete the anastomosis.

The J-pouch is created by first folding the distal colon onto itself and stapling it side-to-side with a GIA stapler (Fig. 19.12A). The pouch is then anastomosed to the rectal stump using end-to-side technique with an EEA stapler (Fig. 19.12B), and by detaching the anvil, which is inserted in the proximal colon segment (Fig. 19.12C). The center rod of the open EEA instrument without the anvil is inserted through an opening in the bowel or through the anus. The rod is then inserted through or near the staple line. In the other segment of bowel, a pursestring suture is placed and the free anvil is inserted in the lumen of the bowel within the pursestring suture (Fig. 19.12D). The anvil is then screwed onto the rod, the device is closed, and the anastomosis is created.

Low Colonic Side-to-Side Anastomosis An alternative side-to-side (functional end-to-end) anastomosis of the rectosigmoid colon can be used when the portion of removed bowel is proximal enough to permit this operation (i.e., 10 to 15 cm of preserved rectum). The GIA instrument is used to perform the colorectal anastomosis. After the segment of colon to be resected is mobilized, the proximal colon to be reanastomosed is closed with either the GIA or the TA-55 instrument. A stab wound is made in the antimesenteric border of the colon approximately 5 cm proximal to the staple line closure. A corresponding stab wound is made in the left anterolateral wall of the rectum at

Low Colonic Side-to-Side Anastomosis An alternative side-to-side (functional end-to-end) anastomosis of the rectosigmoid colon can be used when the portion of removed bowel is proximal enough to permit this operation (i.e., 10 to 15 cm of preserved rectum). The GIA instrument is used to perform the colorectal anastomosis. After the segment of colon to be resected is mobilized, the proximal colon to be reanastomosed is closed with either the GIA or the TA-55 instrument. A stab wound is made in the antimesenteric border of the colon approximately 5 cm proximal to the staple line closure. A corresponding stab wound is made in the left anterolateral wall of the rectum at the proximal point of the planned site of anastomosis. The proximal colon is placed into the retrorectal space, side-to-side along the rectum, the GIA device is placed into the proximal and distal segments, and the instrument is closed and fired. The remaining single defect is closed with either a hand-sewn, double layer of 3-0 sutures or the rotating TA-55 device (Roticulator-55).

Postoperative Care

After resection of the small bowel, a nasogastric tube is usually placed for approximately 48 hours to reduce the volume of intestinal secretions that must pass through the site of anastomosis. In patients who have received pelvic or abdominal irradiation, the upper intestinal tract should remain intubated until bowel function has returned, as signified by the passage of flatus and stool. Typically, patients who have undergone small bowel resection must be maintained without oral intake for approximately 5 days, whereas those who have undergone colonic resection require approximately 7 days without oral intake. The diet is advanced gradually as the patient tolerates it. In patients who have undergone colonic resection and reanastomosis, enemas and cathartics should be avoided (25).

Intravenous fluids must be continued while the patient is receiving nothing by mouth. **In patients whose recovery is likely to be prolonged beyond 7 days, such as those who have previously received whole-abdominal irradiation, consideration should be given to the use of parenteral nutrition,** as discussed in Chapter 18. In such patients, a gastrostomy tube may be useful to avoid prolonged nasogastric intubation.

Urinary Tract Operations

The preoperative evaluation of the urinary tract is important in patients with gynecologic malignancies because of the frequent involvement of the urinary organs, especially the bladder and the distal ureters (26,27). Renal function and ureteric patency must be assessed before surgery.

Cystoscopy

Cystoscopy should be performed as part of the staging for cervical and vaginal cancers unless the disease has been diagnosed early (27). Cystoscopy is also indicated in patients with a lower urinary tract fistula or unexplained hematuria. Cystoscopic examination may demonstrate external compression of the bladder by a tumor, bullous edema produced by the blockage of lymphatic vessels from adjacent tumor growth, or mucosal involvement with tumor. When a mucosal lesion is seen, a biopsy can confirm the diagnosis.

Technique Cystoscopy is performed with the patient in the dorsal lithotomy position. After preparation and draping of the area, the cystoscopic obturator and sheath are inserted into the urethra and carefully advanced into the bladder, after which the obturator is removed. The cystoscope is inserted into the sheath. Approximately 250 to 400 mL of normal saline solution is instilled into the bladder to permit a thorough inspection of the entire mucosa.

Cystostomy

A suprapubic cystostomy catheter is useful in patients who require prolonged bladder drainage. This catheter is particularly useful in patients undergoing radical hysterectomy for cervical cancer or extensive resection of pelvic tumor, because temporary disruption of bladder innervation occurs with these dissections. The suprapubic catheter is easier for the patient to manage than a transurethral Foley catheter, and the rate of bladder infection is lower (27). The other convenient aspect of this catheter is that it can facilitate trials of voiding. The patient can clamp the catheter for a specified interval, void, and then unclamp to check for residual urine. When the residual urine is less than 75 to 100 mL, the catheter can be removed.

Technique The catheter used is an 18-Fr Silastic Foley catheter with a 5- to 10-mL balloon. This catheter is well tolerated by patients, produces minimal local tissue irritation, and is of sufficient caliber that blockage of the catheter lumen is not a major problem. The placement of a suprapubic catheter involves the following steps:

1. The catheter is inserted through a stab incision in the skin, subcutaneous tissue, and fascia, and a small hole is made in the dome of the bladder.
2. The tip of the catheter is inserted into the bladder, and a seromuscular pursestring suture is placed around the defect with 3-0 *Vicryl* or chromic catgut.
3. A second reinforcing layer consisting of either 2-0 absorbable braided *Vicryl* or chromic catgut suture is placed in the bladder.
4. With the Foley balloon distended, the catheter is pulled up so that the bladder is applied snugly to the anterior abdominal wall.
5. The catheter can be attached to a urinary drainage bag or to a smaller leg bag, which is more portable and therefore easier for the patient to manage after discharge from the hospital.

Ureteral Obstruction

Ureteral obstruction is the most common urinary complication in patients with gynecologic malignancies. This problem is seen particularly in patients with cervical or vaginal cancer, either at the time of diagnosis or with recurrent disease. It may result from direct tumor extension into the bladder or distal ureters or from compression by lymph node metastases. In patients with intraabdominal carcinomatosis, most often from ovarian cancer, extensive pelvic tumor may cause significant progressive ureteral obstruction. The most frequent site of lower urinary tract obstruction in gynecologic patients is the ureterovesical junction (26).

Postoperative obstruction is usually incomplete and results from edema, possible infection, and partial devascularization of the distal ureter. However, the obstruction may be complete, and when it is, it most often results from inadvertent suture ligature of the distal ureter when the surgeon is attempting to ligate the blood vessels of the cardinal ligament (27). Chronic obstruction can result from stenosis after pelvic irradiation, particularly if pelvic surgery is also performed.

In patients who have a partial ureteral obstruction, the passage of a retrograde stent at the time of cystoscopy might bypass the site of blockage. The retrograde stent used is a 7- to 9-Fr, flexible, double-J retrograde ureteral stent; it is inserted with the aid of a stent placement apparatus that has an elevator attachment to the cystoscope. Great care must be taken because this procedure has the risk of ureteral perforation. When the stent does not pass readily, performance of a percutaneous nephrostomy is preferable.

In patients in whom complete ureteral obstruction is suspected (i.e., because of a rising serum creatinine level or the development of an acute unilateral pyelonephritis), an intravenous pyelogram (IVP) should be performed if the serum creatinine value is less than 2 mg; an ultrasonogram should be obtained if the level is higher. In patients with complete ureteral obstruction, the problem must be corrected immediately, either by temporary urinary diversion by means of a percutaneous nephrostomy or by reexploration and repair of the ureter. Repair may be affected by either reanastomosis or reimplantation.

Mild degrees of hydroureter are managed by bladder drainage alone in most patients because these problems are usually temporary and resolve gradually as edema subsides. Infection should be treated with appropriate antibiotics.

In patients undergoing radical hysterectomy and bilateral pelvic lymphadenectomy, postoperative ureteral damage from devascularization can be decreased by careful dissection and avoidance of electrocautery directly on the ureter (27).

Retrograde Pyelography

If an excretory urogram cannot be performed (e.g., because of dye sensitivity) or if the study is inconclusive, retrograde pyelography may be necessary. This procedure is potentially morbid and should be performed only if the information to be gained is critical to the decision regarding diversion of the affected kidney (27). Contrast injected beyond a high-grade obstruction can produce pyelonephritis and sepsis and may require urgent drainage through a percutaneous nephrostomy. The attempted passage of a retrograde ureteral catheter or stent may be useful for diagnosis, and it stents the ureter if the obstruction has not resulted from a misplaced suture ligature.

Percutaneous Nephrostomy

In patients with an obstructed ureter that cannot be decompressed by means of a retrograde ureteral stent, a percutaneous nephrostomy tube can be placed under fluoroscopic guidance (28). This procedure is relatively easy to perform and the tube can be changed or replaced as necessary. In addition, an antegrade ureteral catheter or stent can occasionally be passed through a nephrostomy to remove the percutaneous stent in patients in whom a retrograde catheter cannot be passed.

Ureteral Reanastomosis (Ureteroureterostomy)

When the ureter has been transected or damaged beyond repair, it must be revised and reanastomosed or reimplanted into the urinary bladder. If the ureteral injury is above the level of the pelvic brim, a simple reanastomosis is the procedure of choice. The two ends of the ureters are trimmed at a 45-degree angle. A double-J ureteral stent is passed into the distal ureter with one “memory” end inserted into the bladder. The proximal end of the ureter is placed over the stent and sutured to its distal counterpart (29). Interrupted 4-0 absorbable chromic or *Vicryl* sutures are placed at close intervals in a circumferential fashion (Fig.19.13). After several weeks, the absence of leakage can be established by means of an IVP, and the stent can be removed through a cystoscope.

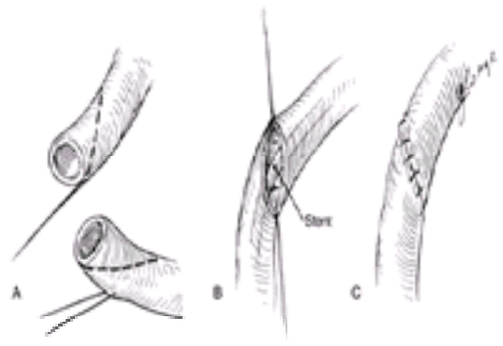


Figure 19.13 Ureteroureterostomy. A: The two ends of the ureters are cut diagonally. **B:** A ureteral stent is inserted into the proximal and distal ureter, and interrupted full-thickness sutures are placed. **C:** The completed anastomosis.

Ureteroneocystostomy

The reimplantation of the distal ureter into the bladder is known as the Leadbetter procedure, or ureteroneocystostomy. This operation is preferred for the ureter that has been disrupted distal to the pelvic brim, as long as the bladder can be sufficiently mobilized on the side of reimplantation (30,31). Integral to successful ureteral reimplantation is the creation of a submucosal tunnel (Fig.19.14). The tunnel minimizes the risk of vesicoureteral reflux and chronic, recurrent pyelonephritis (31).

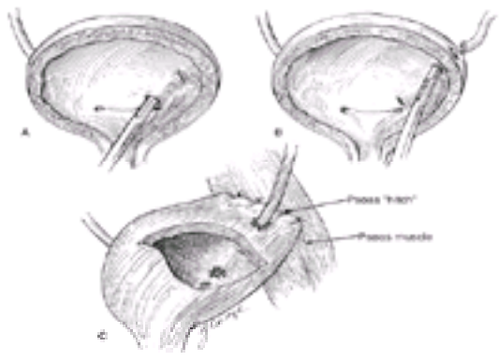


Figure 19.14 Ureteroneocystostomy. A: A submucosal tunnel is created. **B:**The ureter is brought into the bladder. **C:** The ureter is passed through the tunnel and sutured to the bladder serosa and mucosa. The serosa of the bladder is sutured to the psoas muscle to stabilize the anastomosis.

Figure 19.14 Ureteroneocystostomy. A: A submucosal tunnel is created. **B:**The ureter is brought into the bladder. **C:** The ureter is passed through the tunnel and sutured to the bladder serosa and mucosa. The serosa of the bladder is sutured to the psoas muscle to stabilize the anastomosis.

The technique is as follows:

1. The distal ureter is prepared by careful resection of any devitalized tissue while the maximum length is preserved.
2. The bladder base is mobilized, and the dome of the bladder is affixed laterally to the psoas muscle by means of a lateral cystopexy, a “psoas hitch.” This permits stabilization of the bladder as well as extension of the bladder toward the end of the resected ureter, and it is especially important if the ureter is somewhat foreshortened.
3. A cystotomy incision is made and the tunnel is initiated by injection of the submucosal plane with saline solution to raise the mucosa. The mucosa is incised and a tonsil forceps is inserted submucosally for a length of 1 to 1.5 cm to the site where the serosa is to be incised. An incision in the serosa is made over the pointed tip of the clamp to create an opening to the tunnel that passes through the muscularis and mucosa of the bladder wall.
4. The ureter is gently pulled through the submucosal tunnel, and mucosa-to-mucosa stitches are placed with interrupted 4-0 chromic suture material. A ureteric stent, preferably a soft plastic double-J, is passed up the ureter into the renal calyx, and the other end is placed in the bladder lumen. The site of entrance of the ureter is sutured to the bladder serosa with 4-0 chromic catgut or *Vicryl.*
5. A suprapubic cystostomy is performed, and the cystostomy is closed with two layers of interrupted 2-0 absorbable suture. The retroperitoneum is drained with a Jackson-Pratt drain. The ureteral stent is left in place 10 to 14 days and then removed through a cystoscope.

Transureteroureterostomy

Another procedure that can be useful in the carefully selected patient is the transureteroureterostomy. When the distal ureter must be resected on one side and the proximal ureter is too short to permit ureteroneocystostomy, it is possible to implant the distal end of the resected ureter into the contralateral side (32). The distal end of the partially resected ureter is tunneled under the mesentery of the sigmoid colon and approximated, end to side, into the recipient ureter. A ureteral stent is used to protect the anastomosis and is left in place for at least 14 days.

Permanent Urinary Diversion

Permanent urinary diversion must be performed after cystectomy or in patients who have an irreparable fistula of the lower urinary tract. Lower urinary tract fistulas can result from progressive tumor growth or from radical pelvic surgery and/or irradiation.

Urinary Conduit

The most frequently used techniques for urinary diversion are the creation of an *ileal conduit* (Bricker procedure) (33), the creation of a *transverse colon conduit* (26), and the creation of a continent urinary conduit (e.g., the Koch, Miami, or Indiana pouch) (34,35,36,37,38,39,40,41,42 and 43). The ileal conduit has been the most widely used means of permanent urinary diversion, and it is suitable for most patients. A segment of transverse colon can be used if the ileum has been extensively injured (e.g., by radiation therapy). The transverse colon is usually away from the irradiated field, and thus its vascularity is not compromised.

More recently, the *continent urinary conduit* has been developed; this may be helpful for gynecologic oncology patients who require exenterative surgery. The continent ileal conduit (or Koch pouch) requires a longer portion of the ileum (up to 100 cm), a longer operative time (4 to 6 hours), and the technical skills for creation of the continent conduit (35). Furthermore, in some patients a considerable portion of the small bowel may have sustained radiation damage from prior external-beam therapy. Therefore, the procedure may be unsuitable in many patients. The operation has the advantage of creating a conduit for which the patient need not wear an appliance, and the urine can be drained by self-catheterization. The continent stoma is created by intussusception of the small intestine so that it forms a stenotic distal lumen.

Another approach to the continent conduit involves the use of the *continent colon conduit.* In this operation, the intestine from the terminal ileum to the mid-portion of the transverse colon, including the entire ascending colon, the cecum, and the terminal ileum are used to create a urinary reservoir. The colon reservoir (the Indiana or Miami pouch) can be suitable for gynecologic oncology patients, especially those undergoing an exenteration (36,37,38,39,40,41,42 and 43). The Indiana and Miami pouches are technically somewhat easier to perform than the Koch pouch; however, the type of continent conduit created is usually determined by the training and preference of the surgeon.

Technique The technique for the creation of an ileal conduit involves the isolation of a segment of ileum at a site where the intestine appears healthy and nonirradiated. This is typically approximately 30 to 40 cm proximal to the ileocecal junction. The conduit requires a segment of ileum measuring approximately 20 cm and its associated mesentery (32). After isolation of the segment, the ileum is reanastomosed (Fig. 19.15). The ureters are implanted into the closed proximal end of the ileal segment, and double-J ureteric stents are placed into both ureters. A no. 8 pediatric feeding tube made of soft, flexible plastic can also be used for the ureteric stent because it is relatively atraumatic. The “butt” end of the conduit is sutured to the area of the sacral promontory.

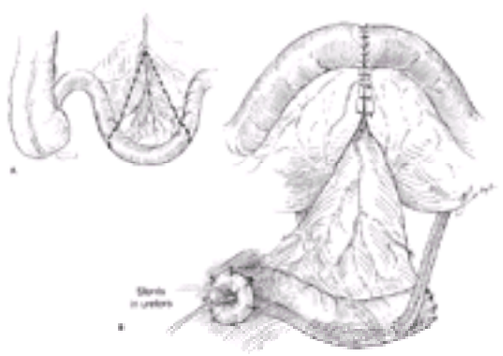
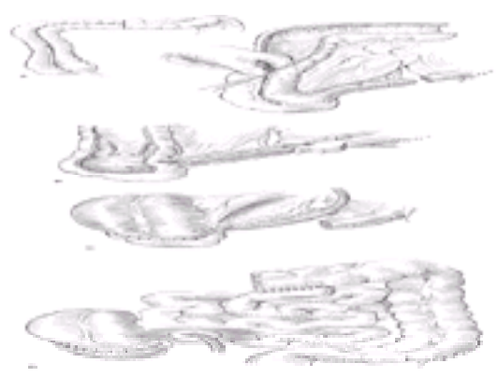


Figure 19.15 Ileal urinary conduit. A: A segment of nonirradiated ileum is used for the conduit. **B:** The ileum is reanastomosed, and the ureters are sewn into the “butt” end of the conduit. Note that the ureters are stented individually.

The distal end of the conduit is brought through the anterior abdominal wall of the right lower quadrant, approximately midway between the umbilicus and the anterior superior iliac crest. The ureteral stents should be left in place for approximately 10 days.

When a transverse colon conduit is selected, the technique is essentially the same. Care must be taken in both techniques to ensure that the vascularity of the intestinal mesentery is not interrupted. The mesentery of the reanastomosed bowel must be reapproximated to prevent herniation of intestinal loops through the defect.

The technique for creation of a Koch pouch has been well described (35). The technique for creation of the Miami pouch (37,38,39,40,41,42 and 43) involves isolation of the intestine from the last 10 to 15 cm of ileum to the mid-portion of the transverse colon. The colon is opened along the antimesenteric border through the taenia coli (Fig. 19.16A). The ileum is used to create the continence mechanism (Fig. 19.16B). The ileocecal valve serves as the principal portion of the mechanism; the terminal ileum is narrowed and several pursestring sutures are placed near the valve to reinforce the continence portion of the conduit (Fig. 19.16C). The ascending colon is sutured or stapled to the transverse colon to create a pouch. An ileotransverse anastomosis is performed to reconstitute the intestine (Fig. 19.16D).



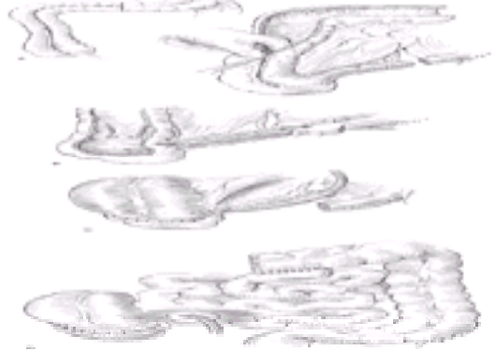


Figure 19.16 Colon continent urinary conduit—the Miami pouch. A: A segment of distal ileum and ascending and transverse colon is isolated, and the segment is opened on its antimesenteric border along the taenia coli. **B:** The ureters are reimplanted into the mesenteric side of the ascending colon, a continence mechanism is created with pursestring sutures, and a double staple line is performed with a gastrointestinal anastomosis (GIA) stapler. *(continued)* **C:** The conduit is closed and the ileal stoma is created. **D:** The intestines are reconstituted with an ileotransverse anastomosis.

Skin Ureterostomy

In rare instances, a terminally ill patient undergoing exploratory surgery has a bladder fistula. In such circumstances, one ureter can be ligated and a skin ureterostomy can be created with the other ureter. The ureter is mobilized from its attachments and brought laterally through the retroperitoneal space to the lateral and anterior abdominal wall. The ureter is tunneled through the fascia and brought out through a stab incision in the skin, where it is affixed to create a small stoma (27).

Reconstructive Operations

Reconstructive operations, particularly pelvic floor reconstruction and creation of a neovagina, are important in patients who are undergoing extensive extirpative procedures such as pelvic exenteration (14,15). Vaginal reconstruction helps to provide support to the pelvic floor, thereby reducing the prospect of perineal herniation. By helping to fill the pelvis, vaginal reconstruction also decreases the incidence of enteroperineal fistulas. Pelvic floor reconstruction should be performed in all patients undergoing a pelvic exenteration, and vaginal reconstruction should be performed simultaneously in most patients. The surgeon must be well acquainted with the types of graft that can be used in the performance of these reconstructive operations and the techniques necessary to accomplish them (44).

Grafts

Grafts used for reconstructive operations in the pelvis are either skin grafts, which can be full- or partial-(split) thickness (44,45 and 46), or myocutaneous grafts, which are composed of the full thickness of the skin, its contiguous subcutaneous tissues, and a portion of a closely associated muscle (47,48,49,50,51,52,53,54,55,56,57,58 and 59). The most frequently used myocutaneous pedicle grafts contain muscle segments from the rectus abdominis muscle of the anterior abdominal wall, gracilis muscle of the inner thigh, the bulbocavernosus muscle of the vulva, the tensor fascia lata muscle of the lateral thigh, and the gluteus maximus muscle.

Skin Grafts

Skin grafts must be harvested under sterile conditions (44). The donor site most frequently used to obtain a split-thickness skin graft is either the anterior and medial thigh or the buttock. Although the thigh may be more readily accessible to the surgeon, the buttock donor site has cosmetic advantages; however, this latter site may be more uncomfortable in the postoperative recovery period. The selection of the donor site should be made before surgery after discussion with the patient.

A dermatome is used to harvest the skin graft. Several different types of dermatome are available, including the Brown air-powered, electrically driven dermatome (Zimmer, Dover, Ohio) and the Padgett hand-driven dermatome (Poolgett Inc., Kansas City, Missouri). The surgeon should select the instrument with which he or she has the greatest facility because an equally good graft can be harvested with either one. The technique for obtaining the skin graft is as follows:

1. The graft width and thickness can be determined by adjusting the settings of the dermatome. A split-thickness graft can be obtained by setting the thickness between 14 and 16 one-thousandths of an inch. Full-thickness grafts are 20 to 24 one-thousandths of an inch.
2. When using the dermatome, the surgeon must apply firm, steady pressure to harvest a graft of uniform thickness. To minimize friction, mineral oil is applied to the skin over which the dermatome is to be passed.
3. The skin to be taken is stretched and flattened by the surgical assistant with the use of a tongue depressor. A second assistant picks up the leading edge of the graft as it is being harvested.
4. The harvested graft is kept moist in saline solution while the recipient site is being prepared.
5. The graft may be “pie crusted” by making small incisions in the surface. This technique maximizes the dimension of the graft while permitting the escape of fluid that might otherwise accumulate between the graft and the recipient site. However, extensive pie crusting may result in contracture when the graft is used to create a neovagina.

Pedicle Grafts

The purpose of the pedicle graft is to provide a substantial amount of tissue along with its blood supply either to repair an anatomic defect or to create a new structure, such as a neovagina (44,45,46,47 and 48). The pedicle graft can be either a full-thickness skin and subcutaneous tissue graft, as is used frequently for closure of a vulvar defect (e.g., a Z-plasty to create a rhomboid flap), or a myocutaneous graft (e.g., rectus abdominis or gracilis).

Before harvesting a pedicle graft, the surgeon should carefully outline the incisions on the skin with a marker pen. During mobilization of the myocutaneous pedicle, the surgeon must carefully isolate and preserve the neurovascular bundle that supplies the muscle.

Vaginal Reconstruction

Vaginal reconstruction in the gynecologic oncology patient is performed either to revise or replace a vagina that has stenosed as a result of prior vaginal surgery and/or radiation, or to create a neovagina when the vagina has been removed (45).

Split-Thickness Graft

When the vagina is fibrotic after irradiation, the scarred vaginal tissue first must be resected before placement of the split-thickness skin graft (45). The skin graft is placed over a vaginal stent that is then inserted into the space created by resection of the old, scarred vagina (Fig. 19.17A). The Heyer-Schulte stent is the vaginal stent preferred for this purpose because it is inflatable, can be easily removed and replaced by the patient, and has its own drainage tube (Fig. 19.17B).

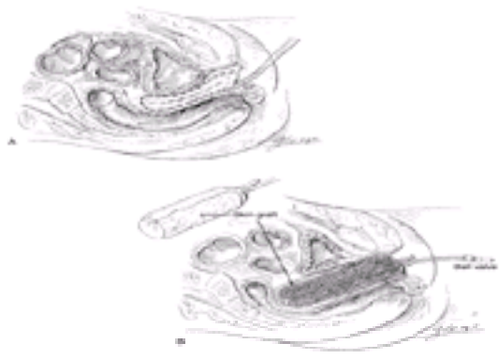


Figure 19.17 Creation of neovagina after radiation. A: The vaginal scar is resected in preparation for vaginal reconstruction with split-thickness skin grafts. **B:** The skin graft is placed around a Heyer-Schulte vaginal stent, and this is inserted into the pelvic space to create a neovagina.

Split-thickness skin grafts can also be used in patients undergoing exenteration, but this approach is less satisfactory than the use of myocutaneous pedicle grafts, as discussed later. When an anterior exenteration is performed, or when a portion of the rectosigmoid colon is resected but primarily reanastomosed, a neovagina can be created with the use of skin grafts. The omentum is mobilized by ligating and dividing the short gastric vessels along the greater curvature of the stomach, preserving the left gastroepiploic pedicle (Fig. 19.18A). The omentum is then placed into the pelvis and sutured to the rectosigmoid posteriorly and laterally to create a pocket for the neovagina. Split-thickness skin grafts are harvested, sewn over a vaginal stent, and inserted into the newly created pelvic space (Fig. 19.18B).

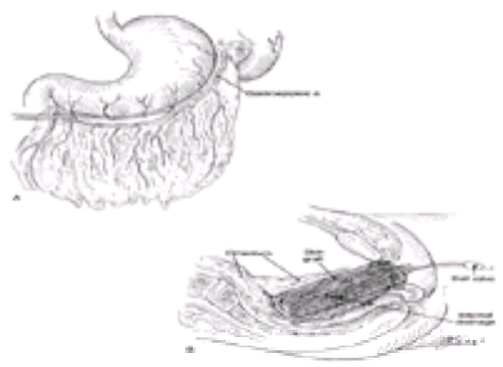


Figure 19.18 Mobilization of the omentum. A: The right gastroepiploic artery and the short gastric arteries are ligated and divided along the greater curvature of the stomach. **B:** The omentum is used to create a pocket for the placement of a split-thickness skin graft.

Transpelvic Rectus Abdominis Myocutaneous Pedicle (TRAM Flaps) Grafts

A single rectus abdominis pedicle graft can be used to create a neovagina (47,48 and 49) or to repair a pelvic or perineal defect (50,51). This is our preferred technique for creating a neovagina during a pelvic exenteration (Fig. 19.19). The technique is relatively straightforward and has the advantage of a single pedicle harvested from the same site as the abdominal incision used to perform the exploratory surgery. This approach avoids the use of separate incisions on the inner aspects of the thigh, as are needed for the gracilis myocutaneous pedicle graft (see later). The disadvantage is that the amount of tissue that can be mobilized from the anterior abdomen is limited, and thus the ability to adjust the size of the neovagina is somewhat limited. If too large a pedicle is created, there will be too much tension for the abdominal closure, and this can also create distortion of the anterior abdominal wall skin.

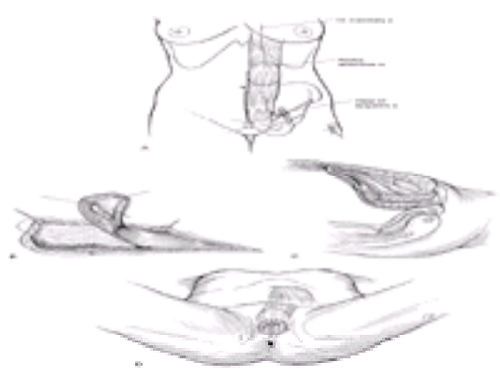


Figure 19.19 The transpelvic rectus abdominis myocutaneous (TRAM flap) pedicle graft. A: The location of the myocutaneous pedicle flap of the rectus abdominis muscle is shown. **B:** The pedicle is harvested, and the tubular neovagina is created by suturing the full thickness of the muscle, subcutaneous tissue, and skin of the anterior abdominal wall. **C:** The pedicle graft is brought down into the pelvis and the leading edge is sutured to the preserved vaginal introitus. *(continued)* **D:** The final result is a neovagina that also helps to protect the pelvic floor from intestinal adhesions.

The pedicle location is shown in Fig. 19.19A. The oval-shaped pedicle should measure approximately 6 to 8 × 10 cm. The skin of the pedicle is incised and the cephalad portion of the rectus abdominis muscle and attached myofascial tissues are transected (Fig. 19.19B). The tubular neovagina is created by suturing together the sides of the pedicle. One end is left open, and this becomes the distal neovagina. The pedicle is harvested, mobilized, and brought into the pelvis (Fig. 19.19C). The pedicle graft is then sutured to the preserved vaginal introitus to complete the procedure (Fig. 19.19D).

Gracilis Myocutaneous Pedicle Grafts

Bilateral gracilis myocutaneous pedicle grafts can be used to construct a neovagina (44,45,52,53). These grafts also provide excellent support for the pelvic viscera. The gracilis myocutaneous graft is harvested (Fig. 19.20A) from the inner aspect of the thigh. A line is drawn from the pubic tubercle to the medial epicondyle delineating the anterior margin of the graft. The graft should be approximately 5 cm wide and 10 cm long. A skin bridge is preserved between the vulva and the pedicle. The myocutaneous pedicle graft is mobilized by transecting the gracilis muscle distally in continuity with the skin and subcutaneous tissue (Fig. 19.20B). The vascular pedicle is proximal, and it must be carefully identified and preserved.

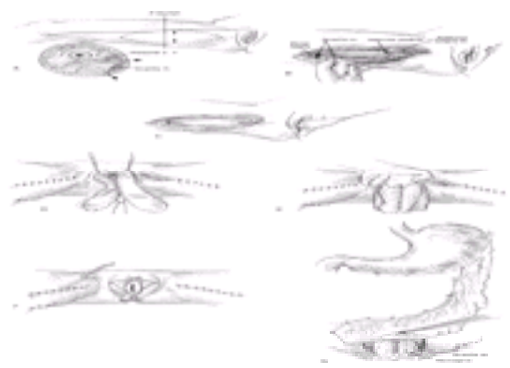


Figure 19.20 The gracilis myocutaneous pedicle graft. A: The pedicle graft is outlined on the inner thigh overlying the gracilis muscle. **B:** The myocutaneous pedicle graft is mobilized. **C:**The pedicle is brought under the skin bridge of the vulva. **D,E:** The two grafts are sutured together. **F:** The neovagina is placed into the pelvis and sutured to the introitus. **G:** An omental pedicle is used to cover the graft. (Reproduced from Berek JS, Hacker NF, Lagasse LD. Vaginal reconstruction performed simultaneously with pelvic exenteration. Obstet Gynecol 1984;63:318–323, with permission from the American College of Obstetricians and Gynecologists.)

The pedicle is harvested, brought under the skin bridge of the vulva, and exteriorized through the introitus (Fig. 19.20C). The two grafts are sutured together to create a hollow neovagina (Fig. 19.20D,Fig. 19.20E). The entire neovagina is placed into the pelvis by posterior and upward rotation and sutured to the introitus (Fig. 19.20F).

The apex is sutured to the symphysis pubis and/or the anterior sacrum. At the completion of the procedure, an omental pedicle is brought down over the graft to reconstruct the pelvic floor (Fig. 19.20G).

Bulbocavernosus Pedicle Grafts

The bulbocavernosus myocutaneous pedicle graft has been used for repair of radiation-induced rectovaginal fistulas (Martius procedure), but the procedure has been adopted for the creation of a neovagina (54,55). The procedure is performed by making an incision over the labium majus, isolating the bulbocavernosus muscle superiorly and anteriorly, and mobilizing it on a posterior vulvar pedicle. The graft is tunneled under a skin bridge at the posterior introitus and sutured to the pedicle of the other side.

Colon Segment

Some authors have preferred to use a segment of colon to create a neovagina (44,46). This technique has had mixed success in the past, but an approach using a portion of the ascending colon may be an improvement over earlier procedures.

Vulvar and Perineal Reconstruction

Whenever feasible, the vulva should be closed primarily after radical vulvectomy (56,57,58,59 and 60). With radical local excision or a separate incision approach for the groin dissection, primary closure of the vulvar skin can be accomplished in almost all patients.

Rhomboid Pedicle Graft

If there is any tension on the skin edges, the skin can be mobilized by means of a Z-plasty using the adjacent skin and subcutaneous tissue. This is called a *rhomboid flap* (56). The technique (Fig. 19.21) involves the repositioning of a rhomboid flap of full-thickness skin and subcutaneous tissue. Use of these pedicle grafts usually allows for primary closure of vulvar defects after radical vulvar surgery, but, if necessary, a split-thickness skin graft can be used. Myocutaneous pedicle grafts, such as a unilateral gracilis graft, can also be used to cover a large vulvar defect.

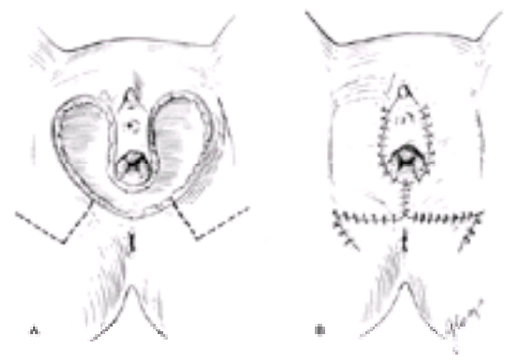


Figure 19.21 A: The rhomboid flap is used to close a posterior vulvar defect. **B:** The pedicle grafts are bilateral Z-plasties that are sutured together in the midline.

Tensor Fascia Lata Pedicle Graft

The tensor fascia lata pedicle graft, harvested from the lateral aspect of the thigh, can be useful in covering large defects of the lower abdomen, groin, and anterior vulva (57). The flap is particularly useful in patients who require extensive resection of large groin recurrences or large, fixed groin nodes.

The graft is obtained by harvesting a myocutaneous pedicle from its proximal origin at the anterosuperior aspect of the iliac bone to its distal insertion on the lateral condyle of the tibia (57). The length of the proposed flap is determined by measuring the distance from the muscle's vascular supply, located 6 to 8 cm distal to the anterior superior iliac spine, to the most inferior or distal point of the recipient site (e.g., the posterior vulva). The blood supply is from the lateral circumflex femoral artery located deep to the fascia lata between the rectus femoris and the vastus lateralis. The posterior border of the graft is defined as a line from the greater trochanter of the hip down to the knee, and the distal border is located approximately 5 cm proximal to the knee. The width of the flap is determined by the width of the defect to be covered, but typically it is 6 to 8 cm with a length of up to 40 cm.

The pedicle graft is harvested after the defect has been created to permit a more accurate measurement of the flap. The flap is first incised distally, and care is taken to avoid injury to the proximal blood supply. Once the flaps are elevated, they are rotated into place and sutured from their most distal point to the proximal. The donor site is closed primarily.

Gluteus Maximus Pedicle Grafts

The gluteus maximus muscles, or a portion thereof, can be used to reconstruct the pelvic floor and the perineum (58,59). This approach might be particularly useful for very large defects, such as those patients who have undergone a total infralevator pelvic exenteration (see Chapter 21).

Vulvovaginoplasty

Although the preferred methods for vulvar and vaginal reconstruction are outlined in the preceding sections, occasionally it is necessary to perform a vulvovaginoplasty, the so-called *William's procedure.* This procedure (60) involves the incision of a horseshoe-shaped flap on the vulva to create a marsupialized pouch that can be used as a neovagina. This operation has the advantage of being relatively simple to perform, and it does not require pelvic dissection. It has the disadvantage of being less anatomically suitable for vaginal intercourse, but its direction can improve with regular use. It may be helpful in a patient who has undergone a pelvic exenteration without vaginal reconstruction.

Pelvic Floor Reconstruction

At the completion of a pelvic exenteration, the pelvic floor must be reconstructed. Probably the most effective procedure is to perform an omental pedicle graft (provided there is sufficient omentum) and to use myocutaneous pedicle grafts whenever possible to reconstruct the vagina. In patients in whom this is not possible, alternatives include the use of a variety of graft materials, either natural or synthetic. A natural material that has been used is dura mater, but this is often unavailable (61,62). All areas that can be directly peritonealized should be carefully covered with peritoneal pedicle grafts. Synthetic grafts using Marlex (Ethicon, Somerville, New Jersey) have been associated with a high incidence (>20%) of infectious morbidity and are therefore much less desirable. However, if a pedicle graft is not feasible, the synthetic material Gore-Tex (Gore, Flagstaff, Arizona) may be the best alternative.

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20 Laparoscopy

Kenneth D. Hatch

Laparoscopy has been widely accepted for numerous operative procedures. Laparoscopy performed with the assistance of video monitors has become the preferred technique because the surgeon can view the operation in real time.

An example of a well accepted use of the laparoscope is for the performance of cholecystectomy. This procedure was adapted by surgeons and accepted by the public because of its associated short hospital stay, quick recovery time, and rapid return to full activity. However, the procedure was incorporated into surgical practice before prospective trials could be established to evaluate its feasibility, morbidity, and cost effectiveness compared with the standard laparotomy. The same criticisms may be made in gynecology for such procedures as laparoscopically assisted vaginal hysterectomy, removal of adnexal masses, and management of endometriosis, which are widely performed by virtually thousands of gynecologists.

In gynecologic oncology, however, there has been a unique opportunity to study the use of operative laparoscopy in a prospective fashion, because of the limited number of specialists in gynecologic oncology performing the procedures, and the need to perform pelvic and/or paraaortic lymphadenectomy to stage several gynecologic malignancies.

Laparoscopic Pelvic and Paraaortic Lymphadenectomy

The performance of a pelvic and paraaortic lymphadenectomy, either a *partial lymphadenectomy (lymph node sampling)* or *complete lymphadenectomy*, is the key procedure for the staging of gynecologic malignancies.

In 1989, Dargent and Salvat (1) in France used the laparoscope to perform limited pelvic lymphadenectomy in women with cervical cancer. This was not widely accepted because of its limited access to the pelvic lymph nodes and the inability to evaluate the lymph nodes in the common iliac and paraaortic chains. In 1991, Childers and Surwit (3) described pelvic and paraaortic lymphadenectomy performed in conjunction with a laparoscopically assisted vaginal hysterectomy and bilateral salpingo-oophorectomy in two women with endometrial cancer. In 1992, Nezhat et al. (2) published a case of laparoscopic radical hysterectomy and pelvic and paraaortic lymphadenectomy, although the dissection went only 2 cm above the aortic bifurcation, an inadequate evaluation. These early publications were limited case reports that gave no information on morbidity, mortality, or complications.

As experience increased, published series from individuals or institutions confirmed shortened hospital stays. Some information on morbidity, complications, and comparability of the procedure with standard operations has been presented (Table 20.1).

Author	No. of Patients	Laparotomy	Additional Lymph Nodes	Additional Positive Lymph Nodes
Querleu, et al. (1991) (4)	39	32	NR	0
Childers, et al. (1992) (6)	8	5	2.8	0
Fowler, et al. (1993) (7)	12	12	7	0
Total	59	49	—	0

NR, not reported.

Table 20.1 Laparoscopic Lymphadenectomy

Querleu et al. (4) performed transperitoneal laparoscopic pelvic lymphadenectomy in 39 patients with cervical cancer. Five patients had metastatic lymph nodes and were treated with radiation therapy. Thirty-two patients underwent abdominal radical hysterectomy and evaluation of the completeness of the laparoscopic lymphadenectomy. The sensitivity for node positivity by laparoscopy was 100%. However, the number of additional lymph nodes found at laparotomy was not stated.

Childers et al. (5) reported 59 patients with endometrial cancer who were staged laparoscopically, followed by vaginal hysterectomy and bilateral salpingo-oophorectomy. Six patients were found to have intraperitoneal disease and did not undergo lymphadenectomy. Twenty-two patients had grade 1 disease with less than one-half myometrial invasion and did not have a lymphadenectomy. Thirty-one patients should have had lymph node staging, but obesity precluded it in two patients, giving a feasibility rate of 93%. Three major and three minor complications were reported. The surgical complications were experienced early in the series and led to alternative techniques as the series progressed. The average hospital stay was 2.9 days, but the operative time, lymph node counts, and cost analysis were lacking.

These early series emphasized pelvic lymphadenectomy, but it remained necessary to do paraaortic lymphadenectomy for laparoscopy to be fully accepted as a technique to stage all gynecologic malignancies. Childers et al. (6) reported both pelvic and paraaortic lymphadenectomy in 16 of 18 patients being treated for cervical cancer. Two patients did not have paraaortic lymphadenectomies because of obesity. Paraaortic lymphadenectomies were performed from the right side of the aorta and included the entire chain from the duodenum to the bifurcation. Eight of the 18 patients underwent laparoscopic staging before planned radical hysterectomy. Three of the eight patients had positive pelvic lymph nodes at the time of laparoscopy and were treated with radiation therapy. The remaining five patients had radical hysterectomies immediately after the laparoscopic lymphadenectomy. The average number of lymph nodes removed at laparoscopy was 31, with an average of 3 additional lymph nodes being found at laparotomy. There were no additional positive pelvic or paraaortic lymph nodes found on laparotomy. For those patients having laparoscopy alone, the average hospital stay was 1.5 days, blood loss 50 mL, and operative time 75 to 175 minutes.

Fowler et al. (7) performed laparoscopic lymphadenectomies on 12 patients with cervical cancer. Two of those had right-sided paraaortic lymphadenectomy performed to the level of the inferior mesenteric artery. All patients underwent laparotomy after the laparoscopic dissection to evaluate the completeness of the lymphadenectomy. An average of 23 lymph nodes was removed by laparoscopy and an additional 7 lymph nodes were removed by laparotomy. There were two patients with positive lymph nodes, and both of these were identified by laparoscopy. The “learning curve” was documented by showing an increase in the percentage of lymph nodes removed by laparoscopy from 63% in the first six patients to 85% in the second six patients. Most important, all of the positive lymph nodes were identified and removed using the laparoscope.

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Childers et al. (8) summarized the Arizona experience in paraaortic lymphadenectomy through 1993 with a report of 61 women with cervical, endometrial, or ovarian cancer. In three patients (5%), obesity prevented the completion of the surgery, and in one patient (0.8%) adhesions were responsible for failure. Lymph node counts were available in 23 patients: for the right-sided dissection, there was an average lymph node count of 3. The six patients who underwent a bilateral paraaortic lymphadenectomy had an average of six nodes removed. The authors also described four patients with lymph nodes sampled above the inferior mesenteric artery. Operative times for the paraaortic lymphadenectomy ranged from 25 to 70 minutes, and hospital stay for the 33 patients with laparoscopic lymphadenectomy was only 1.3 days. There was one vena caval injury that required transfusion and laparotomy, a rate comparable with that of open surgery.

In 1994, Querleu and LeBlanc (9) described a laparoscopic infrarenal paraaortic lymphadenectomy for staging of cancer of the ovary or fallopian tube in nine patients. An average of nine nodes were removed, with an operative time of 111 minutes, an average postoperative stay of 2.8 days, and blood loss less than 300 mL in all patients. None of the lymph nodes was positive.

Spirtos et al. (10) in 1995 reported 40 patients with bilateral partial paraaortic lymphadenectomy (sampling). Five laparotomies were performed, two to remove unsuspected metastases, two for control of hemorrhage, and one because of equipment failure. In two patients, the left-sided dissection was judged to be inadequate, which is an overall failure rate of 12.5%. An average of eight paraaortic lymph nodes were removed: four from the right side and four from the left side. Most of the patients also underwent a pelvic lymphadenectomy and hysterectomy. The mean operative time was 3 hours, 13 minutes. The average hospital stay was 2.9 days.

Possover (11) reported the accuracy of laparoscopic assessment of the pelvic and paraaortic lymph nodes. Eighty-four patients with cervical cancer underwent laparoscopic lymphadenectomy. The surgeon classified the lymph nodes as positive or negative by visualization. The sensitivity and specificity of visualization was 92.3%. When frozen-section analysis was combined with laparoscopic assessment, 100% of the positive lymph nodes were identified. In 13 of the 84 patients, the treatment plan was altered during surgery based on these findings.

Possover et al. (12) analyzed videotapes of 112 paraaortic lymphadenectomies and detailed the ventral tributaries of the infrarenal vena cava. They divided the vena cava into three levels based on the distribution of venous tributaries. This is a significant contribution to anatomic knowledge and is an important guide for beginning laparoscopic surgeons.

A perforator of the inferior vena cava at the level of the bifurcation of the aorta is shown in Fig. 20.1A. A diagram of the most common sites where perforators are encountered during a paraaortic lymphadenectomy is shown in Figure 20.1B.

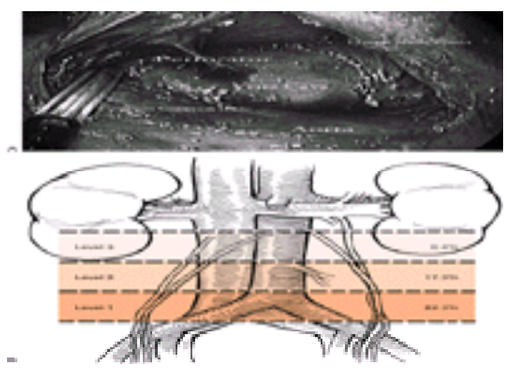

Figure 20.1 Perforators of the vena cava. A: **A vena cava perforator at the level of the bifurcation of the aorta.** B: **Diagram of the most common sites where perforators are encountered during the performance of a paraaortic lymphadenectomy.** The figure shows the anatomic distribution of 237 venous tributaries in 112 patients undergoing laparoscopic lymphadenectomy according to different levels of the inferior vena cava. (From Possover M, Plaul K, Krause N, Schneider A. Left-sided laparoscopic para-aortic lymphadenectomy: anatomy of the ventral tributaries of the infrarenal vena cava. *Am J Obstet Gynecol* 1998;179:1295–1297, with permission.)

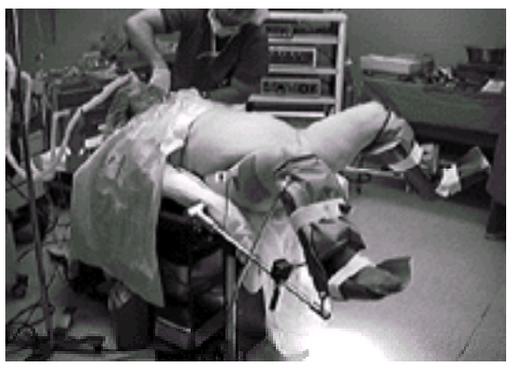

Figure 20.2**Patient position for laparoscopically assisted radical hysterectomy.**

These studies have demonstrated the ability of laparoscopic surgeons to perform pelvic and paraaortic lymphadenectomy. **The American Medical Association Physicians Current Procedure Terminology (CPT 95) first listed laparoscopic pelvic lymphadenectomy and paraaortic lymph node "sampling" in 1995.** Since then, laparoscopic surgery has been used by more oncologic surgeons and has been applied to nearly every disease site in gynecologic oncology.

Indications for Laparoscopic Surgery

The indications for laparoscopic surgery are presented in Table 20.2. These procedures are discussed in the following sections. The advantages and disadvantages of laparoscopy in gynecologic cancer are presented in Table 20.3.

Accepted	Proposed
Endometrial cancer staging	Laparoscopic radical hysterectomy
Laparoscopic hysterectomy	Ovarian cancer staging
Cervical cancer staging	Ovarian cancer debulking
Laparoscopically assisted Schauta operation	Evaluation for exenteration
Second-look laparoscopy	

Table 20.2 Indications for Laparoscopic Surgery

Table 20.2 Indications for Laparoscopic Surgery

Advantages	Disadvantages
Less blood loss	More complications early in operator experience
Shorter hospital stay	Longer operating time
Less ileus	Reliance on technical support
Less pain	Slightly increased costs until expertise achieved
Less pulmonary embolus	Lack of training programs
More rapid return to full activity	
High patient acceptance	

Table 20.3 Laparoscopy for Gynecologic Cancer

Endometrial Cancer

Most women with endometrial cancer present with disease confined to the uterus. The treatment consists of total hysterectomy, bilateral salpingo-oophorectomy, and surgical staging, which includes peritoneal washings, inspection of the abdomen, and retroperitoneal lymph node sampling. **Surgical staging with operative laparoscopy followed by vaginal hysterectomy has been proposed as an alternative to laparotomy** (3,13,14 and 15).

Childers et al. (5,6) reported two patients in 1992 who underwent laparoscopic staging of the retroperitoneal nodes followed by vaginal hysterectomy and bilateral salpingo-oophorectomy, and presented the first large series in 1993. Laparoscopic staging was performed successfully in 93% of the patients, with obesity noted as a limiting factor. Two patients had complications related to the hysterec tomy: one had a transected ureter caused by the endoscopic stapler and one had a cystotomy. The endoscopic stapler is not recommended for use on the cardinal ligaments during a laparoscopically assisted vaginal hysterectomy.

Spirtos et al. (13) reported 13 patients who underwent laparoscopic staging and hysterectomy and compared them with 17 patients who underwent laparotomy. The laparotomy group required significantly longer hospitalization than the laparoscopic group (6.3 vs. 2.4 days, $p < 0.001$), incurred higher overall hospital costs ($19,158 vs. $13,988, $p < 0.05$), and took longer to return to normal activity (5.3 weeks vs. 2.4 weeks, $p < 0.0001$). The patients having laparotomy were significantly more obese and had a higher Quetelet (16) index (30.2 vs. 24.2).

The effect of surgical experience has been demonstrated by Melendez et al. (14). In the first 100 patients with endometrial cancer, the operative time for staging decreased from a mean of 196 minutes for the first 25 patients to 128 minutes for the last 25 patients. Hospital stay decreased from 3.2 days to 1.8 days. **The decrease in operative time and hospital stay, coupled with the diminished use of expensive, disposable instruments, has led to a significant cost savings for laparoscopy. More important are the social benefits to the individual patients.**

Long-term results concerning recurrence rates after laparoscopy have not been reported. Gemignani and coworkers (15) indicated a recurrence rate for laparoscopy of 4.5% with a mean follow-up of 12.4 months, compared with a recurrence rate of 13.9% with median follow-up of 24 months after laparotomy.

The Gynecologic Oncology Group (GOG) began a multicenter trial in 1992 to validate laparoscopic staging and laparoscopically assisted vaginal hysterectomy with bilateral salpingo-oophorectomy as an appropriate method of treatment of endometrial cancer. Based on its evaluation by the Gynecologic Surgery Committee, the technique was granted acceptance in 1996 (despite no published data). Today, laparoscopic surgery is an important modality in the treatment of endometrial cancer.

Cervical Cancer

The use of laparoscopy in the treatment of cervical cancer has been limited by the fact that there did not appear to be an advantage to laparoscopic lymphadenectomy because the standard operation for the primary cervical tumor has been radical abdominal hysterectomy.

Dargent (17) **first suggested that laparoscopic pelvic lymphadenectomy could be followed by a Schauta radical vaginal hysterectomy, and has published the only long-term results of such a procedure. The 3-year survival rate of 51 patients with negative pelvic lymph nodes was 95.5%.** Querleu (18) reported eight patients and demonstrated an average blood loss of less than 300 mL, an average hospital stay of 4.2 days, and decreased pain from the elimination of an abdominal or perineal incision. Hatch et al. (19) reported 37 patients treated by laparoscopic pelvic and paraaortic lymphadenectomy followed by radical vaginal hysterectomy. The mean operative time was 225 minutes, the mean blood loss was 525 mL, and the average hospital stay was 3 days. Blood transfusion was required in 11% of the patients, compared with the range of 35% to 95% reported in the literature for radical abdominal hysterectomy. Complications occurred early in the series and included two cystotomies repaired at surgery without an increase in hospital stay or further complications. In two patients (5.4%), ureterovaginal fistulas developed that were treated by ureteral stents, which were removed 6 weeks later without further operative intervention.

Schneider and colleagues (20) reported on 33 patients in whom bipolar techniques were used for lymphadenectomy and to transect the cardinal ligaments and uterine vessels. Hysterectomy was completed by the Schauta-Stoeckel technique. There were five (15%) intraoperative injuries managed successfully without subsequent sequelae. Four patients required transfusion. Roy et al. (21) reported 52 patients in whom laparoscopic pelvic lymphadenectomy was followed by a radical vaginal hysterectomy in 25 cases or a radical abdominal hysterectomy in 27 cases. The two groups were comparable in blood loss (400 vs. 450 mL), operating time (270 vs. 280 minutes), blood transfusion (five vs. four patients), and postoperative stay of (7 days for both groups). There was an increase in febrile morbidity, wound infection, and ileus in the patients having abdominal radical hysterectomy. With a mean follow-up of 27 months, only one recurrence has been noted.

Radical Abdominal Hysterectomy

Although most reports in the literature have detailed some form of laparoscopically assisted radical vaginal hysterectomy, there also are reports of laparoscopic radical hysterectomy. Nezhat et al. (22) and Canis et al. (23) have reported laparoscopic radical hysterectomy in separate case reports. Spirtos et al. (24) reported laparoscopic radical hysterectomy (type III) with aortic and pelvic lymphadenectomy in ten patients. The average operative time was 253 minutes, length of hospitalization was 3.2 days, and blood loss was 300 mL; no transfusions were necessary. There were no intraoperative or postoperative complications.

The ability of laparoscopic pelvic lymphadenectomy adequately to identify all positive pelvic lymph nodes and to remove a sufficient number of lymph nodes for adequate staging has been demonstrated in the studies by Querleu et al. (4), Childers (5,6), and Fowler (7). The ability to treat the primary tumor adequately using the laparoscopically assisted Schauta procedure depends primarily on the surgeon. The large published series of Schauta operations by Massi et al. (25) and Dargent et al. (26) indicated that the Schauta procedure results in survival rates comparable with those achieved with the Wertheim-Meigs operation. The major obstacle to gaining wide acceptance has been the lack of surgical training and experience with the Schauta procedure, which leads to a high complication rate in the beginning of every series.

The issue of blood loss and transfusion has become very important to patients and surgeons since the identification of the human immunodeficiency virus. Every report on laparoscopic lymphadenectomy and radical hysterectomy has noted a significant decrease in blood loss and transfusion rates. Other societal advantages are the decreased hospital stay and rapid return to normal function, even with radical surgery.

Radical Vaginal Trachelectomy

In 1994, Dargent (17) first presented a series of 28 patients who underwent laparoscopic pelvic lymphadenectomy followed by radical vaginal trachelectomy. After a median follow-up of 36 months, there was only one recurrence in the paraaortic nodes of a 27-year-old patient with stage IB adenocarcinoma. The pelvic lymph nodes had been negative and the margins were free. Among the eight patients who desired pregnancy, three had cesarean section at 36 weeks' gestation and three had spontaneous abortions. The second report on radical vaginal trachelectomy was published in 1998 by Roy and Plante (27). Thirty patients underwent laparoscopic pelvic lymphadenectomy and radical vaginal trachelectomy; only six women had attempted pregnancy at the time of reporting, and four had healthy infants delivered by cesarean section. Despite these early successes, the procedure is still considered investigational for patients with small lesions who desire childbearing.

Ovarian Cancer

Laparoscopy has been used for several decades to manage adnexal masses and as a second-look procedure to avoid laparotomy in patients with persistent disease after primary chemotherapy. More recently, it has been reported to be useful for staging apparently early cancer of the ovary. The ability to perform retroperitoneal evaluation has seen it advocated again for second-look procedures.

Evaluation of the Suspicious Adnexal Mass

Laparotomy is accepted as the standard of care for management of the suspicious adnexal mass. However, it is possible to mismanage adnexal masses regardless of whether laparotomy or laparoscopy is used.

The incidence with which an unexpected malignancy is encountered when managing adnexal masses is reported to be between 0.4% to 2.9% (28,29 and 30). Childers et al. (31) and Canis et al. (32) used laparoscopy for management of suspicious adnexal masses and reported malignancy rates of 14% and 15%, respectively. More than 80% of the masses were managed by laparoscopy. All of the malignancies were properly diagnosed and treated, including 13 staged by laparoscopy. **It is important to perform a frozen-section analysis so that surgical staging and appropriate treatment are not delayed.** Staging requires an infracolic omentectomy, peritoneal washings, multiple biopsies from the peritoneal surfaces and right hemidiaphragm, and pelvic and paraaortic lymph node biopsies.

Several investigators have reported their experiences with staging of early ovarian cancer. Querleu and LeBlanc (9) described the first adequate laparoscopic surgical staging for ovarian carcinoma. Eight patients underwent laparoscopic paraaortic lymph node sampling up to the level of the renal veins. The number of paraaortic lymph nodes per patient ranged from 6 to 17. Childers et al. (33) reported 14 patients undergoing staging for presumed early ovarian cancer. Metastatic disease was discovered in eight (57%), and the appropriate treatment instituted. Boike and Graham (34) reported a stapling technique to perform an infracolic omentectomy on 13 patients. Possover (12) reported 13 patients staged with ovarian cancer, Pomel et al. (35) 10 patients, and Spirtos et al. (10) 4 patients. Thus, 62 patients have been reported in the literature as being staged by laparoscopy, although no long-term results are available. **Therefore, laparoscopy for the staging of ovarian cancer should still be considered investigational.**

The two major concerns over the use of laparoscopy for adnexal masses are (a) delay in diagnosis and thus treatment, and (b) rupture of the adnexal mass that is subsequently found to be malignant, which converts the stage from a possible IA to IC. Although studies on laparotomy show that if the tumor is removed and proper treatment instituted, rupture does not affect the outcome (36,37 and 38), it is prudent to avoid rupture to minimize any theoretical increase in the risk. If the tumor is ruptured, and the treatment is delayed, the prognosis is worsened (39). **Thus, the use of laparoscopy should be limited to suspicious masses that are small enough to be removed intact.**

Second-Look Laparoscopy

Laparoscopy was initially used before planned second-look laparotomy to identify residual disease and thus avoid the laparotomy. This strategy resulted in a reduction in the need for laparotomy by 50% (40).

Improvement in laparoscopic equipment has encouraged investigators to perform the entire second-look procedure by laparoscopy. Childers (33) reported 44 reassessment laparoscopies in 40 women. Twenty-four of the procedures were positive, including five that were only microscopically positive. Five patients (11%) had inadequate laparoscopies because of adhesions, and recurrent disease developed in all of them. Eight of the 20 (40%) patients who were negative later had recurrent disease. All of these data are similar to those obtained with second-look laparotomy. Abu-Rustum et al. (41) reported 31 women with second-look laparoscopy and compared them with 70 patients who had laparotomy and 8 who had both. The rates of positivity were 54.8%, 61.4%, and 62.5%, respectively. The recurrence rates after negative second-look were 14.8% for laparoscopy versus 14.3% for laparotomy. Clough et al. (42) reported 20 patients who had laparoscopy followed by laparotomy at the same surgery, with a positive predictive value of 86% (12 of 14 patients).

Complications

Complications of laparoscopy for malignant disease are higher than for benign disease (43). **The rate depends on the type of case and the experience of the surgeon. Laparoscopic second looks have the highest rate of injury to bowel because of the adhesions from previous surgery.** Vascular injuries from trocars or the dissection of lymph nodes can occur in any procedure.

Postoperative complications of wound infection, ileus, and fever occur, but at lower rates than after laparotomy. Herniation of omentum or bowel into the trocar sites is a complication unique to laparoscopy. Boike et al. (44) reported 19 cases from 11 institutions. No patient had a hernia through a port smaller than 10 cm, and therefore it is recommended that all port sites greater than 10 mm be closed. Kadar (45) reported a 0.17% rate of herniation among 3,560 laparoscopic operations.

Abdominal wall port-site metastases have been reported with nearly every tumor cell type, but are most common with ovarian cancer.

Technique

For endometrial cancer, a *partial lymphadenectomy (lymph node sampling)* is performed: the lymph nodes removed are those medial to the external iliac and superior to the obturator nerve. For cervical cancer, a complete lymphadenectomy is performed, including the lymph nodes between the iliac vessels and the psoas muscle, and the obturator space is dissected in its entirety.

Preoperative Preparation

Patient preparation begins with a clear liquid diet the day before the surgical procedure. Evacuation of the bowel may be accomplished with magnesium citrate or Go-Lytely. **It is important for the bowel to be collapsed during the laparoscopic lymphadenectomy so that proper exposure can be obtained. This is particularly important if the patient is somewhat obese and paraaortic lymphadenectomy is planned.**

Operative Approach

The recommended technique of laparoscopy is as follows:

1. **The patient is positioned in a dorsal lithotomy position with legs in stirrups that support the legs and decrease the tension on the femoral and peroneal nerves** (Fig. 20.2). **It is helpful to have adjustable stirrups that allow for conversion from the low lithotomy to a leg-flexed position for vaginal surgery.** The arms are tucked at the side, an endotracheal tube is positioned, and a Foley catheter is placed in the bladder.
2. **The first trocar is inserted into the umbilicus if the patient does not have a midline incision. If there is a midline incision, then a left upper quadrant insufflation and 5-mm trocar are used. The left upper quadrant approach for patients with previous midline incisions allows the laparoscope to be placed away from possible adhesions that can then be dissected from the umbilicus before placing the 10-mm trocar.**
3. **Additional trocars are then placed in the right and left lower quadrants and in the suprapubic site.** Typically, a 10-mm trocar is placed in the suprapubic site so that the laparoscope can be placed in that port to help with packing the bowel or in dissecting adhesions from around the umbilical port (see Fig. 20.2; Fig. 20.3).

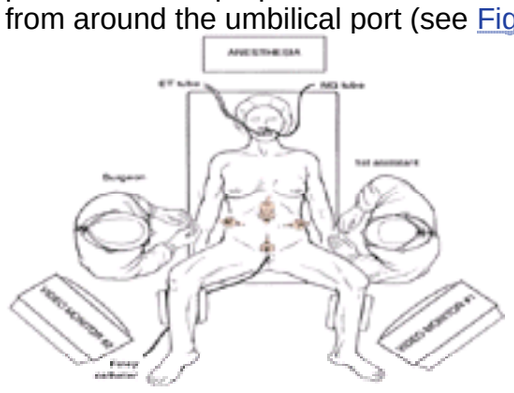

Figure 20.3 The position of the surgeons and placement of the trocars in the abdomen.

4. **The bowel should be carefully packed into the upper abdomen so that adequate exposure of the paraaortic area and pelvis can be obtained.** Sponges or minilaparotomy packs can be placed around loops of bowel to aid in exposure and to blot small amounts of blood. The principles of laparoscopic surgery are the same as those of laparotomy. There must be adequate exposure, identification of the anatomy, and removal of the appropriate tissue.
5. **The lymphadenectomies are best performed by the surgeon on the side opposite the side of dissection** (i.e., the surgeon on the patient's right side dissects the left pelvic lymph nodes). The peritoneal incisions are left open and drains are not placed.
6. **The paraaortic lymphadenectomy is usually performed first.** Both the right- and left-sided aortic lymph nodes are sampled. The peritoneum is incised between the sigmoid mesentery and the mesentery of the cecum. The lymph node chain is isolated and dissection is carried out using electrosurgical techniques as the primary mechanism of hemostasis. Monopolar surgery, bipolar surgery, and the argon beam coagulator have all been used successfully. The landmarks are usually the reflection of the duodenum and inferior mesenteric vessel superiorly and the psoas muscles laterally. The ureter must be identified and placed on traction by the assistant to keep it out of the operative field (Fig. 20.4).

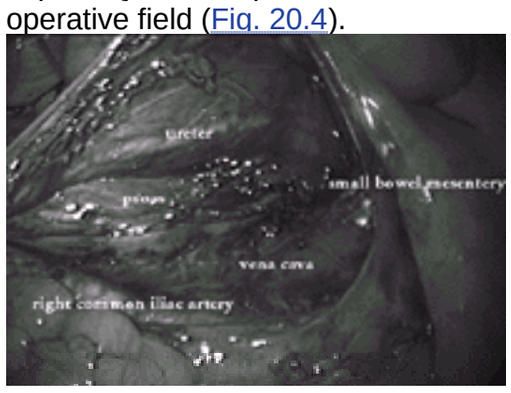

Figure 20.4 The right common iliac vessels and the vena cava after the removal of the right paraaortic lymph nodes.

7. **The proximal common iliac lymph nodes are dissected through the retroperitoneal incision made from the paraaortic lymph nodes down to the middle common iliac lymph nodes.** The remaining common iliac lymph nodes are dissected through the incision for the pelvic lymphadenectomy (Fig. 20.5).

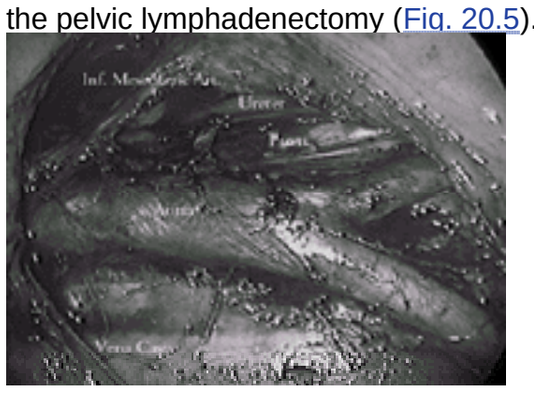

Figure 20.5 Completed bilateral common iliac and paraaortic lymphadenectomy.

8. **Dividing the round ligaments and finding the lateral pelvic space exposes the pelvic lymph nodes.** The obliterated umbilical artery is retracted medially, which opens the entire lateral pelvic space (Fig. 20.6).

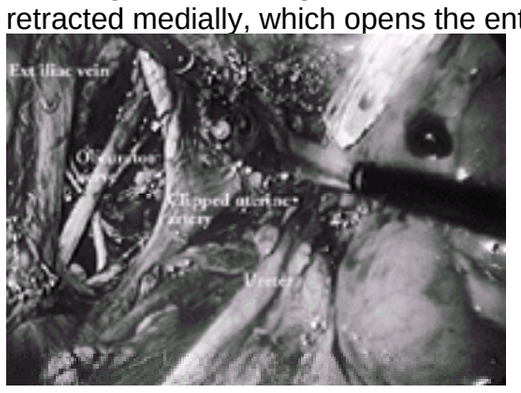

Figure 20.6 The left lateral pelvic space after a lymphadenectomy is completed and the uterine artery is clipped before a laparoscopically assisted radical vaginal hysterectomy.

9. **The disease and clinical circumstance, as outlined previously, determine the extent of the pelvic lymphadenectomy. To perform a *pelvic lymph node sampling*, the lymph nodes are removed medial to the external iliac and anterior to the obturator nerve. For a *complete lymphadenectomy*, the lymph nodes are also removed from between the iliac vessels and the psoas muscle, and from**

9. **The disease and clinical circumstance, as outlined previously, determine the extent of the pelvic lymphadenectomy. To perform a *pelvic lymph node sampling*, the lymph nodes are removed medial to the external iliac and anterior to the obturator nerve. For a *complete lymphadenectomy*, the lymph nodes are also removed from between the iliac vessels and the psoas muscle, and from the obturator fossa.**
10. **All port sites 10 mm or larger should have the fascia and peritoneal layers closed to prevent herniation of bowel.** Several instruments are available that pass the suture through the skin incision lateral to the port and back up on the opposite side. The skin is closed and a local anesthetic is injected around the port sites to decrease postoperative pain.

Postoperative Management

Patients are given liquids the day of surgery and the diet is advanced rapidly. Early ambulation is encouraged. The patient's progress is usually rapid. Adynamic ileus is unusual after laparoscopic surgery, but any abdominal distention, worsening of pain, or vomiting must be taken seriously. Unsuspected bowel injuries manifest themselves by abdominal distention, pain, and free air. The CO_2 should be absorbed within hours, so any free air in the abdomen is highly suspicious.

Summary

The skills to manage gynecologic malignancies by laparoscopic techniques are acquired through a commitment on the surgeon's part to learn the technique. It requires up-to-date equipment and a team familiar with the procedures. Hands-on experience in an animal laboratory and proctored learning in the operating suite are highly recommended. In properly selected patients, laparoscopic surgery appears to result in shorter hospital stays, earlier return of function, and results comparable with laparotomy, although the results of prospective, randomized trials are awaited.

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21 Pelvic Exenteration

Kenneth D. Hatch

The first series of pelvic exenterations for gynecologic cancer was published in 1946 by Alexander Brunschwig (1). This initial report was of 22 patients, 5 of whom died of the operation itself. **H**is original procedure included sewing both ureters into the colon, which was then brought out as a colostomy. Since these beginnings, there have been major improvements in the selection of patients, operative technique, blood product use, antibiotic availability, and intensive medical management.

The operation gained wider acceptance when Bricker (2) published his technique of isolating a loop of ileum, closing one end, anastomosing the two ureters to this end, and bringing the other out as a stoma. This eliminated the hyperchloremic acidosis and markedly diminished the recurrent pyelonephritis and renal failure that were experienced with the wet colostomy. The popularity of the Bricker ileal loop was aided by the development of watertight stomal appliances.

Failure of the small bowel anastomosis to heal because of radiation fibrosis in some patients led to the use of a segment of nonirradiated transverse colon for the conduit (3). Further reductions in bowel complications occurred with the use of surgical staplers, which also decreased the operative time, blood loss, and subsequent medical complications (4). Further refinements in the urinary diversion led to the continent urinary reservoir, which is described in Chapter 19.

As a higher percentage of patients became long-term survivors, the desire to improve quality of life led to reconstructive techniques for the vagina and the colon. Today, the patient undergoing pelvic exenteration may have a colonic J-pouch rectal anastomosis, vaginal reconstruction, and continent urinary diversion, allowing her to enjoy a near-normal quality of life without major alterations in her physical appearance.

The terminology of pelvic exenteration has changed as the operations have been tailored to remove the tumor and only those organs that are involved. The **total exenteration** performed by Brunschwig included the bladder, uterus, vagina, anus, rectum, and sigmoid colon (1). It usually included a large perineal phase (Fig. 21.1). This would lead to a permanent colostomy and urinary stoma. Rutledge et al. (5) and Symmonds et al. (6) reported decreased morbidity and acceptable survival when performing **anterior exenterations,** which removed the uterus, bladder, and various amounts of the vagina (Fig. 21.2). Total pelvic exenteration with rectosigmoid anastomosis (supralevator) became possible with the development of circular staplers. The rectum is excised to within 2 to 3 cm of the anal canal and the levator support of the anal canal and perineal body is preserved (Fig. 21.3). The **posterior exenteration** removes the uterus, vagina, and portions of the rectosigmoid and anus. It is rarely performed today. Vaginal reconstructive techniques are discussed in Chapter 19.

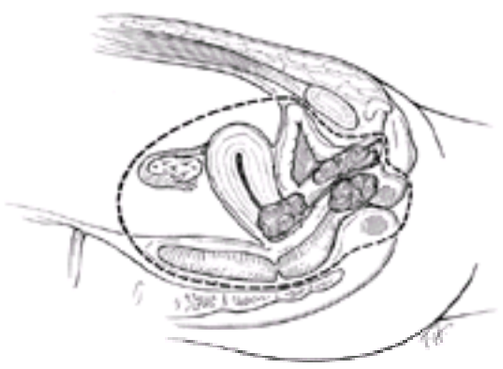


Figure 21.1 Total pelvic exenteration with perineal phase. This operation includes removal of the bladder, uterus, vagina, anus, rectum, and sigmoid colon, as well as performance of a perineal phase, depending on the extent of the disease.

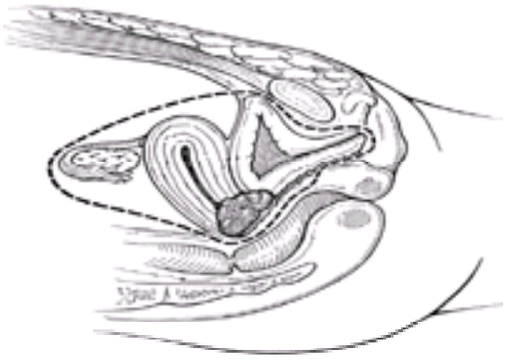
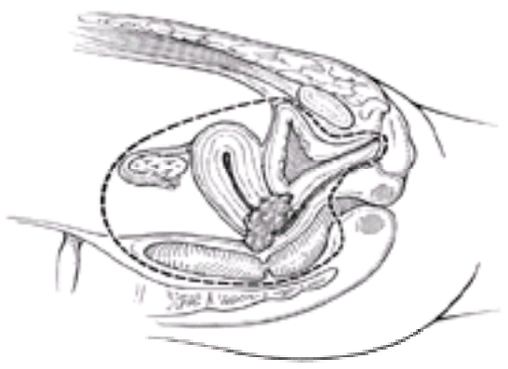


Figure 21.2 Anterior pelvic exenteration. This operation includes removal of the bladder, uterus, and varying amounts of the vagina, depending on the extent of disease.



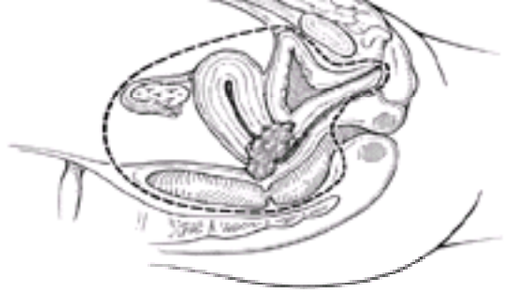


Figure 21.3 Supralevator total pelvic exenteration. This operation removes the uterus, vagina, and portions of the rectosigmoid colon with colonic reanastamosis.

Indications

The most common indication for pelvic exenteration is recurrent or persistent cancer of the cervix after radiation therapy. Some of the early series reported exenterations as primary therapy for stage IVA cervical cancer and cancer of the vulva with urethral, vaginal, or rectal invasion. With modern radiation therapy, the use of exenteration as primary therapy is rare.

Exenteration has also been used for endometrial cancer, vaginal carcinoma, rhabdomyosarcoma, and other, miscellaneous rare tumors whenever ultraradical central resection of the cancer is feasible and there is no evidence of systemic or lymph node spread.

Patients with endometrial cancer have a high likelihood of spread beyond the pelvis and are in general poor candidates for exenterative surgery. The survival rate for highly selected patients with endometrial cancer undergoing exenteration is less than 20% at 5 years (7). To debulk ovarian cancer optimally, a modified posterior exenteration is often performed, which includes *en bloc* resection of the pelvic peritoneum, uterus, tubes, ovaries, and a segment of rectosigmoid. It usually preserves most of the rectum and allows for a low rectal anastomosis. Because there is ovarian cancer left behind, the procedure violates the principle that exenterative surgery is meant to be curative. **In the treatment of ovarian cancer, modified exenteration is performed as part of a cytoreductive procedure and is followed by chemotherapy.**

Patient Selection

The medical evaluation begins with histologic confirmation that cancer is present. The patient should have no other potentially fatal disease and her general medical condition must be adequate for a prolonged operative procedure (up to 8 hours) with considerable fluid shifts and blood loss.

The search for metastatic disease is imperative. The physical examination should include careful palpation of the peripheral lymph nodes and fine-needle aspiration (FNA) cytologic analysis if any suspicious nodes are found. Particular attention should be paid to the groin and supraclavicular nodes. A random biopsy of nonsuspicious supraclavicular lymph nodes has been advocated but is not routinely practiced (8). A computed tomography (CT) scan of the lungs detects disease missed on routine chest radiography. An abdominal and pelvic CT scan is mandatory to detect liver metastasis and enlarged paraaortic nodes. CT-directed FNA cytologic analysis of any abnormalities should be undertaken. **CT scanning should not be relied on for determining resectability on the basis of apparent absence of fatty planes lateral to the tumor.**

Magnetic resonance imaging (MRI) has been evaluated by Popovich et al. (9) for preoperative assessment of candidates for pelvic exenteration. Twenty-three patients were evaluated before pelvic exenteration for presence and location of the recurrent tumor, tumor extension to the bladder, rectum, or pelvic side wall, and presence and location of lymphadenopathy. In four patients, the MRI was falsely positive for pelvic sidewall infiltration, and in one patient it was falsely negative. **Radiation fibrosis and/or chronic inflammation cannot be differentiated from cancer with current imaging techniques.**

Extension of the tumor to the pelvic sidewall is a contraindication to exenteration; however, this may be difficult for even the most experienced examiner to determine because of radiation fibrosis. If any question of resectability arises, the patient should be given the benefit of exploratory laparotomy and parametrial biopsies. Laparoscopy has been described as useful in assessing the patient's lymph nodes as well as resectability of disease in the pelvis. In the hands of highly skilled laparoscopic surgeons, this may be an option (10). **The clinical triad of unilateral leg edema, sciatic pain, and ureteral obstruction is nearly always due to unresectable cancer on the posterolateral pelvic sidewall.**

Despite careful preoperative evaluation, there is approximately a 30% risk that patients will undergo exploratory laparotomy and be judged unsuitable candidates for exenteration. Miller et al. (11) have reported that 111 of 394 patients undergoing exploration at the University of Texas M. D. Anderson Cancer Center had findings that led to abortion of the exenterative procedure. Reasons for aborting the procedure were peritoneal disease in 49 patients (44%), node metastasis in 45 (40%), parametrial fixation in 15 (13%), and hepatic or bowel involvement in 5 (4.5%).

Preoperative Patient Preparation

The patient must be counseled extensively concerning the seriousness of the operation. She should be prepared to spend several days in the intensive care unit and have a prolonged hospitalization of up to several weeks. She must understand that her sexual function will be altered and she may have one or two stomas. In addition, there is no guarantee of cure. The most difficult subject to approach is the possibility that there is unresectable disease and that the procedure will need to be aborted.

A mechanical and antibiotic bowel preparation is given (see Chapter 19, Table 19.1). Intravenous fluids are started at the time of the bowel preparation to avoid dehydration. The patient should have the stoma sites marked by the ostomy team, and management of the ostomies should be discussed. If the patient is severely malnourished, total parenteral nutrition (TPN) may be started in advance of surgery. Because these patients will not have significant oral caloric intake for a week or longer, postoperative TPN should be given.

Operative Technique

The patient is placed in the low lithotomy position using stirrups that support the hips, knees, and thighs that can be repositioned during the surgery. This position allows the operators to perform the abdominal and perineal phases of the operation simultaneously. Intermittent pneumatic compression devices are applied to the calves as prophylaxis for deep venous thrombosis. Combined epidural and general anesthesia allow the epidural to be maintained after surgery for better pain control while keeping the patient alert and able to maintain better respiratory function.

The abdominal incision is made in the midline and should be adequate for exploration of the upper abdomen as well as for performing the pelvic surgery. The liver and omentum should be palpated carefully. The rest of the abdomen is explored and the paraaortic nodes are palpated. Both the right and left paraaortic nodes are sent for frozen-section analysis. If these are negative, pelvic spaces are opened by dividing the round ligament at the pelvic sidewall. The prevesical, paravesical, pararectal, and presacral spaces are all developed and the ligaments are evaluated for resectability. Enlarged or suspicious pelvic lymph nodes should be removed and sent for frozen-section evaluation. **Positive lymph nodes, peritoneal breakthrough of tumor, or tumor implants in the abdomen or pelvis should lead to abandonment of the operation.**

The procedure begins by ligating the internal iliac artery just after it crosses the internal iliac vein. This sacrifices the uterine artery, vesical artery, and obliterated umbilical artery. The remainder of the hypogastric artery is left intact. It carries the internal pudendal and inferior hemorrhoidal arteries that are important in maintaining the blood supply to the anal canal and lower rectum, where a potential low rectal anastomosis will be performed. The obturator artery should also be preserved because it is the major blood supply to the gracilis muscle, and a gracilis neovagina may be planned. The cardinal ligaments are divided at the sidewall and the broad attachments of the rectum to the sacrum are divided. The vaginal attachments to the tendinous arch are divided. The vaginal arteries and vein are located at the lateral margin of this pedicle. The specimen is completely mobilized and the penetration of the rectum and vagina through the pubococcygeal muscle can be

artery, and obliterated umbilical artery. The remainder of the hypogastric artery is left intact. It carries the internal pudendal and inferior hemorrhoidal arteries that are important in maintaining the blood supply to the anal canal and lower rectum, where a potential low rectal anastomosis will be performed. The obturator artery should also be preserved because it is the major blood supply to the gracilis muscle, and a gracilis neovagina may be planned. The cardinal ligaments are divided at the sidewall and the broad attachments of the rectum to the sacrum are divided. The vaginal attachments to the tendinous arch are divided. The vaginal arteries and vein are located at the lateral margin of this pedicle. The specimen is completely mobilized and the penetration of the rectum and vagina through the pubococcygeal muscle can be identified. Various sites for ligation of pubococcygeal muscle for total exenteration versus anterior exenteration are identified (Fig. 21.4).

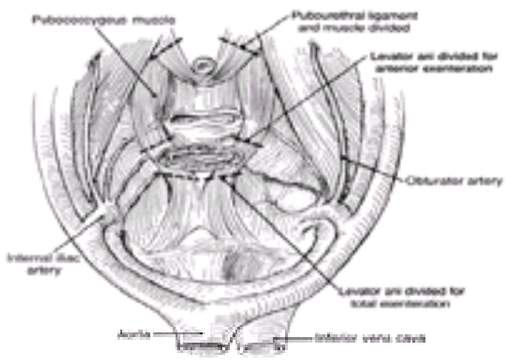


Figure 21.4 Cross-sectional diagram of pelvis showing lines of excision through the pubococcygeal muscle for anterior and total exenterations.

Anterior Exenteration

Anterior exenteration may be planned for lesions confined to the cervix and the anterior upper vagina. The uterus, cervix, bladder, urethra, and anterior vagina are removed and the posterior vagina and rectum are preserved. Intraoperative bimanual palpation helps select the appropriate patient. The peritoneal reflection of the cul-de-sac can be incised and the rectum dropped away with a finger in the rectum and a finger in the vagina to ensure that the tumor is adequately resected. One surgeon conducts the perineal phase and the other surgeon conducts the abdominal phase.

The perineal incision includes the urethral meatus and the anterior vagina. A long curved clamp is placed beneath the pubis and directed caudad and anterior to the urethra. Another clamp is placed lateral to the pubourethral ligaments and directed out under the symphysis pubis, first at 2 o'clock and then at 10 o'clock. This isolates the right and left pubourethral ligaments, which can be clamped, divided, and ligated. The posterior vaginal incision is then made with at least 4 cm of margin under direct vision from the vaginal side. The specimen is then ready to remove. Hemostasis is provided by suture ligatures and a pelvic pack is placed while the continent urinary diversion is performed. The omentum is mobilized and brought down the left pelvic gutter into the pelvis. It is used to cover the denuded area of the rectum and to provide a receptacle for neovaginal construction by a split-thickness skin graft. The omentum is sewn to the posterior vaginal mucosa over the rectum and to the pelvic sidewalls. The skin is harvested and placed around a sterile mold. It is then placed into the cylinder formed by the omentum. If there is not enough omentum, the bulbocavernosus flaps may be used (12).

Supralevator Total Exenteration

Supralevator total exenteration with low rectal anastomosis for patients whose disease extends off the cervix on to the posterior vagina should have the segment of rectum removed *en bloc* with the specimen. This usually entails resection of the rectum to within 6 cm of the anal verge (Fig. 21.3). To remove the specimen, it is best to divide the sigmoid with the stapler to allow for easier exposure to the presacral space. The space is developed in the median avascular plane down to where the rectum exits between the levator muscles. The superior rectal and middle rectal arteries are sacrificed. The incision in the vaginal mucosa is 1 to 2 cm inside the hymenal ring. The supralevator attachments of the bladder, urethra, and vagina are divided, leaving the specimen attached only by the rectum. The hand is placed to encircle the rectum and traction is placed cephalad. The thoracoabdominal stapling device is then placed across the lower rectum with a 4-cm margin. Preservation of some of the lower rectum is desirable for the patient to have better continence and stool storage functions. The specimen is then removed from the field. Hemostasis is provided and a pack is placed while the continent urinary diversion is performed. The left colon is mobilized, sacrificing the sigmoidal arteries and leaving the inferior mesenteric vessels. The sigmoid is then used for a colonic J-pouch and a low anastomosis is performed using the stapling device. The omentum should be mobilized and brought down to reinforce the stapled anastomosis and to cover the denuded area in the pelvis.

Because there is more of the vagina removed in this operation than in the anterior exenteration, the omentum may not be satisfactory for a split-thickness skin graft neovagina. The patient is more likely to require a myocutaneous graft from the gracilis muscles in the medial thigh or the rectus abdominis muscle. Because of the smaller opening in the vaginal introitus, the rectus abdominis myocutaneous graft is preferred.

Total Exenteration with Perineal Phase

If the tumor has extended down the lower vagina and involves the levator muscles, it is necessary to remove them for a chance of cure. The specimen is mobilized from above in a way similar to that described in the preceding operations (Fig. 21.5). The perineal incision is made around the anus and as far lateral as necessary to gain clearance from the tumor. The anococcygeal and pubococcygeal muscles are divided as necessary for margins. This leaves a large pelvic and perineal defect, which is best filled with bilateral gracilis myocutaneous flaps. Alternatively, the rectus abdominis muscle can be used. The omentum is harvested and used as a pedicle flap to provide additional blood supply and a barrier to bowel adhesions. A permanent colostomy is placed and continent urinary diversion is undertaken.

Figure 21.5 A surgically removed specimen from a total pelvic exenteration. Note the bladder above with a fistulous tract to the vagina, and the rectum below.

Posterior Exenteration

Posterior exenterations are now rarely performed except occasionally for cancer of the vulva involving the rectum after radiation therapy. When cervical cancer recurs after radiation therapy, even if it is confined to the posterior vagina and rectum, the distal ureters, bladder, and urethra should be removed to avoid the morbidity and mortality of urinary tract fistulas, stenosis, and denervation.

Low Rectal Anastomosis during Pelvic Exenteration

The introduction of the end-to-end circular stapling device has greatly facilitated and popularized the performance of low rectal resection and reanastomosis for a variety of general surgical and gynecologic malignancies (13). **The automatic circular stapling device has many advantages over the traditional hand-sewn anastomosis. It allows use of a shorter anal or rectal stump, causes less tissue inflammation, creates a higher collagen content, and facilitates faster healing** (14). These are most likely due to a better blood supply at the stapled anastomosis compared with a sutured anastomosis (15).

The anastomotic leak rate for low rectal anastomosis is reported to range from 0% to 43% (16,17) in patients without previous radiation. **The most important variables in the anastomotic leak rate are the distance from the anus to the anastomosis, the vascularity of the cut ends, the tension on the anastomotic line, and the elimination of the pelvic cavity** (18,19). Graffner et al. (20) showed in a randomized series that the anastomotic leak rate in previously unirradiated patients is the same for those patients with diverting colostomies as for those without.

There are a few reports in the gynecologic literature concerning the low rectal anastomosis in women with previous pelvic radiation therapy. Berek et al. (21) reported 11 patients with no anastomotic leaks, and 7 of these patients had their bowel continuity reestablished with the end-to-end stapling device. Harris and Wheeless (22) reported 17 patients with a 12.4% anastomotic leak rate and a 12.4% stricture rate. Both groups advise using a diverting colostomy in the previously radiated patient. Hatch et al. (23) reported using diverting colostomies in 12 of 31 previously irradiated patients. Six patients (50%) later had non–cancer-related rectovaginal fistulas requiring permanent colostomy. Of the 19 patients without protective colostomies, 6 (31.6%) had non–cancer-related rectovaginal fistulas. In the series of Hatch et al. (23), **the most important factor in fistula prevention was the use of an omental wrap to bring a new blood supply to the irradiated pelvis.** For patients who did not have a diverting colostomy, total parenteral nutrition was used for 14 to 21 days.

Removal of the rectum alters the physiology of stool storage and defecation. The rectum is the reservoir for the collection of feces and transmits impulses to the sensory nerves to initiate the urge to defecate. Inhibitory reflexes from the rectum to the anus are necessary while the rectum is filling to ensure continence. After resection of most of the rectum, reservoir capacity, sensation, and rectoanal reflex are significantly altered (24). **The most important factor in restoring normal bowel function is restoration of the reservoir capacity. Capacity can be increased by preserving as much rectum as possible or by a colonic J-pouch.** The length of rectum necessary for return to acceptable function is 6 cm or more (25,26). When the anastomosis is above 12 cm, there is little alteration of function (27).

The colonic J-pouch has been popularized by colorectal surgeons to treat rectal cancer with low rectal resection. It has replaced coloanal anastomosis because of its superior results. **Studies comparing colonic J-pouch with coloanal anastomosis have shown (a) a decreased anastomotic leak rate; (b) a better continence rate; (c) fewer stools per day; (d) better control of urgency; and (e) better control of flatus** (28,29,30 and 31). Prospective, randomized trials have confirmed the observational studies (32,33) (Table 21.1).

Factor	Colorectal (n = 52)	J-Pouch (n = 45)	p Value
Anastomotic leak	8 (15%)	1 (2%)	0.03
Stool frequency	3.5	2	0.001
Incontinence score	5	2	0.001
Use of loperamide	19	1	0.001
Medication to induce stooling	10	21	0.07

From Hallböök O, Pahlman L, Krog M, et al. Randomized comparison of straight and colonic J pouch anastomosis after low anterior resection. Ann Surg 1996;224:58-65, with permission.

Table 21.1 Randomized Comparison of Colorectal versus Coloanal J-Pouch in 100 Patients

The most significant drawback to the colonic J-pouch is the inability of some patients to empty the pouch. This is most likely due to the length of the staple line used to construct the pouch. Hida et al. (34) prospectively randomized patients to a 5- versus a 10-cm pouch, and found the 5-cm to be superior for evacuation without compromising the other parameters (Table 21.2). Most authors report using a diverting colostomy when creating the colonic J-pouch, which has led to a decrease in the anastomotic leak rate.

	5 cm (n = 20)	10 cm (n = 20)	p Value
Sphincter function			
Resting pressure	97.8	90.6	NS
Squeeze pressure	214	194	NS
Reservoir function			
Threshold volume	40	70	<0.001
Maximum volume	98	129	0.003
Evacuation (mL within 5 min)	430	279	<0.001

NS, not significant.
From Hida J, Yasutomi M, Fujimoto K, et al. Functional outcome after low anterior resection with low anastomosis for rectal cancer using the colonic J-pouch: prospective randomized study for determination of optimum pouch size. Dis Colon Rectum 1996;39:986-991, with permission.

Table 21.2 Randomized Study of 5-cm J-Pouch versus 10-cm J-Pouch

There are some important anatomic considerations for patients undergoing pelvic exenteration with a continent urinary diversion. The continent urinary diversion uses the right colic artery up to its anastomosis with the middle colic artery. A colonic J-pouch uses the sigmoidal and left colic vessels. Adequate mobilization of the descending and left colon requires mobilization of the splenic flexure and rotation of the left colon into the pelvis. If a diverting loop colostomy is performed, it may interrupt the vascular supply from the marginal artery of Drummond. Care must be taken to preserve this vascular supply so that the colonic J-pouch and the resultant colorectal anastomosis have an adequate vascular supply.

The overall survival rate of patients with pelvic exenteration and low rectal anastomosis at the University of Alabama at Birmingham was 68%. This is superior to that of patients with anterior exenteration (53%) (35), although the difference is not statistically significant. For both groups of patients, survival significantly improved if there was no spread of disease beyond the cervix and/or vagina. **Patients with disease confined to the cervix and/or vagina who underwent a pelvic exenteration and a low rectal resection had a corrected survival rate of 94%, versus 70% for patients who underwent an anterior exenteration.** Although this difference is not statistically significant, it suggests that the more extensive procedure may improve survival by virtue of its larger tissue margin around apparently confined tumor. **The survival rate for patients with disease in the bladder, rectum, or parametria is 38%.** If the recurrent disease extends as far as the puborectalis portion of the levator muscle, the patient should be considered for a total pelvic exenteration with removal of the levator muscles.

Postoperative Care

70% for patients who underwent an anterior exenteration. Although this difference is not statistically significant, it suggests that the more extensive procedure may improve survival by virtue of its larger tissue margin around apparently confined tumor. **The survival rate for patients with disease in the bladder, rectum, or parametria is 38%.** If the recurrent disease extends as far as the puborectalis portion of the levator muscle, the patient should be considered for a total pelvic exenteration with removal of the levator muscles.

Postoperative Care

Patients are best managed in an intensive care unit with an arterial line and Swan-Ganz catheter. Swan-Ganz catheter monitoring facilitates administration of blood products, colloids, and crystalloids, particularly in those patients whose urine output is not a reliable predictor of fluid status (36). Patients have a large abdominal and pelvic peritoneal defect that exudes serum, and they may have significant third-space fluid shifts. Inadequate fluid replacement may lead to intravascular compromise and decreased perfusion of the kidneys. The hematocrit should be kept stable above 30%, and the prothrombin and partial thromboplastin times should be kept normal with fresh frozen plasma. Once the need for the Swan-Ganz catheter is past, the catheter can be J-wired and a central line placed for use in TPN.

A first-generation cephalosporin is given immediately before surgery for infectious prophylaxis. It is continued after surgery until the patient has remained afebrile for 48 hours. If febrile episodes persist or become severe, antibiotics are changed based on culture results. If no cultures are available, antibiotic therapy is extended to cover anaerobic and gram-negative organisms. If there is fecal spill during surgery, antibiotic coverage is usually extended to anaerobic and gram-negative organisms.

Complications

Although the mortality rate is less than 5%, as many as 50% of patients may have a major complication (37,38 and 39). The most significant intraoperative complication is hemorrhage, with blood loss of 1,500 to 4,000 mL being typical (40,41). Postoperative hemorrhage is often handled by percutaneous embolization because reexploration carries a high morbidity. The length of surgery (4 to 7 hours), large volume of blood loss, and inability to monitor urinary output because of the urinary diversion make the accurate replacement of fluids very difficult. The Swan-Ganz catheter is invaluable in monitoring the replacement of blood, colloids, and crystalloids, which may reach 1,500 mL/hour during intraoperative management.

Nonsurgical complications such as myocardial infarction, pulmonary embolism, heart failure, stroke, and multiorgan failure account for a 2% to 3% mortality rate and are slightly more common in the elderly patient.

Gastrointestinal Complications

Gastrointestinal complications carry high morbidity and mortality rates. A small bowel anastomotic leak or fistula is a serious complication, with a mortality rate of 20% to 50%. **The incidence of small bowel fistula ranged from 12% to 32%** (42) **in patients who had an ileoileal anastomosis in previously irradiated bowel.** Small bowel fistulas have been virtually eliminated by the use of transverse colon conduits and attention to pelvic floor reconstruction. Today, the continent urinary diversion commonly practiced uses an ileocolonic anastomosis with a low small bowel fistula rate.

The incidence of small bowel obstruction is 4% to 9%. Initially conservative management with nasogastric decompression and TPN should be attempted because reoperation has been associated with an 8% to 10% risk of mortality. The obstructions are most common in the distal ileum at the site of the ileal anastomosis. Avoiding the ileal anastomosis and using pelvic floor reconstruction has decreased the morbidity of small bowel obstruction.

Urinary Tract Complications

The standard urinary diversion for several decades was the urinary conduit using a segment of terminal ileum. The high complication rate of the ileoileal anastomosis led to development of the transverse colon conduit (43). There have been no bowel anastomotic leaks reported with this technique, and ureterocolonic anastomotic leaks also are rare.

The continent urinary diversion using the Miami pouch (see Chapter 19) also has a low rate of intestinal fistula formation and urinary leaks. If urinary leaks or fistulas do occur, conservative management with percutaneous drainage is recommended. The mortality rate from surgical reexploration for urinary complications may reach 50%.

The most common long-term complication is pyelonephritis, requiring rehospitalization in 14% of patients. The incidence of ureteral stricture has been decreased by the use of ureteral stents, and is approximately 8% (44).

Results

The 5-year survival rate has improved significantly over time (Table 21.3). Patients who have had anterior exenterations have a better survival rate (30% to 60%) than those with total exenteration (20% to 46%), no doubt reflecting the smaller dimensions of the recurrent disease (45). **The clinical factors that have been reported to affect survival most significantly are length of time from initial radiation therapy to exenteration** (46), **size of the central mass** (47,48) **and preoperative pelvic sidewall fixation determined by clinical examination.**

Author, year	N	Operative Mortality (%)	5-Year Survival (%)
Brunschwig, 1963 (45)	535	16.0	20
Symmonds et al., 1975 (6)	198	8.1	33
Rutledge et al., 1977 (5)	296	13.5	42
Shingleton et al., 1989 (46)	143	6.3	50
Lawhead et al., 1989 (42)	65	9.2	23
Soper et al., 1989 (37)	69	7.2	40
Morley et al., 1989 (38)	100	2.0	61
Stanhope et al., 1990 (47)	133	6.7	41

Table 21.3 Operative Mortality and 5-Year Survival Rates for Pelvic Exenteration

The important pathologic factors are positive nodes, positive margins, and spread of tumor to adjacent organs. The occurrence of metastatic cancer in the pelvic lymph nodes after radiation therapy is a poor prognostic finding at the time of exenteration (Table 21.4). Stanhope and Symmonds (49) achieved the highest 5-year survival rates, at 23%. In their analysis, they eliminated confounding high-risk factors such as positive margins and metastasis to other peritoneal surfaces.

	Negative Nodes		Positive Nodes	
Author, Year	N	5-Year Survival (%)	N	5-Year Survival (%)
Barber and Jones, 1971 (48)	299	21.7	97[a]	5.1
Symmonds et al., 1975 (6)	68	42	30	15
Rutledge et al., 1977 (5)[b]	—	—	30	6.6
Stanhope and Symmonds, 1985 (49)	—	—	26	23
Rutledge et al., 1987 (50)				
All cell types	—	—	30	18.2
Cervix cancer	—	—	24	21.9
Hatch et al., 1988 (35)	54	52	7	14
Morley et al., 1989 (38)	87	70	13	0

[a] Thirty-nine patients with gross disease unresected and 10 with metastasis to ovaries.
[b] Includes positive inguinal nodes.

Table 21.4 Survival of Patients with Positive Nodes at Time of Exenteration for Postirradiation Recurrence

Rutledge et al. (5) in 1977 reported a 7% 5-year survival rate in 28 patients with positive nodes. This publication included patients who had

Rutledge et al. (5) in 1977 reported a 7% 5-year survival rate in 28 patients with positive nodes. This publication included patients who had positive pelvic and inguinal nodes and those who died of operative complications. Ten years later, Rutledge and McGuffee (50) reported a 19.5% survival rate in 44 patients with positive nodes. They noted an increase in the incidence of positive nodes in the later cases and suggested that the patients were more highly selected to eliminate other risk factors, and fewer died of operative complications. There was also a decrease in the number of posterior exenterations performed. These patients had vulvar, urethral, and rectal cancers and had been managed more aggressively despite significant risk factors for higher recurrence rates. The 5-year survival rate was 21.9% for recurrent cervical cancer after radiation therapy, after eliminating death from other causes. Given this rate of survival, **patients with positive pelvic nodes and no other poor prognostic factors can be considered candidates for exenteration.**

Morley et al. (38) reported a 73% 5-year survival rate for 57 patients with squamous cell cancer of the cervix, versus 22% for 9 patients with cervical adenocarcinoma. Crozier et al. (51) reported a median survival of 38 months for 35 patients with adenocarcinoma and 25 months for 70 control patients with squamous cell carcinoma. They concluded that patients with cervical adenocarcinomas who meet the criteria for pelvic exenteration have results similar to those of patients with squamous carcinomas.

Chronologic age is not a contraindication to exenteration. Matthews et al. (41) compared 63 patients aged 65 years or older with 363 patients younger than 65 years of age who underwent pelvic exenteration. The operative mortality rates were 11% and 8.5%, and the 5-year survival rates were 46% and 45%, respectively.

Quality of Life

The quality of life after pelvic exenteration is significantly improved by organ reconstruction. Hawigorst-Knapstein et al. (52) reported 28 patients who were periodically assessed in a prospective study by examination, interview, and questionnaires in the postoperative period. The women were divided into groups of two, one, or no ostomies. A separate comparison was made of women with or without vaginal reconstruction. At all points of evaluation, the patients' quality of life was most affected by worries about progression of the tumor. One year after surgery, the patients with two ostomies reported a significantly lower quality of life and poorer body image than patients with no ostomy. **Those women with vaginal reconstruction reported fewer problems in all categories related to quality of life and significantly fewer sexual problems.**

Ratliff et al. (53) prospectively evaluated 95 patients who underwent pelvic exenteration and gracilis myocutaneous vaginal reconstruction. Forty patients completed the study, and 21 (52.5%) reported that they had not resumed sexual activity after surgery. Of the 19 patients who resumed sexual activity, 84% did so within 1 year of surgery. The most common problems were in adjusting to the self-consciousness of the urostomy or colostomy. Vaginal dryness and vaginal discharge were also significant problems. These findings indicate the need for adequate counseling after the exenterative surgery.

Pelvic exenteration provides the only hope for cure in women with recurrent pelvic malignancies after radiation therapy. Most procedures are done for recurrent cervical cancer. Operative morbidity and mortality can be decreased by careful patient selection, attention to intraoperative technique, excellent postoperative care, and early management of complications. The 5-year survival rate is acceptable given the lack of satisfactory alternative treatments. With modern reconstructive and rehabilitative techniques, the patient can maintain a near-normal lifestyle.

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22 Communication Skills

Robert Buckman

In gynecologic oncology, as in all branches of medicine, every clinical intervention has two distinct aims. One is to produce objective improvement in the patient's medical condition (“helping the patient get better”) if that is possible. The second aim, regardless of whether medical improvement is possible, is to produce amelioration of the patient's subjective symptoms (“helping the patient *feel* better”). Communication skills are essential for both. This chapter sets out a basic and practical approach to acquiring and improving effective communication skills.

Why Communication Skills Matter

Good communication skills facilitate the clinician's ability to take an accurate clinical history and therefore to make a correct diagnosis and an appropriate plan of management. Hence, communication skills are a central component of every clinician's management skills. In addition, however, good communication skills change the patient's attitude to the entire medical intervention. Good communication alters the patient's response to (and assessment of) the clinical outcome. In other words, effective communication changes the way the patient feels about the outcome. Communication skills may affect what the patient perceives has happened to her, and her assessment (and feelings) about her management, her treatment, and her healthcare team (1).

There are also significant medicolegal implications. Communication skills have been shown to be a determinant of more objective outcome measures such as litigation. Approximately three-fourths of complaints against medical practitioners are caused not by matters of medical management but by failures or obstacles in communication. Levinson and Chaunceton (2) further showed that communication skills were a major factor in distinguishing those clinicians who are sued from those who are not. Furthermore, many insurance companies in North America now reduce their malpractice premiums for physicians who have attended specific programs in communication skills.

Communication Skills as Learnable Techniques

Since the late 1970s, clinicians have become increasingly aware of the need for improved communication skills, but it has been difficult to define and test techniques that can be acquired by practitioners. In the late 1970s and early 1980s, it was widely believed that communication skills were intuitive—almost inherited—talents *(“You've either got the gift or you haven't”).* This was coupled with the belief that somehow the physician would be able to feel or sense what the patient was experiencing, and to divine what the patient wanted, and would then be able to respond intuitively in an appropriate way. This belief alienated a large proportion of health care professionals who found the whole topic (as taught at that time) excessively “touchy-feely,” intangible and amorphous, with no guidelines that could lead even a highly motivated practitioner to improve his or her skills.

Since the mid-1980s, researchers and educators have shown that communication skills can be taught and learned (and retained over years of practice), and that they are acquired skills, like any other clinical technique, and not inherited or granted as gifts from on high (3,4,5 and 6).

The main part of this chapter describes two practical protocols that can be used by any health care professional to improve her or his communication skills. They are (a) a basic protocol, the *CLASS protocol*, that underlies all medical interviews; and (b) a variation of that approach, the *SPIKES protocol*, for breaking bad news.

Illustrations of Practical Techniques

The CLASS and SPIKES protocols are summarized briefly using simple and practical guidelines or rules. Both protocols have been published in greater detail elsewhere as a textbook (7), a booklet (8), and in illustrated form with videotaped scenarios using simulated patients in CD-ROM and video formats (9). Review of this video material can enhance the understanding of these communication techniques.

CLASS: Protocol for Effective Communication

There are probably an infinite number of ways of summarizing and simplifying medical interviews, but few (if any) are practical and easy to remember. The five-step basic protocol for medical communication set out in the following sections, which has the acronym *CLASS*, has the virtue of being easy to remember and to use in practice. Furthermore, it offers a relatively straightforward, technique-directed method for dealing with emotions. This is important because one study showed that most (over 85%) oncologists believe that dealing with emotions is the most difficult part of any clinical interview (10).

In brief, the CLASS protocol identifies five main components of the medical interview as essential and crucial. They are *Context (the physical context or setting), **L**istening skills, **A**cknowledgment of the patient's emotions, **S**trategy for clinical management, and Summary* (Table 22.1).

C—Physical context or setting
L—Listening skills
A—Acknowledge emotions and explore them
S—Management strategy
S—Summary and closure

Table 22.1 The CLASS Protocol

C—Context (or Setting)

The context of the interview means the physical context or setting, of which there are three major components (Table 22.2). The first is *arranging the space* optimally. The second component is to get your own *body language* right. Next, pay attention to *eye contact*, to whether *touch* is helpful, and to *making introductions.*

Arrangement: Introductions, sitting down, placement of patient, appropriate distance.
Body language: Drop shoulders, sit comfortably and attentively.
Eye contact: Maintain eye contact except during anger or crying ("not when hot").
Touch (optional): Touch patient's forearm if you and patient are comfortable with touch.
Introductions: Tell the patient who you are and what you do.

Table 22.2 The Elements of Physical Context

A few seconds spent establishing these features of the initial setup of the interview may save many minutes of frustration and misunderstanding later (for both the professional and the patient). These rules are not complex, but they are easy to forget in the heat of the moment.

Spatial Arrangements

The Setting

Try to ensure privacy. In a hospital setting, if a side room is not available, draw the curtains around the bed. In an office setting, shut the door. Next, get any physical objects out of the way. Move any bedside tables, trays, or other impediments out of the line between you and the patient. Ask for the television or radio to be turned off for a few minutes. If you are in an office or room, move your chair so that you are adjacent to the patient, not across the desk. There is evidence that conversations across a corner occur three times more frequently than conversations across the full width of a table (11).

Also, clear any clutter and papers away from the area of desk nearest to the patient. If you have the patient's chart open, make sure you look up from it and do not talk to the patient while reading the chart. If you find any of these actions awkward, state what you are doing *("It may be easier for us to talk if I move the table/if you turn the television off for a moment").*

Then—the most important rule of all—sit down. This is an almost inviolable guideline. It is virtually impossible to assure a patient that she or he has your undivided attention and that you intend to listen seriously if you remain standing up. Only if it is absolutely impossible to sit should you try and hold a medical interview while standing. Anecdotal impressions suggest that when the doctor sits down, the patient perceives the period of time spent at the bedside as longer than if the doctor remains standing. Thus, not only does the act of sitting down indicate to the patient that he or she has control and that you are there to listen, but it saves time and increases efficiency. Before starting the interview itself, take care to get the patient organized if necessary. If you have just finished examining the patient, allow or help her to dress to restore the sense of personal modesty.

Distance

It is important to be seated at a comfortable distance from the patient. This distance (sometimes called the *body buffer zone*) seems to vary from culture to culture, but a distance of 2 to 3 feet between you usually serves the purpose for intimate and personal conversation (11). This is another reason why the doctor who remains standing at the end of the bed ("six feet away and three feet up," known colloquially as "the British position") seems remote and aloof.

The height at which you sit can also be important; normally, your eyes should be approximately level with the patient's. If the patient is already upset or angry, a useful technique is to sit so that you are below the patient, with your eyes at a lower level. This often decreases the anger. It is best to try and look relaxed, particularly if that is not the way you feel.

Positioning

Make sure that whenever possible, your are seated closest to the patient and that any friends or relatives are on the other side of the patient. Sometimes relatives try to dominate the interview, and it may be important for you to send a clear signal that the patient has primacy.

Have Tissues Nearby

In almost all oncology settings, it is important to have a box of tissues nearby. If the patient or relative begins to cry it is important to offer tissues, which not only give overt permission to cry but allow the person to feel less vulnerable when crying.

Your Body Language

Try to look relaxed and unhurried. To achieve an air of relaxation, sit down comfortably with both your feet flat on the floor. Let your shoulders relax and drop. Undo your coat or jacket if you are wearing one, and rest your hands on your knees. (In psychotherapy, this is often called "the neutral position.")

Eye Contact

Maintain eye contact for most of the time while the patient is talking. If the interview becomes intense or emotionally charged—particularly if the patient is crying or is very angry—it is helpful to the patient for you to look away (to break eye contact) at that point.

Touching the patient

Touch may also be helpful during the interview if (a) a nonthreatening area is touched, such as the hand or forearm; (b) you are comfortable with touch; and (c) the patient appreciates touch and does not withdraw.

Most of us have not been taught specific details of clinical touch at any time in our training (12). We are, therefore, likely to be ill at ease with touching as an interview technique until we have had some practice. Nevertheless, there is considerable evidence (although the data are somewhat "soft") that touching the patient (particularly above the patient's waist to avoid misinterpretation) is of benefit during a medical interview (13). **It seems likely that touching is a significant action at times of distress and should be encouraged, with the proviso that the professional should be sensitive to the patient's reaction.** If the patient is comforted by the contact, continue; if the patient is uncomfortable, stop. Touch can be misinterpreted (e.g., as lasciviousness, aggression, or dominance), so be aware that touching is an interviewing skill that requires extra self-regulation.

Starting Off

Introductions

Ensure that the patient knows who you are and what you do. Many practitioners, including the author, make a point of shaking the patient's hand at the outset, although this is a matter of personal preference. Often the handshake tells you something about the family dynamics as well as about the patient. Frequently the patient's spouse also extends his hand. It is worthwhile making sure that you shake the patient's hand before that of the spouse (even if the spouse is nearer) to demonstrate that the patient comes first, and the spouse (although an important member of the team) comes second.

L—Listening Skills

As dialogue begins, the professional should show that she or he is in "listening mode." [For a general review of interviewing skills, see Lipkin et al. (14).] The four main points to attend to are covered in the following sections. They are *the use of open questions, facilitation techniques, the use of clarification*, and *the handling of time and interruptions* (Table 22.3).

Switch on your listening skills and techniques to show that you are an effective listener.
1. Open Questions
Questions that can be answered in any way (e.g., "how are you?" "what did that make you feel?")
2. Facilitating
Pausing or silence when patient speaks
Nodding, smiling saying, "hmm-mm," "tell me more about that," and the like
Repetition (i.e., repeating one key word from patient's last sentence in your first sentence)
3. Clarifying
Making overt any ambiguous or awkward topic
4. Handling Time and Interruptions
With pagers and phones: acknowledge the patient who is with you as you answer
Tell patient about any time constraints and clarify when discussion will resume

Table 22.3 Fundamental Listening Skills

Open Questions

Open questions are simply questions that can be answered in any way or manner of response. In other words, the question does not direct the respondent or require her to make a choice from a specific range of answers. In taking the medical history, of course, most of the questions are, appropriately, closed questions *(“Do you have swelling of the ankles?” “Have you had any bleeding after your menopause?”).* In therapeutic dialogue, when the clinician is trying to be part of the patient's support system, open questions are an essential way of finding out what the patient is experiencing as a way of tailoring support to the patient. Hence, open questions *(“What did you think the diagnosis was?” “How did you feel when you were told that...” “What did that make you feel?”)* are a mandatory part of the “nonhistory” therapeutic dialogue.

Facilitation Techniques

Silence

The first and most important technique in facilitating dialogue between the patient and clinician is silence (15). **If the patient is speaking, do not talk over her.** Wait for the patient to stop speaking before you start your next sentence. This, the simplest rule of all, is the one most often ignored, and is most likely to give the patient the impression that the doctor is not listening.

Silences also have other significance: they can be—and often are—revealing about the patient's state of mind. Often, a patient falls silent when she has feelings that are too intense to express in words. A silence, therefore, means that the patient is thinking or feeling something important, not that she has stopped thinking. If the clinician can tolerate a pause or silence, the patient may well express the thought in words a moment later.

If you have to break the silence, the ideal way to do so is to say *“What were you thinking about just then?”* or *“What is it that's making you pause?”*, or something to that effect.

Other Simple Facilitation Techniques

Having encouraged the patient to speak, it is necessary to prove that you are hearing what is being said. The following techniques enhance your ability to demonstrate this.

In addition to silence, you can use any or all of the following simple facilitation techniques: nodding, pauses, smiling, saying *“Yes,” “Mmm hmm,” “Tell me more,’* or anything similar.

Repetition and Reiteration

Repetition is probably the single most important technique of all interviewing skills (apart from sitting down).

To show that you are really hearing what the patient is saying, use one or two key words from the patient's last sentence in your own first one *(“I just feel so lousy most of the time.” “Tell me what you mean by feeling lousy.”).* Reiteration means repeating what the patient has told you, but in your words, not hers *(“Since I started those new tablets, I've been feeling sleepy.” “So you're getting some drowsiness from the new tablets.”).* Both repetition and reiteration confirm to the patient that she has been heard.

Reflection

Reflection is the act of restating the patient's statement in terms of what it means to the clinician. It takes the act of listening one step further, and shows that you have heard and have interpreted what the patient said *(“If I understand you correctly, you're telling me that you lose control of your waking and sleeping when you're on these tablets.”).*

Clarifying

As the patient talks, it is very tempting for the clinician to go along with what the patient is saying, even when the exact meaning or implication is unclear. This may lead very quickly to serious obstacles in the dialogue.

It is important to be honest when we do not understand what the patient means. Many different phrases can be used *(“I'm sorry—I'm not quite sure what you meant when you said...” “When you say...do you mean that...?”).* Clarification gives the patient an opportunity to expand on the previous statement and/or to amplify some aspect of the statement, now that the clinician has shown interest in the topic.

Handling Time and Interruptions

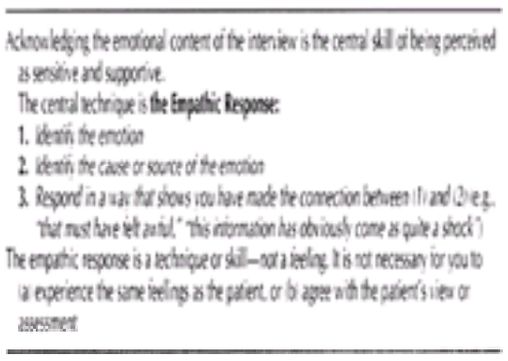
As clinicians, we seem to have a notorious reputation for being impolite in our handling of interruptions—by phone, pager, or other people. Too often, we appear abruptly to ignore the patient we are with and go immediately to the phone or respond immediately to the pager or to our colleague. Even though we may not realize it, this appears as a snub or an insult to the patient we are with.

If you cannot hold all calls or turn off your pager (and most of us cannot), then at least indicate to the patient that you are sorry about the interruption and will return shortly *(“Sorry, this is another doctor that I must speak to very briefly—I'll be back in a moment.” “This is something quite urgent about another patient—I won't be more than a few minutes.”).* The same is true of time constraints *(“I'm afraid I have to go to the O.R. now, but this is an important conversation. We need to continue this tomorrow morning on the ward round...”).*

A—Acknowledgment (and Exploration) of Emotions

The Empathic Response

The empathic response is an extremely useful technique in an emotionally charged interview, yet is frequently misunderstood by students and trainees (Table 22.4).



Acknowledging the emotional content of the interview is the central skill of being perceived as sensitive and supportive.

The central technique is **the Empathic Response:**

1. *Identify the emotion*
2. *Identify the cause or source of the emotion*
3. *Respond in a way that shows you have made the connection between (1) and (2) (e.g., "that must have left you ful," "this information has obviously come as quite a shock.")*

The empathic response is a technique or skill—not a feeling. It is not necessary for you to (a) experience the same feelings as the patient, or (b) agree with the patient's view or assessment.

Table 22.4 Acknowledgement of Emotions—the Empathic Response

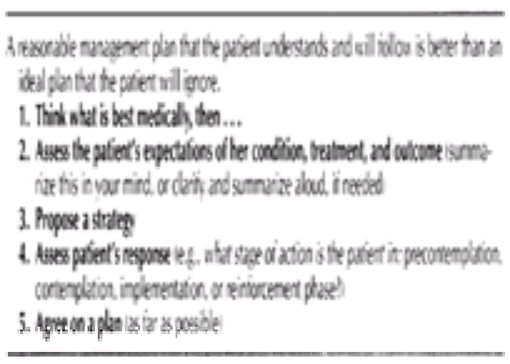
The empathic response has nothing to do with your own personal feelings: if the patient feels sad, you are not required that moment to feel sad yourself. It is simply a technique of acknowledgment, showing the patient that you have observed the emotion she is experiencing. It consist of three steps:

1. ***Identifying the emotion that the patient is experiencing.***
2. ***Identifying the origin and root cause of that emotion.***
3. ***Responding in a way that tells the patient that you have made the connection between 1) and 2).***

Often, the most effective empathic responses follow the format of *"You seem to be..."* or *"It must be..."* (e.g., *"It must be very distressing for you to know that all that therapy didn't give you a long remission."* or even *"This must be awful for you."*). **The objective of the empathic response is to demonstrate that you have identified and acknowledged the emotion that the patient is experiencing, and by doing so you are giving it legitimacy as an item on the patient's agenda.** In fact, if the patient is experiencing a strong emotion (e.g., rage or crying) you *must* acknowledge the existence of that emotion or all further attempts at communication will fail. If strong emotions are not acknowledged in some way, you will be perceived as insensitive, and this will render the rest of the interaction useless.

S—Management Strategy

There are several useful techniques to ensure that you construct a management plan with which the patient concurs and will follow (Table 22.5). The following are useful guidelines:



A reasonable management plan that the patient understands and will follow is better than an ideal plan that the patient will ignore.

1. **Think what is best medically, then . . .**
2. **Assess the patient's expectations of her condition, treatment, and outcome** (summarize this in your mind, or clarify and summarize aloud, if needed)
3. **Propose a strategy**
4. **Assess patient's response** (e.g., what stage of action is the patient in: precontemplation, contemplation, implementation, or reinforcement phase?)
5. **Agree on a plan** (as far as possible)

Table 22.5 Management Strategy

1. ***Determine what you judge to be the optimal medical strategy.*** In your mind (or out loud), define the ideal management plan.
2. ***Assess (in your own mind or by asking the patient) what are her own expectations of her condition, treatment, and outcome.*** Be aware if there is a marked "mismatch" between the patient's view of the situation and the medical facts, because you are going to have to work harder to make the plan appear logical and acceptable.

   Bearing in mind your conclusions from steps 1 and 2, propose your strategy. As you explain it to the patient,
3. ***Assess the patient's response.*** For example, make note of the patient's progress in forming an action plan (the stages are often defined as the precontemplation, contemplation, implementation, and reinforcement phases). Acknowledge the patient's emotions as they occur and continue in a contractual fashion to arrive at a plan that the patient has "bought into" and which she will follow.

S—Summary

The summary is the closure of the interview. In gynecologic oncology, the relationship with the patient is likely to be a continuing one and a major component of the patient's treatment. The closure of the interview is an important time to emphasize that point.

It is relatively straightforward to cover three areas in the summary (Table 22.6). They are (a) a *précis* or reiteration of the main points covered in the dialogue; (b) an *invitation* for the patient to ask questions; and (c) *a clear arrangement for the next interaction ("a clear contract for the contact").* This part of the interview is not necessarily long, but does require considerable focus and concentration.

Ending of the interview has three main components:

1. A précis or **summary** of the main topics you have discussed
2. **Identification** of any important issues that need further discussion. Even if you do not have time to discuss them in this interview, they can be on the agenda for the next
3. A clear **contract** for the next contact

Table 22.6 Summary and Closure

SPIKES: A Variation of CLASS for Breaking Bad News

Among the various types of medical interviews, breaking bad news is a special case, and one of exceptional importance for both parties in the clinician–patient relationship (7,16,17).

Bad news can best be defined as "any news that seriously adversely affects the patient's view of her future" (18). In other words, the "badness" of bad news is the gap between the patient's expectations of the future and the medical reality. In gynecologic oncology, bad news is common at many stages in a patient's history: (a) initial diagnosis, (b) recurrence or disease progression, (c) clinical deterioration, (d) development of new complications, and (e) change from therapeutic to palliative intent. It is necessary to have a protocol that will function in all of these circumstances.

The SPIKES protocol has been designed specifically for these purposes and allows assessment of the patient's expectations before sharing the information (Table 22.7).

S—**Setting** = Context and listening skills
P—Patient's **perception** of condition and seriousness
I—**Invitation** from patient to give information
K—**Knowledge**—giving medical facts
E—Explore emotions and **empathize** as patient responds
S—Strategy and **summary**

[a] A variant of the basic CLASS approach.

Table 22.7 The SPIKES Protocol for Breaking Bad News[a]

S—Setting (= Context + Listening Skills)

In the SPIKES protocol, for the sake of convenience, we have combined two phases of the CLASS protocol—the *context* (Table 22.2) and *listening skills* (Table 22.3)—into "setting."

P—The Patient's Perception of the Situation

The cardinal rule of breaking bad news is to find out what the patient already knows or suspects before going on to share the information. To condense this into a slogan, one might say *"Before you tell, ask."*

The exact words used to find out how much the patient already understands are a personal choice (Table 22.8). *("Before I go on to tell you about the results, why don't you tell me what you've been thinking?" "When you first developed that swelling of the abdomen, what did you think was going on?" "Had you been thinking this was something serious?"* or *"What did the referring medical team tell you about your medical condition?")*

Ask patient to say what she knows or suspects about the current medical problem
(e.g., "What did you think when…?" or "Did you think it might be serious…?")
As patient replies:
Listen to level of comprehension and vocabulary
Note any mismatch between the actual medical information and the patient's perception of it (including denial)

Table 22.8 Patient's Perception of Condition

As the patient replies, pay particular attention to her *vocabulary* and *comprehension* of the subject. When starting to give information, it is very helpful if one can start at the same level of knowledge as the patient (19).

I—Getting a Clear Invitation to Share News

Next, try to get a clear invitation to share the information (Table 22.9). Most patients want full disclosure. There has been a steady increase in the desire for honest information from Oken's (20) study in 1961, when 95% of surgeons did not tell their patients a cancer diagnosis. Twenty-five years later, Novack and colleagues' (21) study showed a dramatic reversal of this proportion. Regarding the proportion of patients who state they want to be informed, Jones' (22) study in 1981 showed that 50% of (British) patients wanted to know. Since then, there have been many studies that all put the proportion of patients who want full disclosure at above 90% (23,24 and 25).

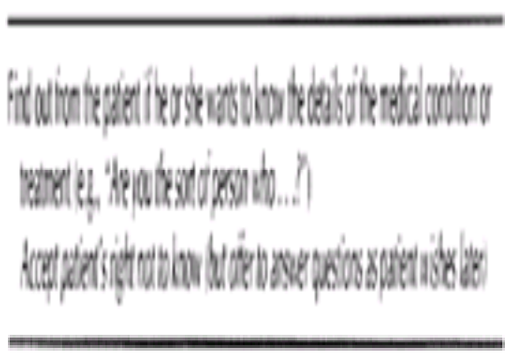


Table 22.9 Invitation from Patient to Give Information

Hence, disguising the information or lying to the patient is highly likely to be unsatisfactory. The phrase one uses to obtain a clear invitation is again a matter of personal choice and judgment *("Are you the sort of person who'd like to know exactly what's going on?" "Would you like me to go on and tell you exactly what the situation is and what we recommend?"* or *"How would you like me to handle this information? Would you like to know exactly what's going on?")*

K—Knowledge (Explaining the Medical Facts)

Having obtained a clear invitation to share information, one begins by giving the medical facts and simultaneously being aware of (and sensitive to) the patient's reaction to that information. In other words, giving the knowledge and responding to emotions proceed simultaneously.

The most important guidelines for giving the medical facts are (Table 22.10):

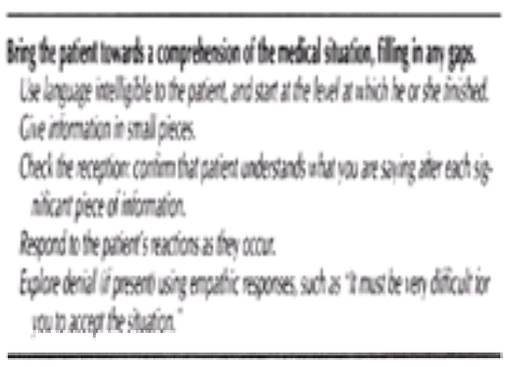


Table 22.10 Knowledge—Giving Medical Facts

- **Begin at the level of comprehension and use the vocabulary that the patient indicated** (this is called *"aligning"*).
- **Use plain, intelligible English** (avoid the technical jargon of the medical profession—"Medspeak").
- **Never talk for more than a few minutes at a time.**
- **Check that the patient understands the information before going further** (use phrases such as *"Do you follow what I'm saying?" "Is this clear so far?" "Am I making sense so far?"*).
- **Use a narrative approach to make sense of what has occurred: explain the sequence of events, and how the situation seemed as events unfolded** *("When you became short of breath we didn't know whether it was just a chest infection or something more serious. So that's when we did the chest x-ray...")*.
- **Respond to all emotions expressed by the patient as they arise** (see next section).

E—Emotions (Exploration and Empathic Response)

The acknowledgment of emotions is more important in an interview about bad news than it is in most other interviews (see the "A-Acknowledgment" section in the CLASS protocol, previously; Table 22.4).

The doctor can effectively use an empathic response on his or her own feelings if they are becoming intense *("I'm finding this very upsetting, too.").*

The value of all empathic responses lies in the fact that one is making an observation that is almost unemotional in itself about an issue that is heavily charged with emotion (whether the patient's or the doctor's). This is why an empathic response cools the temperature of a fraught moment and facilitates the exploration of the situation without causing escalation.

S—Strategy and Summary

Close the interview with a management strategy and closure, as described in the S-Strategy and S-Summary sections for the CLASS protocol (Table 22.5).

Dealing with Hope and False Hopes

Many clinicians and patients often say *"But you can't take away hope."* Frequently this is used by clinicians as an excuse for not telling the patient the truth. Usually, the real rationale behind this is to protect the clinician from discomfort, not the patient.

Clinicians are more likely to create major problems for themselves if they promise cure when that is not possible or hold out unrealistic hopes. Supporting the patient and reinforcing realistic hopes is part of the foundation of a genuinely therapeutic relationship.

The important thing is not *whether* to tell the truth (there is a moral, ethical, and legal obligation to do so if that is what the patient wants), but *how* to tell the truth. Insensitive and ineffective truth-telling may be just as damaging and counterproductive as insensitive lying. In practice, the preceding protocols allow the truth to be told at a pace determined by the patient and in a way that allows recruitment and reinforcement of the patient's coping strategies.

Communication in Palliative Care

In palliative care, communication skills are even more important than in acute care—and may sometimes be the only therapeutic modality available to the clinician (26). In palliative care, communication may have at least three distinct functions: (a) in taking the history, (b) in breaking bad news, and (c) as therapeutic dialogue (i.e., support of the patient).

Even when the prognosis is acknowledged to be grave, there may be stages in which some hoped-for improvement or stabilization is not achieved. In these circumstances, the SPIKES protocol can be helpful, even when the clinician and the patient already have a long-standing relationship.

At other times, simply listening to the patient and acknowledging the various emotions and reactions she is experiencing is in itself a therapeutic intervention. This is particularly true in discussions about dying. When a patient realizes and acknowledges that she is dying, there is no "answer" the clinician can give. Instead, listening to the questions, issues, and emotions is a valuable service.

Talking to Family Members

Family members are an important component of the psychological context surrounding the patient. Often they may assist the clinician in confirming the medical facts and supporting the patient as she responds to the information. **Sometimes, however, individual family members may be at a different phase of acceptance or understanding of the medical information than the patient. This is called *discordance*, and can be a serious and additional problem for the clinician.** The important guideline is to seek and maintain clarity in talking to the relative. The clinician must stress that he or she is looking after the patient (not the relative), and empathic responses can be used to acknowledge and explore the emotions underlying the relative's state.

This is particularly true in a potential conflict such as when a relative tells a clinician "My mother is not to be told the diagnosis." This is a common and awkward situation and it requires care and effort to emphasize the primacy of the patient's right to knowledge (if that is what she wants) while at the same time underlining the relative's importance and value as part of the patient's support system.

Another exceptionally difficult situation for the clinician is telling a relative that the patient has died. The central principle is to use a narrative approach to the events, but to be prepared at any instant to respond to the relative if he or she asks whether the patient has died.

Communication with Other Health Care Professionals

The medical profession is only human, and sometimes under great stress, and as such may become short-tempered, rude, aggressive, or impatient. This is almost unavoidable. With good communication skills, the resulting damage can be reduced, but probably not prevented altogether.

The two principles that are most useful are (a) *clarification* and (b) *acknowledgment* of the situation (using empathic responses). Whenever one responds to an emotion by acknowledging it with a relatively unemotional empathic response, the dispute will deescalate. It is also worth remembering the old adage that "an ounce of prevention is worth a pound of cure." Giving information early (a "preemptive information strike") prefaced as a "For Your Information" discussion, may prevent major disputes or discontent later (*"Why didn't you tell me...?"*).

Motivation and Manners

Like any clinical intervention, effective communication requires motivation to be successful. If one is motivated to be a good clinical communicator, it is achievable. Some of it depends on having a basic strategy for the task, and the protocols presented here should be helpful. The rest is largely a matter of having an awareness of the effect of what one says and does on the patient and family. There is a great deal of courtesy and common sense mixed in with the specific strategies.

Communication tasks are of enormous importance in the relationship between doctor and patient. As has been said, "Do this part of your job badly and they will never forgive you: do it well and they will never forget you."

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23 Palliative Care and Pain Management

J. Norelle Lickiss and Jennifer A. M. Philip

Comprehensive care of a woman with gynecologic cancer involves anticancer treatment (directed at either cure or control of the cancer), good symptom relief, and personal and family support. Once there is clearly progressive disease, it is important to clarify how and where the patient will be cared for when dependency increases, and the patient herself needs to address the personal issues involved in preparation for death. These matters should not be suddenly raised at time of crisis. **Elements of care apart from anticancer strategies are sometimes grouped under the term *palliative care.*** With the “mixed management” now advocated for eventually fatal illnesses (Fig.23.1), delineation of palliative care from the rest of care is neither necessary nor clear.

Figure 23.1 Alternative models for end of life care. A: Traditional model for cancer care. **B:** Revised model for cancer care. **C:** Mixed management of various eventually fatal illnesses. (From The Committee on Care at the End of Life. *Approaching death: improving care at the end of life.* Institute of Medicine. Washington, DC: National Academy Press,1997:85, with permission.)

In recommending mixed management in 1998, the Institute of Medicine (Washington, DC) highlighted the deficiencies of models of care involving the introduction of palliation/symptom relief and death preparation only when anticancer treatment has failed (1). The Institute of Medicine expanded on the earlier work of the World Health Organization, which, in 1991, urged a move toward palliative care concurrent with anticancer treatment (2).

The organization of palliative care varies from place to place, but equality of access for all patients should be the goal, with emphasis on facilitating comfort, autonomy, dignity, and personal rehabilitation and development, especially in the face of an incurable illness. Efforts must be directed at assisting the patient to have realistic expectations and well grounded hope in what will not fail her, notably in the fidelity of her carers, and in recognition of her own unique value as a person, come what may.

In general, effective antidisease therapy offers the best chance of good symptom relief if the patient is a “responder,” but the quality of life of a “nonresponder” to chemotherapy may be worse than that of an untreated patient. Expertise in palliative therapeutics comparable with expertise in surgery, chemotherapy, and radiation therapy is essential in a multidisciplinary team, especially once the goal of treatment is restoration and maintenance of good-quality life. This chapter is concerned mainly with palliative medicine.

Just as the last movement of a symphony is a crucial section of the work, so the last phase of life is crucial to the completion of a human life. **It is the responsibility of the medical and nursing professions to facilitate maximum autonomy and dignity during this final phase.** The attitude of the physician to this last phase of life and to death itself may color clinical judgment. In general, it is crucial for the bond between the patient and her primary care physician to be strengthened at this time. Continuity of as many professional relationships as possible is desirable.

Practical Aspects of Palliative Care

The care of a woman with advanced gynecologic malignancy, with regard to those elements conventionally referred to as “palliative care,” involves several components: assessment, delineation of therapeutic possibilities, implementation of treatment, evaluation of outcome, continuing review and reassessment, and prognostication. **The concept of the patient as subject should be understood: the patient is a person with capacities to perceive, know, understand, love, receive love, and establish priorities within a specific existential, geographic, and cultural context, and within a network of personal relationships.**

Assessment

It is essential to make a comprehensive assessment, which includes listening to the patient's experience with her cancer, from the prediagnostic phase to the details of treatment. Her perception of her care system should be sought, together with her current hierarchy of problems.

A comprehensive assessment involves at least:

- **Ascertainment of the patient's current symptoms and other problems, in her order of priorities**
- **Clarification of the nature and the extent of the neoplastic process,** with careful consideration of any other pathologic process that may be contributing to the current problems
- **Delineation of the personal and social context within which the patient is living** and from which she may draw support
- **Elucidation of her current personal objectives**

An adequate assessment may involve interaction not only with the patient, but with family members and friends. The woman should give consent to the transfer of information to her partner in all but exceptional circumstances, although cultural considerations may influence this issue.

Therapeutic Decision Making

On the basis of a comprehensive assessment, with or without further investigations to elucidate the mechanism of troublesome symptoms, it is normally possible to delineate the therapeutic possibilities. The latter must take account of the patient's priorities.

Palliative care is concerned with the facilitation of freedom, and the choice among therapeutic options should reflect this. In general, the least restrictive alternative involving the least dependence on medical facilities and the least use of the patient's time, resources, and personal energy should be selected. For example, it is inappropriate to resort to intravenous (or spinal) techniques for pain relief if oral, transcutaneous, or subcutaneous techniques have not been adequately explored. **Careful consideration of relevant antitumor measures (surgery, radiation therapy, or chemotherapy) is always mandatory because control of the neoplastic process usually offers the best chance of alleviating symptoms.**

Factors that should be considered when evaluating therapy include the stage of disease, rate of disease progression, the likely natural history, the burden of investigation and treatment compared with potential gain for the patient, the potential to prevent future symptoms, and the potential for rehabilitation (physical, psychological, social, or spiritual).

The burden of decision making is considerable, and ways of reaching decisions vary according to social, cultural, economic, and medical contexts, and usually involve several members of a team. **Decisions concerning treatment should normally involve the patient, who should be adequately informed about the advantages and disadvantages of the various options.** Such involvement may help the patient to regain control at a potentially chaotic time in her life. Although the patient should share in decision making, her attending clinician should indicate the course of action he or she favors, and ultimately take the responsibility for any intervention, so that a distressing outcome does not engender guilt in the patient and her family. This being said, the physician should not compromise his or her better judgment or conscience in the face of patient or family pressure. There are no circumstances that justify a physician's declaring that “there is nothing more that can be done.”

Evaluation of Outcomes

Evaluation of palliative interventions is best performed by the informed patient, although the observations of the medical and nursing staff are also important. Monitoring in some form is essential, because time, often the patient's most precious possession, should not be wasted by ineffective interventions. Formal outcome measures based on subjective criteria, of which there are many examples (3,4,5 and 6), should ideally be introduced into routine clinical practice.

Discussing Prognosis

Mention needs to be made of the art of prognostication, because the matter inevitably arises. Although there are various factors that allow a gynecologic oncologist to give a particular patient a probability figure for survival, **in the case of the individual patient, the outcome is fairly uncertain and it is cruel indeed for a clinician to be too specific about the likely duration of survival.** In the face of a question concerning prognosis for incurable patients, it is reasonable to offer some time boundaries within which death is likely to occur. Such boundaries are useful for thinking and planning, and certainly reinforce the fact that, as for all mortals, time is finite and the “horizon is in view.” Time boundaries do not give a patient or her family an agonizing date around which to focus, nor do they suggest that what is still quite uncertain can be predicted precisely. The completion of life is too serious a matter to be diverted by such a false focus.

There are many indicators that a patient is actually dying, and these are well known to clinicians, nurses, and family members. There may be a change in the tempo of the disease, a manifest change in the function of critical organs, or a rapid deterioration in strength or physical performance in the absence of reversible factors, such as gross anemia, septicemia, hypercalcemia, or drug interactions. **What is medically possible at this stage, such as treatment of renal failure, septicemia, or hypercalcemia, may not necessarily be medically wise.**

There are also psychological signs that a patient is dying. An experienced clinician notes the gradual withdrawal of the patient from interest in the wider world, from interest in personal friends, and even the gradual loosening of bonds with those very close. In some patients, this “cutting of the moorings” is very obvious; intrapersonal activity may be very intense and expressed only to a trusted few. The patient herself may clearly articulate her awareness that she is now close to death, or she may choose not to speak of it. The essence of clinical response is to respect the mystery of the individual.

Symptoms and Their Relief

Symptoms are subjective, even though the person with severe symptoms may have objective manifestations, such as vomiting. **A patient in severe pain may show no signs of distress,**yet she may admit to a trusted confidant that the pain is almost unbearable. Her behavior is influenced by cultural and environmental factors, as well as by personal and interpersonal relationships. Accurate assessment of symptoms requires skill, patience, active listening, and unconditional regard for the patient.

Symptoms vary in their significance. Certain symptoms (e.g., vaginal bleeding) may cause much emotional distress, whereas other symptoms that are more serious in their physiologic consequences (e.g., severe constipation) may not evoke the same fear. It is important to give the patient a chance to express her fears and to offer some simple explanation for the symptom, because this will at least reduce her anxiety.

Suffering, defined as a sense of impending personal disintegration (7), may or may not be related to symptoms such as pain. Suffering is a complex concept, and its alleviation is one of the goals of clinical practice.

Symptoms may arise from the tumor itself, from the treatment, and/or from unrelated causes. In gynecologic cancer, symptoms tend to cluster, and some major symptom complexes are as follows:

Pelvic mass symptoms, from pressure and infiltrative effects on the bladder, rectum, pelvic blood vessels, ureters, lymphatics, or nerves.

Abdominal mass symptoms, from compression and dysfunction of the stomach, small bowel, and large bowel.

Perineal symptoms, including referred pain to the perineum or pain and discomfort from ulceration, particularly with urination or defecation.

Pulmonary symptoms, including dyspnea or debilitating coughing.

Systemic symptoms, including fatigue and depression.

Symptoms may precede signs or radiographic evidence of disease spread. This is particularly true in the case of pain from lumbosacral plexus infiltration. Magnetic resonance imaging or a computed tomographic scan may demonstrate a lesion suspected on the basis of

Pulmonary symptoms, including dyspnea or debilitating coughing.

Systemic symptoms, including fatigue and depression.

Symptoms may precede signs or radiographic evidence of disease spread. This is particularly true in the case of pain from lumbosacral plexus infiltration. Magnetic resonance imaging or a computed tomographic scan may demonstrate a lesion suspected on the basis of symptoms. Waiting for objective signs may be disastrous in certain circumstances, such as in the early diagnosis of remediable spinal cord compression. Feinstein (8) pointed out the prognostic significance of symptoms at the time of diagnosis of certain tumors, and symptoms are also of value in pointing to potential complications.

There is now considerable literature concerning the understanding and therapy of major symptoms in cancer (9,10 and 11), and attention is given here to those seen more commonly.

Pain Management

Pain has been defined by the International Association for the Study of Pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage.” Because of its subjective nature, there are difficulties both in measuring and in relieving pain.

The advances in pain management of the 1990s have been based on a more adequate understanding of pain physiology, classification of pain mechanisms, and research with respect to specific drug management (12,13,14,15 and 16). Conolly (17) cogently stated,“What is needed now is not a stunning new understanding of pain pharmacology, but the consistent and rational application of what is already known.” Cancer pain assessment and treatment guidelines have been developed by the American Society of Clinical Oncology and other authorities(18,19).

Many approaches to pain management have been published (10,18,19). The following simple schema provides some guidelines in the face of the complexity of recent research and practice.

Pain management may be considered to have four steps:

1. **Reduce the noxious stimulus at the periphery.**
2. **Raise the pain threshold.**
3. **Use appropriate doses of opioid drugs.**
4. **Recognize neurogenic pain and treat correctly.**

Step One—Reduce the Noxious Stimulus at the Periphery

This step demands an adequate understanding of the mechanism of the pain stimulus in the individual patient. Pain in gynecologic cancer may be due to soft tissue infiltration, bone involvement, neural involvement, muscle spasm (e.g., psoas spasm), infection within or near tumor masses, or to intestinal colic: massive fecal loading can be overlooked as a cause of severe lower abdominal and pelvic pain. The history should include the mode of onset, characteristics, distribution, aggravating factors, trends over time, and response to therapeutic endeavors. The history, together with a clinical examination, provide the fundamental guide to the likely pain mechanism. Pain caused by treatment (e.g., radiation therapy) requires as close attention as that caused by tumor.

Therapeutic approaches vary according to the mechanism that is operative. Consideration should be given to specific therapeutic measures (e.g., radiation therapy, chemotherapy, antibiotics, regional neural blockade, or surgery), regardless of whether peripherally acting analgesic drugs are being used.

Bone metastases frequently cause inflammatory changes with release of inflammatory mediators, including prostaglandins. **When the pain is clearly arising from bone metastases, the use of drugs that interfere with prostaglandin synthesis [e.g., nonsteroidal antiinflammatory drugs (NSAIDS)] is logical.** These drugs should be avoided or used with caution in patients who have a history of peptic ulceration, excessive alcohol consumption, bleeding diatheses, renal impairment, or known idiosyncratic reactions to *aspirin* or related drugs. Where the use of NSAIDS is precluded, *acetaminophen (paracetamol)* is useful, although the mechanism of action of this drug is obscure. It may have central effects as well as some peripheral action. Although *acetaminophen* is fairly well tolerated and safe, it should be used in reduced dosage in patients with extensive liver damage. **Bisphosphonates have been shown to reduce pain due to bone metastases in patients with breast cancer or multiple myeloma, but experience in gynecologic cancer is limited**(20,21).

Peripherally acting drugs such as *acetaminophen* and NSAIDS are also useful for pain arising in nonosseous sites and for postoperative pain. They should rarely be omitted from drug analgesic regimens, even in moribund patients. Rectal preparations may prove useful in patients who are unable to take oral drugs.

Muscle spasm requires muscle relaxants such as *diazepam*, as well as gentle massage. Psoas spasm from a psoas abscess or direct tumor infiltration is not infrequent in gynecologic cancer. It should be suspected if there is pain in a lumbosacral distribution associated with difficulty achieving full extension of the hip.

Step Two—Raise the Pain Threshold

All people should be considered to have a threshold above which they will be troubled by pain. This threshold is dynamic, and may be varied by many factors. **The threshold for pain may be raised by comfort, care, concern, diversion, and various forms of relaxation, and lowered by depression, anxiety, loneliness, and isolation.** A wide range of strategies exist to facilitate coping with pain, and simple nonpharmacologic measures should be tried initially. The diagnosis of a disturbed threshold in an individual patient is difficult, but the narrative approach to assessment of the patient gives clues: as the patient is given a chance to tell the story of her diagnosis, treatment, and pattern of her pain, she imparts information not only about the cancer but about herself, and excessive distress is readily perceptible.

Occasionally, anxiety and depression are so clearly pathologic that the patient is impeded in her attempts to relate to her loved ones and to come to terms with her disease. In such circumstances, a formal psychiatric consultation may be of assistance and anxiolytics or antidepressants may prove helpful. **In general, threshold issues, including extreme anguish, feelings of futility, loss of sense of meaning, personal guilt, and other forms of spiritual pain require a different approach, with help from skilled counselors, pastors, and, above all, those people who are close to the patient.**

Step Three—Precise and Appropriate Use of Opioid Drugs

There is abundant literature on opioid use, with a range of opioids available(13,14 and 15,17,18 and 19). There are still difficulties obtaining opioids for medical use in some developing countries despite the initiatives of the World Health Organization.

Some types of pain are relatively unresponsive or partially responsive to opioids. These include pain caused by nerve irritation, extreme muscle spasm, incident pain (i.e., pain exacerbated by a particular activity such as movement), or pain that is heightened by unaddressed anguish.

A variety of opioids are available. **In practice, low-potency opioids such as *codeine* or *dextropropoxyphene*, or high-potency opioids such as *morphine*, are combined with peripherally acting drugs such as *acetaminophen* or *aspirin.*** Low- and high-potency opioids should not be given concurrently, but a change from one opioid to another is frequently justified and usually this involves a change from another opioid to *morphine. Morphine* remains the preferred initial opioid of high potency, but in some patients consideration may need to be given to alternative high-potency opioids, such as *fentanyl, methadone, oxycodone*, and *hydromorphone.*

Regardless of the choice, opioids should be given at regular intervals in accordance with the half-life of the drug concerned, rather than haphazardly in response to a severe pain stimulus. Opioids have a therapeutic range, and doses can be carefully titrated against response.

Morphine

Oral *morphine* is available in two forms, an immediate-release solution or tablet that reaches a peak within 30 minutes of ingestion, and controlled-release preparations that take several hours to reach peak concentrations (22,23). **Immediate-release *morphine* is best given every 4 hours, with a double dose (or 1.5 times the standard dose in the frail) at bedtime and a break of approximately 8 hours overnight to permit sleep for both patient and caregivers.** Many find the following schedule to be useful: 6 a.m., 10 a.m.,2 p.m., 6 p.m., and 10 p.m.

A reasonable starting dose of oral *morphine* in a patient not already on an opioid drug would be 5 to 10 mg in a patient of average size or 3 to 5 mg in the frail or elderly patient, with repetition of the original dose in 1 to 2 hours if there has been inadequate relief of pain.

Over the next 24 to 48 hours, dose finding is undertaken by prescribing regular doses every 4 hours together with one or two “breakthrough” doses equal to the standard dose. The correct dose may range from 2 mg to over 100 mg every 4 hours, but most patients need less than 50 mg every 4 hours.

Controlled-release *morphine* tablets represent a significant advance in convenience of administration, with the proviso that dose finding should usually be undertaken with the use of an immediate-release preparation. Once the correct dose has been determined, the total 24-hour dose can be given in one (every 24 hours) or two fractions (every 12 hours), according to the controlled-release preparation being used. It is essential that the tablets not be crushed. Breakthrough doses of immediate-release *morphine* at a dose equivalent to the 4-hourly dose can still be administered if required. For example, a patient taking 20 mg oral *morphine sulfate* mixture every 4 hours can be converted to 60 mg controlled-release *morphine* each 12 hours, with additional breakthrough doses of 20 mg of *morphine sulfate* mixture if required.

Controlled-release *morphine* should not be used (a) in patients with uncontrolled or unstable pain, (b) in patients with extensive upper abdominal or retroperitoneal disease that is likely to interfere with gastrointestinal motility, or (c) when there is severe fecal impaction. Immediate-release oral *morphine* or subcutaneous *morphine* is a better choice in such circumstances.

If parenteral *morphine* is essential, the subcutaneous route is satisfactory, either with intermittent injections through an indwelling butterfly needle every 4 hours or with a continuous infusion through a battery-driven syringe driver. The intramuscular route is also used sometimes. In general, a parenteral dose of one half or one third of the oral dose appears equianalgesic. If oral or subcutaneous *morphine* is efficacious but the side effects are troublesome, the epidural route is occasionally advantageous.

Intravenous *morphine* infusions, although occasionally useful, may be associated with the development of tolerance, which may not always be overcome by the addition of further *morphine* (24). Cessation of the infusion and resumption of appropriate subcutaneous doses every 4 hours is often helpful in this circumstance. Simultaneously, it is important to review other aspects of management, such as the possible need for NSAIDS or drugs relevant to neuropathic pain, and to pay appropriate attention to psychological factors.*Heroin (diamorphine)* offers no advantage over *morphine* except higher solubility, and it may be regarded as a prodrug because its efficacy depends on metabolism to *morphine*.

The efficacy of the regular dosing approach to *morphine* administration depends on the contribution of an active metabolite (*morphine 6-glucuronide*), which is a more powerful analgesic than *morphine*. **Hepatic impairment, if severe, interferes with *morphine* metabolism to glucuronides. Renal impairment, even if only moderate, interferes with excretion of the active metabolites.** In both of these circumstances, dose reduction is essential. In a patient with renal impairment, it may be necessary to extend the dose interval from 4th-hourly to 6th- or even 8th-hourly.

Some physicians and nurses, as well as patients, continue to harbor misconceptions about the use of *morphine*. When *morphine* is to be commenced, counseling should address three issues to counteract the following widely held fears:

The use of *morphine* with careful dose finding and monitoring does not, in most patients, lead to addiction (although physical dependence, a separate issue, occurs).

The introduction of *morphine* does not mean that the patient is actually dying, but rather that *morphine* is the most appropriate opioid at that time. It is the type of pain and its severity, not the prognosis for the patient, that dictate whether an opioid should be introduced. *Morphine*, correctly used, does not hasten death.

Patients and their families need to be reassured that the introduction of *morphine* does not mean that there will be no adequate analgesic available at a later stage in the illness, when the situation may be worse. *Morphine* does not lose its effectiveness, but increased doses may be needed later in response to tumor progression.

Side Effects Side effects to *morphine* do occur, but can in large part be avoided by precise prescribing.

Constipation occurs in most patients and prophylactic laxatives should be prescribed. Fecal impaction, occurring as a result of opioids given without a laxative, may cause a variety of distressing symptoms such as nausea, vomiting, pelvic pain, or confusion. It may also cause altered absorption of oral medications (25).

Nausea and vomiting may occur as a result of gastric stasis, stimulation of the chemoreceptor trigger zone, or constipation. Nausea is particularly common when opioids are commenced or when the dose is changing, but a tolerance to this side effect develops in most patients within 48 hours. Suitable antinauseants such as *metoclopramide* 10 mg four times daily or *haloperidol* 0.5 to 1.5 mg twice daily should be available if required. Regular prophylactic antiemetics should be prescribed for at least the first 48 hours if there is a history of *morphine*-induced nausea or vomiting.

Drowsiness may occur when doses are increased, but usually settles within 24 hours. If this symptom persists, the morphine level is probably above the therapeutic range for that patient. Other causes of drowsiness should be excluded, such as sedating drugs or hypercalcemia. If the pain is not well controlled in the presence of drowsiness, another approach is usually required, such as an alternative opioid or an alternative route of administration (e.g., spinal).

Pruritus is troublesome for a small number of patients because of the histaminogenic properties of *morphine.* It usually settles within 48

probably above the therapeutic range for that patient. Other causes of drowsiness should be excluded, such as sedating drugs or hypercalcemia. If the pain is not well controlled in the presence of drowsiness, another approach is usually required, such as an alternative opioid or an alternative route of administration (e.g., spinal).

Pruritus is troublesome for a small number of patients because of the histaminogenic properties of *morphine.* It usually settles within 48 hours and can be managed with judicious use of *promethazine.* Anticholinergic side effects of *morphine* are usually not troublesome.

Tolerance to *morphine* may be a significant clinical problem if the *morphine* is not introduced and calibrated correctly. When the drug is used correctly, increased requirements during the course of an illness usually signify an increase in the noxious stimulus because of disease progression, rather than a reduction in the effectiveness of *morphine*.

Use of Alternative Opioids

Although *morphine* is currently the preferred initial opioid, other potent opioids must be considered when:

1. Pain persists despite careful drug calibration.
2. Unacceptable side effects persist despite careful drug calibration.
3. Drowsiness or toxicity occurs at levels of the drug required to control the pain.

In these circumstances, careful attention should be given to the mechanism of the pain, along with steps 1, 2, and 4. If all steps have been well addressed, an alternative opioid should be considered. Availability varies, but gynecologic oncologists should become familiar with a narrow range of opioids (Table 23.1).

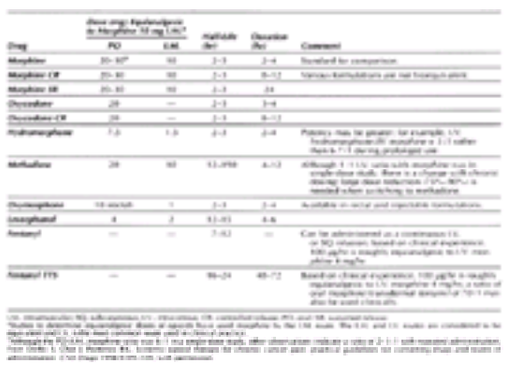

Table 23.1 Opioid Analgesics Used for the Treatment of Chronic Pain

***Oxycodone* (available as tablets, suspension, and suppositories) is approximately equianalgesic with *morphine*,** being most often used in a dose of 5 to 20 mg every 4 to 6 hours. Some patients tolerate oxycodone better than *morphine* at the same dose, and vice versa. However, in general terms, the side effect profile is similar.

***Meperidine (pethidine)* is of very little value in palliative care.** It has poor oral bioavailability and a short half-life, requiring frequent administration, approximately 2-hourly. At high doses (>1 g/day) or when renal failure is present, the metabolites lead to neurotoxicity, including delirium, agitation, and seizures. If a patient is already receiving *meperidine* subcutaneously or intramuscularly, conversion to *morphine* can be achieved with approximately 10% of the *meperidine* dose given as subcutaneous *morphine*, or 30% of the *meperidine* dose given as oral *morphine* every 4 hours.

***Methadone* is occasionally useful, but its long half-life (which varies with dose) is sometimes disadvantageous, and its sedative action outlasts its analgesic activity.** It has mechanisms of action that differ slightly from those of *morphine*. Conversion from *morphine* to *methadone* may be difficult, with subsequent dose reduction frequently required. *Methadone* has a similar side effect profile to *morphine.*

Fentanyl is receiving increasing attention with the development of a transdermal preparation enabling continuous administration of a short-acting opioid (26,27). Some dose calibration should usually occur with *morphine, oxycodone*, or subcutaneous or intravenous *fentanyl* before transdermal therapeutic system (TTS) *fentanyl* is applied. The patch forms a depot of drug in the dermis, resulting in a 17- to 48-hour delay before maximum plasma concentration is reached. After TTS removal, serum *fentanyl* concentrations decline approximately 50% in 16 to 17 hours. In practice, this means when the patch is applied, the immediate-release drug should be continued for at least 8 hours. If adverse effects develop, they will continue after TTS *fentanyl* removal and the patient should be monitored closely. When a patient who is using TTS *fentanyl* experiences an increase of pain, a short-acting opioid should be given concurrently, and the dose used to calculate the extra opioid requirement can then be incorporated into the TTS *fentanyl* dose.

Transdermal therapeutic system *fentanyl* is an attractive option because of the convenience of the delivery system and the less troublesome constipation compared with *morphine.*Expense may dictate that TTS *fentanyl* is used only for patients who do not tolerate *morphine.*

When using TTS *fentanyl*, it must be remembered that:

- **It is a delivery system useful for chronic pain only.** It may be hazardous for unstable pain and should not be used after surgery or in rapidly changing pain states.
- **Because of depot formation in the dermis, a delayed response occurs** that is particularly important in toxicity or overdose situations.
- **A short-acting opioid should be available for breakthrough needs** (e.g., *oxycodone*, immediate-release *morphine*).

Step Four—Recognize Neurogenic Pain and Treat Correctly

Neurogenic pain frequently develops in gynecologic cancer. It may be due to tumor infiltration or occasionally may result from therapeutic interventions. It may be flashing or burning in nature, but is often an unpleasant ache in an area of altered sensation corresponding to a peripheral dermatome.

When pain is neurogenic in origin, an opioid and a peripherally acting drug should usually be supplemented by tricyclic antidepressants, anticonvulsants, or corticosteroids. Other drugs, such as *clonazepam*, also may be of value. Medications should be started at low doses, and gradually increased as tolerated. A typical prescription for a patient with lumbosacral plexopathy would be oral *paracetamol*, *morphine* (5 to 10 mg subcutaneously), oral *amitriptyline* (25 to 100 mg at night) and a low dose of corticosteroid (e.g., oral *dexamethasone* 2 to 4 mg in the morning).

Regional blockade with local anesthetic techniques may be worthy of consideration. Epidural *morphine* with *lidocaine* is useful in carefully selected patients, and *ketamine* has an emerging role in some patients. In general, the management of neurogenic pain may be difficult, but relief is usually possible.

Gastrointestinal Symptoms

Anorexia

Anorexia is a common and significant symptom with a multitude of causes and serious nutritional consequences. **The best initial approach to management includes careful preparation of small meals, elimination of reversible gastric stasis or constipation, emotional support, and direct nutritional supplements. Progestational agents** have been demonstrated in randomized, double-blinded, placebo-controlled trials to increase appetite and food intake and to lead to weight gain in a number of patients, without undue side effects, but the expense is considerable(28). **Corticosteroids** have been shown to improve appetite and daily activity of patients with cancer, but this effect is short lived, with return to baseline responses by 28 days (29). Because patients must then undergo the problems of corticosteroid withdrawal, patient selection is critical.

Mouth Symptoms

Mouth symptoms, including xerostomia, altered taste, and oral candidiasis, can be most distressing. In addition, pain can occur from treatment-related mucositis and infective ulcers, so mouth care is crucial in very ill patients. Oral candidiasis responds to antifungal agents such as *nystatin* mouthwashes (every 2 to 3 hours), *amphotericin* lozenges, and, if necessary, a systemic *triazole* derivative such as *fluconazole.* Pain from mucositis may be relieved by *sucralfate* suspension and by *acetaminophen* with *morphine* (orally or subcutaneously).

A dry mouth can result from many factors in the critically ill patient: previous radiation therapy, mouth breathing, nasal oxygen, air conditioning, and drugs, particularly those with anticholinergic effects. Management of xerostomia may include minimization of contributory nonessential medications, frequent small drinks with a small amount of lemon/orange to stimulate saliva production, use of artificial saliva or *glycerin* preparations, and *pilocarpine* drops to stimulate saliva locally with minimal systemic effects (30).

Nausea and Vomiting

Nausea, vomiting, and bowel colic are common in advanced gynecologic cancer and each symptom requires precise diagnosis so that rational therapy may be applied (31,32). **Nausea, with or without vomiting, is mediated finally by the vomiting center situated in the reticular formation of the medulla oblongata, an area rich in histaminic and muscarinic receptors. The vomiting center is influenced by several connections,** each of which can be the causal pathway for nausea (Fig. 23.2 and Table 23.2).

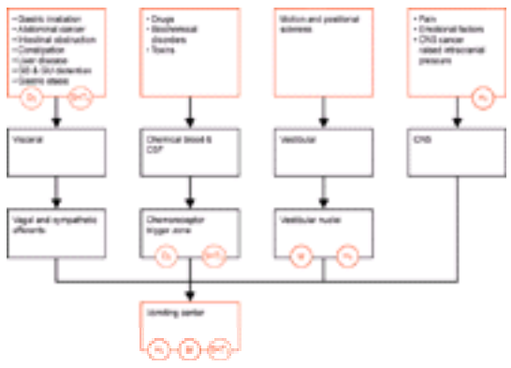

Figure 23.2 Diagrammatic representation of the reflex pathways leading to emesis. The sites of the neurotransmitter receptors are indicated. GB, gallbladder; GU, genitourinary; D_2, dopamine type 2 receptor; $5HT_4$, 5-hydroxytryptamine (serotonin) group 4; CNS, central nervous system; H_1, histamine type 1 receptor; CSF, cerebrospinal fluid; $5HT_3$, 5-hydroxytryptamine (serotonin) group 3; M, muscarinic cholinergic receptor. (Adapted from Lichter I. Which antiemetic? *J Palliat Care* 1993;9:42–50, with permission.)

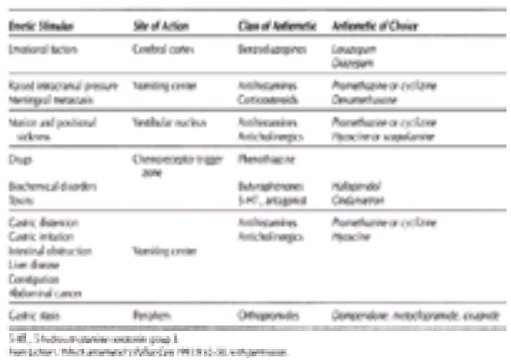

Table 23.2 Emetic Stimuli, Sites of Action, and Antiemetics of Choice

These include:

- **The cerebral cortex** (e.g., anxiety-conditioned responses)
- **The vestibular center,** which is rich in histaminic (H_1) and muscarinic receptors (e.g., cerebral metastases)
- **The chemoreceptor trigger zone,** which is rich in dopaminergic and serotonergic receptors (e.g., nausea induced by hypercalcemia, uremia, and some drugs, including chemotherapeutic agents)
- **The gastrointestinal tract** (e.g., gastric stasis, intestinal obstruction, fecal impaction, abnormalities of gut motility), which has dopaminergic, muscarinic, and some serotonergic receptors

Once the likely mechanism has been determined by means of a careful history, clinical examination, and investigations if indicated, the appropriate antinauseant can be prescribed (Table 23.2 and Table 23.3).

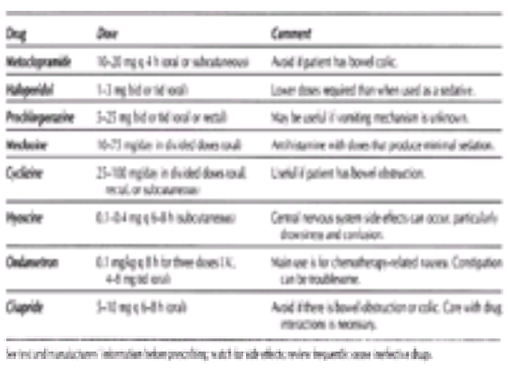

Table 23.3 Commonly Used Antinauseant Drugs

When anxiety dominates the scene, anxiolytics may be crucial in reducing the nausea. **When vestibular mechanisms are suspected** or when no specific pathway can be identified, relatively less sedating antihistamines (e.g., *cyclizine* and *meclozine*) that act directly on the vomiting and vestibular centers may be useful. *Prochlorperazine* has some affinity for dopaminergic, muscarinic, and histaminic receptors and is moderately useful, although less specific.

Nausea clearly related to the chemoreceptor trigger zone requires a drug with high affinity for dopaminergic receptors, such as *haloperidol.* A dose of 1.5 to 3 mg or less at night (orally or subcutaneously) may be sufficient. Nausea related to chemotherapy has become less of a problem for many patients with the introduction of serotonin antagonists such as *ondansetron*, but continued care must be taken with respect to side effects, which can include constipation.

Nausea arising from stimuli in the gastrointestinal tract associated with slowing of the gut should respond to gastrokinetic antinauseants such as *metoclopramide* or *domperidone*, which promote gastric emptying and increase gut motility. These actions are counterproductive in a patient with a very high gastrointestinal obstruction, and vomiting will be aggravated.*Cisapride* acts on muscarinic receptors, producing prokinetic action on the entire gut. Without dopaminergic activity, *cisapride* does not produce extrapyramidal side

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Drugs available by more than one route are advantageous. Both *metoclopramide* and *haloperidol* may be used subcutaneously as well as orally.

In addition to the established antinauseant drugs, **corticosteroids, which act by an unknown mechanism, are also useful in suppressing nausea,** and the drugs are frequently used in premedication programs before chemotherapy. Caution must be exercised if the patient has a history of active peptic ulceration, tuberculosis, diabetes mellitus, or psychosis.

Constipation

Constipation, a common symptom, may be due to changing diet, inactivity, opioid use without laxatives, or varying degrees of tumor-induced intestinal obstruction. Fecal impaction is a common cause of major symptoms, including nausea, spurious diarrhea, pain, and even confusion, especially in the elderly; the diagnosis should not be missed if avoidable misery is to be prevented.

Opioid-induced fecal impaction is usually avoidable but, if present, requires vigorous local treatment such as fecal softeners (e.g., *docusate-sodium*), large bowel stimulants (e.g., *senna*), stimulant suppositories, or careful enemas. Occasionally osmotic laxatives (e.g., *lactulose*) may be helpful. Fecal impaction caused by hold-up at the sigmoid colon (with an empty, dilated rectum) sometimes requires high *docusate-sodium* enemas if oral laxatives fail to relieve it; suppositories may be ineffective. Constipation due to mechanical obstruction requires either surgical intervention or acceptance of the problem as an end-stage event.

Medical Management of Intestinal Obstruction

Obstruction may occur at any level of the gastrointestinal tract in patients with gynecologic cancer and frequently involves several different levels. It is a common late-stage problem, particularly in patients with ovarian cancer.

In general, surgery provides the best palliative relief of symptoms, if successful. This is particularly true for the few patients who have a nonmalignant cause for the obstruction, such as adhesions from radiation therapy or previous surgery. Similarly, bowel obstruction in a patient for whom chemotherapeutic options have not been exhausted justifies active surgical intervention if the patient fails to respond to nasogastric suction and intravenous fluids. In patients who have exhausted reasonable chemotherapeutic options, or who have a poor performance status, the approach may be more conservative.

One option for conservative management is a trial of corticosteroids (e.g., *dexamethasone*,4 to 8 mg parenterally daily for 3 to 5 days). The obstruction may be relieved, presumably by decreasing inflammatory edema, thereby improving luminal diameter, and this treatment may be repeated in the future (33,34). There is need for caution when using corticosteroids in patients with a history of diabetes mellitus, peptic ulceration, recent infection, impending bowel perforation, significant psychiatric disorder, or tuberculosis. **Corticosteroids are best used in patients considered unsuitable for surgical intervention.**

In a patient with end-stage obstruction, when the aforementioned measures have failed to relieve the problem, the totally symptomatic approach developed at St. Christopher's Hospice may be helpful (35). In brief, this approach avoids the use of both nasogastric suction and intravenous fluids. It relies on careful mouth care, with a little food and drink as desired. **The patient remains mildly dehydrated, but this is beneficial and decreases the amount of vomiting.** Centrally acting antinauseants (e.g., *cyclizine, haloperidol*) are used, if necessary, in combination with low doses of analgesics. Gastrokinetic antinauseants (e.g., *metoclopramide* or *domperidone*) are contraindicated in patients with a high obstruction. ***Hyoscine hydrobromide* may serve multiple purposes in patients with bowel obstruction, acting on the vomiting center and also reducing gastrointestinal secretions and intestinal tone, effectively increasing bowel capacity.** This alleviates nausea for the patient with complete obstruction and avoids multiple small vomits, although infrequent large-volume vomits continue. *Hyoscine butyl bromide* is similar but lacks the central effects.

A subcutaneous butterfly needle with or without a battery-driven syringe driver can be used to deliver appropriate doses of antinauseants, such as *haloperidol* 2 to 6 mg/day, as well as *hyoscine hydrobromide* 0.1 to 0.2 mg or *hyoscine butyl bromide* 10 to 20 mg every 6 hours. With careful calibration of dose, the patient need not be drowsy. *Morphine* may be given in the same syringe if pain is present. If colic is not controlled with *morphine*, additional *hyoscine* may be useful. Rectal *prochlorperazine*, 50 to 100 mg/day, may be tried instead of *haloperidol.* *Cyclizine* (oral, parenteral) is often very helpful. *Octreotide*, starting at a dose of 50µg subcutaneously every 8 hours, can provide additional relief of symptoms by reducing secretions and colic. Doses above 600 µg/day probably do not afford additional benefit, and tolerance to this medication may occur.

This treatment should abolish the nausea, but occasional vomiting, once or twice a day, still occurs. Some patients prefer bouts of even copious vomiting to a continuous nasogastric tube. If the obstruction is very high, percutaneous gastrostomy may be considered. Under all these circumstances, electrolytes should neither be monitored nor corrected. Electrolyte imbalance becomes inevitable and should be allowed to take its course.

The symptomatic approach to bowel obstruction represents a major advance in palliative therapeutics and has significantly improved the last phase of life for a large number of women dying with intestinal obstruction, although very high obstruction continues to be a therapeutic challenge.

Diarrhea and Tenesmus

Diarrhea in a patient with advanced gynecologic cancer is probably best considered as a sign of fecal impaction until proven otherwise. True irritative diarrhea can occur by tumor involvement of the bowel wall or after radiation therapy. *Loperamide* may be useful in the management of such patients.

When fecal soiling is associated with an enterovaginal or rectovaginal fistula, surgical diversion should be considered if at all possible. If such surgery is not possible, the emphasis is on nursing procedures calculated to keep the vagina and perineum as clean and comfortable as possible, and to support the patient in her distress. Antibiotics, especially *metronidazole*, locally as well as systemically, may reduce some of the distressing odor when necrosis has occurred. A urinary catheter may assist in restoring urinary continence.

Case reports of the successful use of *somatostatin* to reduce bowel fistula drainage have been described (36). The use of stool bulking agents (e.g., *cellulose*) may reduce the amount of fecal ooze if the fistula is colonic.

Tenesmus usually responds to anticholinergic derivatives, corticosteroids, and opioids. Occasionally, resection of tumor as a palliative procedure may be justified. In severe cases, spinal local anesthetics or sacral nerve blocks may be necessary.

Ascites

Abdominal distention due to intractable ascites can be a major cause of distress. **Diuretics, particularly *spironolactone*, 50 to 150 mg/day, if necessary coupled with a loop diuretic, may prove helpful initially.** Recurrent paracentesis has a limited but definite place, whereas shunting procedures are not reliable and have been associated with significant morbidity and mortality. Cytotoxic agents (systemic or intraperitoneal) may be worthy of consideration, but their potential is limited in a late-stage patient. The actual discomfort is usually controlled with a combination of a peripherally acting drug such as *acetaminophen* and a low dose of an opioid.

Respiratory Symptoms

A clinical history, physical examination, and a chest radiograph should differentiate between dyspnea caused by a pleural effusion, bronchial obstruction, diffuse lung involvement, reduced excursion due to massive ascites, bronchial asthma, chronic obstructive airway disease, cardiac failure, and respiratory infection. However, **in advanced cancer, dyspnea may be multifactorial, with advanced cachexia and resultant muscle asthenia contributing to the situation.** Treatment of contributing comorbidities such as cardiac failure should be considered in all patients. Drainage of a pleural effusion, with early consideration of a pleurodesis, may afford prompt relief of dyspnea, cough, and chest wall discomfort. Radiation therapy to a bronchial lesion causing hemoptysis, cough, or obstruction may produce prolonged palliation of symptoms.

When the dyspnea is due to diffuse lung involvement, and/or the cause of dyspnea is not reversible or not responsive to specific maneuvers, the careful use of *morphine* may improve the situation significantly, especially if the respiratory rate is increased (10). Oral *morphine* should be commenced at doses of 2 to 5 mg every 4 hours and increased until drowsiness develops or until no further benefit is gained. In practice, this usually means doses of approximately 10 to 20 mg every 4 hours. **The mechanism by which *morphine* reduces dyspnea is poorly understood, but includes both central and peripheral actions.** If a patient is already receiving *morphine* calibrated correctly for pain relief but becomes dyspneic because of tumor progression,*morphine* may be increased by a further 30% to 50% to give relief.

For the patient with an obstructing bronchial lesion or with carcinomatous lymphangitis, corticosteroids may afford some relief of dyspnea by reducing peritumor edema. This can be achieved at doses equivalent to 8 to 16 mg *dexamethasone*, with reduction to the lowest possible dose when an effect has been achieved.

The role of oxygen in dyspneic patients with advanced cancer who are not seriously hypoxic is controversial. Some patients find that oxygen masks or even nasal prongs inhibit communication, restrict their movements, and induce claustrophobia. These patients may find an open window or a fan to be effective. Other patients appear to obtain benefit from oxygen and feel unable to manage without it: whether this represents at least in part a psychological dependence is uncertain. **Some patients who have been previously oxygen dependent because of dyspnea can become less so with careful use of *morphine.***

Anxiolytics may be valuable in modest doses. Benzodiazepines (e.g., 2 mg *diazepam* orally or 0.5 mg *lorazepam* sublingually)may have significant benefit for the anxious patient. For the patient who is in the last few days of life, an infusion of subcutaneous *midazolam* at low doses (e.g., 5 to 15 mg over 24 hours in the patient who is *benzodiazepine* naive)can afford significant relief of dyspnea.

Urinary Tract Symptoms

Urinary tract symptoms are common in women with far-advanced gynecologic cancer. Bilateral ureteric obstruction, with subsequent infection, pain, and acute renal failure, may justify mechanical measures such as nephrostomy or ureteric stent insertion if the prognosis on other grounds is for at least several good-quality months of life. Although some patients clearly benefit, fine judgment is required in the individual case, and such patients should be managed in consultation with a gynecologic oncologist. For patients with no reasonable treatment options and problematic symptoms, it usually is prudent to refrain from mechanical intervention.

Improved patency of ureters may be achieved by short courses of corticosteroids (e.g., oral *dexamethasone*, 4 mg/day for 3 to 5 days), but should only be considered if short-term goals are to be achieved (37).

Bladder symptoms may benefit from the use of NSAIDS to reduce detrusor irritability or drugs with an anticholinergic action to reduce bladder contractility. Catheterization may be unavoidable in some circumstances. Urinary incontinence resulting from fistulas to the vagina or rectum is usually best managed with diversion if feasible. If not, urinary catheterization may assist in keeping the perineum dry.

Edema

Deep venous thrombosis should be excluded, particularly if other signs such as pain, increased temperature of the affected limb, or superficial venous dilatation are present. Anticoagulation in patients who have a deep venous thrombosis may lead to a reduction of symptoms, but the decision to anticoagulate a patient with advanced cancer must be made in the context of the patient's prognosis and goals.

If the swelling is due to lymphatic obstruction, the management must be individualized. Physical therapies, in experienced hands, are most helpful for moderate to severe lymphedema. Massage, bandaging, and fitting of support garments may add much to a patient's comfort. Compression bandages or support hosiery should not be applied to grossly edematous legs because venous circulation may be further compromised.

Low doses of corticosteroids may improve the situation and probably should be tried for a few days if leg swelling is a dominant symptom unrelieved by simple measures. Paradoxically, corticosteroids can increase lower limb edema by causing fluid retention with chronic administration.

Small doses of diuretics are frequently tried for the patient with lymphedema, but success is anecdotal. Usually *spironolactone* is used at doses of 50 to 150 mg/day, with the addition of *furosemide* if there is no response. Both of these drugs can render the frail patient profoundly dehydrated and can cause troublesome postural hypotension.

Weakness

Weakness or fatigue can be profound when there is a large tumor burden, but there are many reversible causes of this symptom. These include nutritional deficiencies (see Chapter 18), hypotension, hypokalemia, hypoglycemia or hyperglycemia, hypoadrenalism, hypercalcemia, renal failure, infection, and anemia. At least some of these may be readily treated in appropriate circumstances. Anemia *per se* does not require correction in every patient because the benefit may be short lived and not proportionate to the expenditure of resources. A patient who is confined to bed because of advanced disease usually tolerates a hemoglobin of 7.0 g/dL or less. However, if the hemoglobin is low and weakness is a dominant symptom, transfusion may be justified.

Hypercalcemia

Hypercalcemia (raised ionized plasma calcium level) is a recognized complication of malignancy and a potent cause of symptoms, ranging from lethargy, weakness, and constipation to severe nausea, vomiting, confusion, and exacerbation of pain. In general, anticancer therapy directed at removing the cause of the hypercalcemia is most useful if still feasible.

Hypercalcemia usually heralds a poor prognosis (38), and for the relatively asymptomatic or already obtunded patient, aggressive treatment may not be warranted. However, the presence of troublesome symptoms may make palliative antihypercalcemic therapy worthwhile.

Treatment of hypercalcemia depends on its severity. The following measures are necessary in moderate or severe cases:

- **Rehydration with intravenous normal saline** (2 to 3 L/day or more). **This may be coupled with a loop diuretic** (e.g., *furosemide*) to maintain a diuresis in patients receiving aggressive hydration, particularly in older patients.
- **Infusion of a bisphosphonate** (e.g., *pamidronate* 45 to 90 mg intravenously in 250 mL of crystalloid over 4 to 8 hours). The dose of bisphosphonate depends on the level of calcium. The duration of response varies according to the drug given and the clinical circumstances, but may be in the order of 35 days for *pamidronate* (39).

Improvement of symptoms with these measures can be expected within 2 to 3 days, as calcium uptake in bone increases. Therefore, intravenous hydration should be continued for this period. **When calcium is extremely high and intravenous therapy is not causing a rapid reduction, subcutaneous *calcitonin* administration combined with bisphosphonate therapy provides a more rapid reduction of calcium levels.** Tachyphylaxis develops to *calcitonin* within 2 to 3 days.

Should hypercalcemia recur, the bisphosphonate dose may be repeated. The rate of relapse depends in part on the availability of effective therapy for the underlying tumor, as well as on the biologic characteristics and tempo of the neoplastic process.

Care of the Dying Patient

The process of dying is fraught with uncertainties. **Space, time, privacy, and peacefulness are the essence of good care.** When it is clear that the patient is dying, the goal is dignity and peace, best served by precise control of major symptoms. This usually involves continuation of indicated drugs in correct dosage, preferably given subcutaneously or rectally.

Sometimes it is justifiable to offer direct sedation when, in spite of adequate symptom control, distress is extreme and opportunities for verbal communication no longer exist. This is particularly the case if an agitated delirium is present. Management in these instances depends on the predominant features: if hallucinations are prominent, an antipsychotic may be most useful, such as *haloperidol* 0.5 to 5 mg twice a day. However, if agitation and distress are present, a benzodiazepine should be used, either alone or in combination with an antipsychotic. In such circumstances, sublingual *lorazepam*0.5 to 2.5 mg every 4 to 6 hours may be valuable. Alternatively, parenteral *midazolam* (e.g., 2 to 5 mg subcutaneously or intramuscularly) may assist in achieving appropriate sedation, whereas a subcutaneous infusion of 10 to 50 mg every 24 hours may be helpful if the situation is protracted. **Large doses of opioids are not appropriate for sedation of the dying.**

Complex equipment should be avoided if possible, as should tubes of all sorts, to facilitate maximum physical contact with loved ones. Nursing care must remain excellent, with particular emphasis on pressure care, mouth care, and “grooming.” **Teaching family members to assist with the care of their loved one can do much to enhance intimacy and diminish the sense of helplessness many families feel.** In the face of imminent death, respect for individual religious and cultural customs is mandatory.

It is essential that medical and nursing staff accept and understand the personal significance of the final phase of life.

Death serves as the master-test of our journeyman years. It tests the height we have reached, the value of our inner metaphysics; it examines its strength, its utility, durability, and suitability in mobilization and in the most terrible reality: it introduces a factor alien to the subject and thus summons us directly from the subjectively ideal sphere, from the freely suspended realm of ideal self-definitions, to the “cosmic” realm of danger and diffusion, and of the gathering from the bustle of this world of death in which the self finally proves itself, after all (40).

If the clinician and other professional staff regard dying as a battle failure, the patient may understandably feel like a battlefield (and some do!). From the patient's perspective, the following issues are seen as significant in end-of-life-care:(a) receiving adequate pain and symptom management, (b) avoiding inappropriate prolongation of dying, (c) achieving a sense of control, (d) relieving the burden on caregivers, and (e) strengthening relationships with loved ones (41).

No patient should die in despair. Unrealistic expectations may increase, not relieve, suffering (42). It is particularly important at this time that the medical system recognizes as its goal the relief of human suffering. If a patient prefers to die “raging against the dying of the light” (Dylan Thomas) rather than in peaceful acquiescence, that, too, must be respected. Good palliative care is concerned with the enrichment of life, even when facing the human task common to all, that of dying.

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24 Psychological Issues

Barbara L. Andersen

For most women, a diagnosis of gynecologic cancer is a crisis. There follows a period of extreme emotional distress, but this slowly dissipates with recovery. For others, cancer may become a chronic stressor, a way of life, either because the disease is disseminated and can be controlled only with radical treatments or because their coping strategies are not adequate for this life experience. In any case, management of patients with gynecologic malignancies needs to go beyond routine medical care and take into account the psychological and behavioral aspects of the disease.

A review of the data on psychological and behavioral issues surrounding gynecologic cancer is presented. In addition, practical information that can be used to conceptualize and deal with a woman's personal response to her disease is summarized.

A Biobehavioral Model of Cancer Stress and Disease Course

The stability of many cancer mortality rates, particularly those cancers with a high incidence such as breast and ovarian, makes it imperative that new, innovative steps be taken to improve survival and enhance quality of life. Psychological interventions result in significant improvements in quality of life [see Andersen (1) for a review]. Further, both qualitative (2) and quantitative (3) summaries of the *psychoneuroimmunology* literature conclude that psychological distress and stressors (i.e., negative life events, both acute and chronic) are reliably associated with changes–downregulation–in immunity. Thus, addressing the mental health needs of those with cancer has important quality-of-life benefits, and the biologic or health consequences of psychological interventions are being tested as well.

Figure 24.1 provides a representation of a model of the psychological and behavioral factors and biologic mechanisms by which disease or health outcomes might be influenced. The rationale and empiric support for this novel viewpoint are detailed in the following sections.

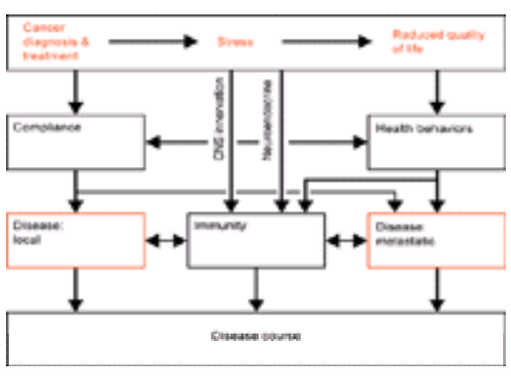

Figure 24.1. A behavioral model of the psychological (stress and quality of life), behavioral (compliance and health behaviors), and biologic pathways from cancer stressors to disease course. CNS, central nervous system. (From Andersen BL, Kiecolt-Glaser JK, Glaser R. A biobehavioral model of cancer stress and disease course. *Am Psychol* 1994;49:389–404, with permission.)

Stress and Quality of Life

The model first considers the occurrence of stress and lowered quality of life that come with diagnosis and treatment. These are objective, negative events, and although negative events do not always produce stress and lowered quality of life, data from many studies document severe, acute stress at diagnosis. For example, Andersen et al. (4) studied **women with newly diagnosed gynecologic cancer and found that anxious, depressed, and confused feelings characterize patients' initial psychological reactions. In addition, lengthy cancer treatments and disruptions in major life areas occur, producing chronic stress. Emotional distress, in combination with the other life disruptions, can result in a stable, but lower, quality of life.** Other permanent sequelae, such as sexual problems and/or sterility, may affect intimate relationships and social support. Unemployment, underemployment, job discrimination, and difficulty in obtaining health insurance can also become chronic stressors.

Health Behaviors

Important adverse health behavioral sequelae can occur and include an increase in negative behaviors and/or a decrease in positive ones. There are many circumstances that can result in negative health behaviors. People who are depressed and/or anxious are more likely to self-medicate with alcohol and other drugs, and, in addition, alcohol abuse can potentiate distress. Distressed people often have appetite disturbances or dietary changes that are manifest by eating less often or eating meals of lower nutritional value. Although there are individual differences in behavioral changes of this type, women may be at greater risk. Distressed people may report sleep disturbances, such as early-morning awakening, sleep-onset insomnia, and middle-night insomnia. Cigarette smoking and caffeine use, which often increase during periods of stress, can intensify the physiologic effects of psychosocial stress, such as by increasing catecholamine release.

Conversely, people who are stressed may abandon their previous positive health behaviors, such as engaging in regular physical activity. If these behaviors can be maintained, positive outcomes can accrue because there is a positive relationship between physical activity or fitness and psychological health. For example, MacVicar and colleagues (5) found that among patients with breast cancer receiving chemotherapy but also participating in a program of aerobic interval training, there were positive mood effects as well as increased functional capacity for the women.

The model suggests that health behaviors may, in turn, affect immunity. Problematic health behaviors can have direct as well as interactive effects on immunity. For example, substance abuse has direct effects on immunity as well as indirect effects through alterations in nutrition, and poor nutrition is associated with a variety of immunologic impairments. Conversely, there is growing evidence that positive health behaviors such as physical activity can have positive consequences for both the immune and endocrine systems, even among people with chronic diseases. In summary, these lines of data suggest that distressed people tend toward negative health behaviors that may potentiate their stress and, concurrently, exert downregulating immune effects, and positive health behaviors, such as exercise, may have the converse effect.

The model suggests that health behaviors may be directly related to disease progression. Considering all the health behaviors noted previously, the strongest case can be made for the importance of nutrition and diet. A variety of data link nutritional and dietary factors and risk for cancer, particularly breast cancer (6). More germane to the model are data suggesting that increased fat intake, obesity at diagnosis, and weight gain may be related to recurrence and survival. Alternatively, some suggest that fiber, rather than fat, is the critical dietary factor, in that fiber is postulated to modify serum estrogen levels by increased fecal excretion of estrogens. Taken together, these data suggest that behavioral factors relevant to nutrition, fat/fiber balance, and energy expenditure (vis-à-vis weight gain) may be relevant to disease progression.

Compliance

The second behavioral factor noted in the model is treatment (non)compliance. Compliance problems cross a wide range of diseases, therapies, and individual patient characteristics. In cancer, some patients become discouraged and fail to complete treatment. A general implication of such behaviors is the invalidation of clinical trials, but a specific implication for the individual patient is that his or her survival may be compromised if an inadequate dosage of therapy is received. **The model suggests that poor compliance can effect either local or metastatic control of the disease, or both, and which route is selected depends on the treatment regimen as well as the characteristics of an individual patient's noncompliance.**

Interaction of Health Behaviors and Compliance

The model specifies that the processes governing compliance and health behaviors may interact or even be synergistic. That is, **those who are compliant with treatment may expect better health outcomes, and thus comply with diet, exercise, sleep, and other behaviors indicative of "good health."**

Biologic Pathways

Stress sets into motion important biologic effects involving the autonomic, endocrine, and immune systems (7). Stress may be routed to the immune system by the central nervous system through activation of the sympathetic nervous system or through neuroendocrine-immune pathways (i.e., the release of hormones; Fig. 24.1). In the latter case, a variety of hormones released under stress have been implicated in immune modulation (i.e., catecholamines, cortisol, prolactin, and growth hormone).

Although there is no stress pathway (effect) to immunity, there is evidence for the importance of the immune responses in host resistance against cancer progression (hence, in Fig. 24.1, the arrows going in both directions from immunity to local and metastatic disease). Experts in immunology and oncology cite the following important findings with regard to the specific importance of natural killer (NK) cell activity (8): (a) patients with a variety of solid malignancies and large tumor burdens have diminished NK cell activity in the blood; (b) low NK cell activity in patients with cancer is significantly associated with the development of distant metastases; and (c) in patients treated for metastatic disease, the survival time without metastasis correlates with NK cell activity.

In considering these mechanisms, a central issue is whether an immune response can be affected by stress, and if it can, whether or not the magnitude of the effect has any biologic significance. Both acute as well as chronic stressors can produce immunologic changes in relatively healthy people. Some of the largest effects, usually found in NK cell assays, are found for chronic stressors and/or ones that have interpersonal components (9). Many of the qualities of chronic stressors (continued emotional distress, disrupted life tasks, e.g., employment, and social relationships) occur with the decrements in quality of life found in studies of patients with cancer.

This relationship between stress and immunity has been tested by Andersen and colleagues (10). Women diagnosed and surgically treated for stage II (70%) or III (30%) invasive breast cancer were studied (N = 116). Before beginning adjuvant therapy, all women completed a validated questionnaire assessing stress about the cancer experience (Impact of Events Scale) and provided a 60-mL blood sample. A panel of NK cell and T-cell assays were conducted: (a) NK cell lysis; (b) the response of NK cells to recombinant g-interferon (IFN-g) and recombinant interleukin-2; (c) blastogenic response of peripheral blood leukocytes (PBLs) to phytohemagglutinin A (PHA) and concanavalin A (ConA); and (d) the proliferative response of PBLs to a monoclonal antibody (MAb) to the T-cell receptor (T3). Multiple regression models were used to test the contribution of psychological stress in predicting immune function. All regression equations controlled for variables that might also be expected to exert short- or long-term effects on these responses, such as age, stage of disease, and length of time of surgical recovery, and ruled out other potentially confounding variables (e.g., nutritional status) that might also be influential. These controls reduced the plausibility of alternative, rival hypotheses for the findings. Significant effects were found and replicated between and within assays, including the following: (a) stress significantly ($p < 0.05$) predicted NK cell lysis; (b) stress significantly ($p < 0.01$) predicted the response of NK cells to recombinant IFN-g, replicated across 4 effector to target cell ratios (E:T ratios); (c) stress significantly predicted the response of PBLs to ConA ($p < 0.05$) and PHA ($p < 0.05$), and the proliferative response to the T3 MAb ($p < 0.05$). The data show that the physiologic effects of stress inhibited a panel of cellular immune responses, including cancer-relevant NK cell cytotoxicity and T-cell responses.

Disease Course

Are there adverse health (illness) consequences of stress? There are few data on this important issue, and most come from nonexperimental designs with healthy (but stressed) adults. One of the more compelling studies is that of Cohen and colleagues' (11) experiment with healthy volunteers. Subjects were inoculated with either a cold virus or a placebo. Analyses revealed that rates of both respiratory infection and clinical colds increased in a dose–response manner with increases in psychological stress across five different strains of cold viruses. These relationships remain to be experimentally tested with patients with cancer, but the data with healthy samples suggest the covariation of stress and selected health outcomes.

Diagnosis

Patients with cancer face difficult circumstances throughout their illness, but the shock of learning the diagnosis is the first, and often the most difficult, experience. The term *existential plight* has been used to describe this period and the emotional turmoil that continues for the immediate months (12). The emotions and sources of distress may include:

1. ***Depression*** from life disruption and doubts concerning the future.
2. ***Anxiety*** anticipating cancer treatment.
3. ***Confusion*** from dealing with a complex medical environment.
4. ***Anger*** from the loss of childbearing capacity and the opportunity to choose whether to have children.
5. ***Guilt*** from concerns that previous sexual activity may have "caused" the cancer. The guilt may be mixed with concerns about how future sexual activity will be disrupted after cancer treatment.

In a prevalence study of psychiatric illness among patients with cancer, Derogatis et al. (13) **estimated that approximately 50% of patients with cancer would justify a psychiatric diagnosis and, of those, 85% had symptoms of depression and/or anxiety.** Most diagnoses (68%) were classified as an *adjustment disorder*—a maladaptive emotional reaction to a life stressor. In a similar investigation of 83 women with gynecologic cancer, Evans et al. (14) reported that 23% met appropriate psychiatric criteria for major depression, 24% met criteria for *adjustment disorder with depressed mood*, and 14% had other psychiatric diagnoses. In a study of depressive symptomatology, Cain et al. (15) studied 60 newly diagnosed patients with cervical, endometrial, or ovarian malignancies. They classified the depression as severe in 35% of the patients, moderate in 35%, and mild in 30%.

Initial Diagnosis To clarify the pattern of mood disturbance common to a diagnosis of cancer, we asked women to complete a self-report inventory on the emotions they experienced during their initial evaluation (4). Their responses were compared with those from two matched groups, one with benign gynecologic disease anticipating surgery and the other with no disease (i.e., healthy women). Findings were as follows:

1. Only women with cancer described themselves as significantly depressed.
2. In contrast, high anxiety was reported by both groups with disease, whether benign or malignant.
3. There were no differences in the level of anger between the groups.
4. High levels of confusion were reported only by the patients with cancer.
5. There were equivalent levels of fatigue among the disease groups.

Recurrence **Patients with recurrent cancer have an even greater level of distress than women receiving their initial diagnosis. This appears to result from higher levels of depression and anger.** In contrast, the levels of anxiety and confusion are comparable with those reported by women receiving their first diagnosis. Thus, the worries of a poorer prognosis, the anger about treatment failure, and the anticipatory concerns about beginning further treatment are evidenced.

Intervention **Severe emotional distress consequent to cancer diagnosis and during cancer treatments can be reduced with psychologic efforts.** Two studies, both using nonequivalent control group designs, have explored the effectiveness of brief psychological interventions for patients with gynecologic cancer.

Capone et al. (16) provided a crisis-oriented intervention to newly diagnosed women. The structured counseling assisted women to express feelings and fears related to their diagnosis or upcoming treatment, provided information about treatment sequelae, and attempted to enhance self-esteem, femininity, and interpersonal relationships. For sexually active women, an additional sexual therapy component included information on how to reduce anxiety when resuming intercourse. The format involved at least four individual sessions during the surgical hospitalization; the length of each session or total therapy time was not specified. Two psychologists were the therapists. Fifty-six newly diagnosed women (51% were stage I, 22% stage II, 15% stage III, and 12% stage IV or unstaged) receiving treatment at a university medical center participated; the participation rate was 87%. The sociodemographic characteristics were as follows: mean age was 50 years, 60% had at least a high school education, 64% were married, 79% were white, and 21% were black. A nonequivalent control group was obtained by recruiting previously treated women as they returned for posttreatment follow-up. Standardized outcome measures were used to assess emotional distress and self-concept and were supplemented with self-reports of return to employment and frequency of intercourse. Data were gathered before treatment and at 3, 6, and 12 months after treatment for the intervention women and at the same posttreatment intervals for the comparison women. Analyses indicated no differences between groups or within the intervention group on the measures of emotional distress or self-concept. A trend in the percentage of women returning to work favored the intervention participants (e.g., 50% vs. 25% at 3 months). In contrast, substantial differences were found between the groups in the return to and frequency of intercourse across all posttreatment assessments (e.g., 16% of the intervention group vs. 57% of the control women reported less or no sexual activity at 12 months posttreatment).

The second quasiexperimental investigation was reported by Houts et al. (17) and examined the efficacy of a peer counseling model. The structured intervention included encouragement to maintain interpersonal relationships, make positive plans for the future, query the medical staff regarding treatments, side effects, and sexual outcomes, and maintain normal routines. These interventions were delivered in three telephone contacts (before treatment and at 5 and 10 weeks after treatment), with provision of a booklet and audiotape description of the coping strategies at the pretreatment hospital visit. Two social workers were the peer counselors; subjects were not informed that former patients with cancer were also trained as social workers. Thirty-two women with diagnosed gynecologic cancer (stage not specified) participated (14 intervention and 18 control); the participation rate was 78%. The sociodemographic characteristics included a mean age of 50 years and at least a high school education in 65%. Fifty-one percent of the women were married. Control subjects were recruited on alternate weeks. A standardized outcome measure assessed emotional distress and an experimenter-derived measure assessed coping strategies. Data were gathered before treatment and at 6 and 12 weeks after treatment. Analysis indicated no differences between the groups at any point in time. **In summary, the quasiexperimental design suggested that interventions for gynecologic patients with cancer produced limited gains, except in the area of sexual functioning. The latter finding is consistent with longitudinal descriptive data of gynecologic patients with cancer showing low morbidity in the areas of emotional distress, marital adjustment, and social adjustment but moderately severe problems with sexual functioning** (4,18).

These and other studies involving patients with newly diagnosed cancer [see Andersen (1) for a review] focus on the trauma of learning that one has a potentially life-threatening illness. **Regarding psychological support, a crisis intervention or brief therapy model appears to be most appropriate.** This provides a rapid early assessment of the patient's emotional distress and other difficulties, a present-day focus on the problems facing her, limited therapeutic goals, and a therapist who is actively making suggestions for coping, problem management, and prompt interventions. **Therapeutic components may include *emotional support* and *comfort*,** which acknowledges the difficulty of the situation and provides a context for the patient openly to discuss her fears and anxieties about the disease. They also include information about the disease and treatment, ***behavioral coping strategies*** (e.g., role-playing difficult discussions with family or the medical staff), and ***cognitive coping strategies*** (i.e., identifying the patient's troublesome worries and thoughts and providing alternative appraisals of the situation). ***Relaxation training*** **to lower anxiety and/or bodily tension and enhance the patient's sense of control can be useful.**

The studies of women with cancer, specifically gynecologic or breast cancer, highlight the need for *focused interventions for sexual functioning* (18). Briefly, **at least three components are essential: *sexuality information*** (e.g., male and female sexual anatomy, the sexual response cycle, sexual dysfunctions, and potential sources of difficulty after cancer treatment), ***medical interventions*** (e.g., hormonal therapy, reconstructive surgery), and ***specific sex therapy*** suggestions.

Because psychological interventions may not alleviate all problems, pharmacologic agents may be potentially useful. Unfortunately, they are rarely used. A survey of psychotropic drug prescriptions for patients with cancer found that antidepressants, for example, were prescribed for only 1% of these patients. One third of the prescriptions were written for conditions other than depression (19). This finding is especially surprising in view of the demonstrated effectiveness of pharmacologic agents in controlled trials with psychiatric patients as well as patients with cancer. For example, *thioridazine* (75 mg daily) is superior to placebo in relieving the distress of patients with cancer experiencing anxiety or depression (20). In another study, 80% of depressed radiation therapy patients given *imipramine* showed improvement, compared with 42% of such patients who did not receive the drug (21). More research is needed to determine which agents alleviate distress among specific groups of patients.

Cancer Treatment

It is most important for a woman to receive information about the treatment plan for her disease. Despite efforts to allay concerns and provide accurate information, misconceptions abound, and anxiety will remain high as patients approach surgery, radiation therapy, or chemotherapy.

Patients experiencing high levels of distress have many other difficulties. These include problems understanding and remembering all that they are told. This may include *simple information* (e.g., what time they are to be admitted) or more *complex information* (e.g., what organs the surgery will remove and the nature of side effects). There may be difficulty in managing personal affairs (e.g., contacting one's insurance company or arranging for child care during recovery), and difficulty may also be experienced with expected behaviors (e.g., being a “patient” and allowing others to care for one's needs). In addition, most patients are unfamiliar with major medical treatments.

Even for those with some previous knowledge, cancer treatment can be qualitatively different. For example, a woman's mother, sister, or a close friend may have related her experiences with hysterectomy. Even if the surgery involved an abdominal rather than a vaginal approach, the preoperative and postoperative experience for the woman with cancer will be notably different from the patient's expectations (e.g., bowel preparation, length of recovery, vaginal shortening, bladder disruption). Thus, **it is normal for any patient to experience cognitive, emotional, and behavioral difficulties, and it is the rare patient who does not require supportive assistance as treatment approaches.**

Surgery

Although there have been few investigations of patients' psychological reactions to cancer surgery, there are numerous descriptive studies of the reactions of relatively healthy people undergoing surgery for benign conditions (e.g., uterine fibroids). This research has indicated that **there is a direct relationship between the magnitude of preoperative and postoperative anxiety;** that is, those patients who are the most anxious before surgery are also the most anxious afterward, albeit less so. In addition, the magnitude of postoperative distress often correlates with behavioral indicants of recovery (e.g., time out of bed, pain reports, days in hospital). Research that has examined emotional distress during recovery has differentiated the outcomes for patients undergoing surgery for benign versus malignant conditions. Gottesman and Lewis (22) noted greater and more lasting crisis feelings and a stronger sense of helplessness among patients with cancer for as long as 2 months after discharge from the hospital.

Gynecologic cancer surgery may pose further emotional burdens. **Women of childbearing age who are nulliparous or have not yet achieved their desired family size are often distraught and have feelings of loss after hysterectomy.** Acceptance of this change may not come for months, and in the interim it may be difficult for the woman to socialize with sisters or female friends who are pregnant or who have young children. Because the age of childbearing among women in the United States has risen, the likelihood of this situation occurring for women with gynecologic cancer will increase. **Radical surgical procedures, such as radical vulvectomy or pelvic exenteration, which produce genital and/or pelvic disfigurement and involve long hospitalization and lengthy recovery, produce depression, feelings of isolation, and significant body concerns** (23,24).

Intervention

Efforts to reduce distress from surgery or to facilitate recovery are typically of a psychotherapeutic or informational nature. ***Informational interventions*** **(including detailed descriptions of the procedure, sensations, or side effects to be anticipated) and** ***behavioral coping strategies*** **(e.g., relaxation training or distraction exercises for pain management) have in general proved effective.** In this regard, prepared patients tend to have shorter hospital stays, use fewer medications, and report less severe pain than patients receiving standard hospital care and preoperative nursing information (25,26). It is hypothesized that this type of preparation reduces stress by helping to build accurate expectations and by enhancing feelings of control and predictability for the patient.

Radiation Therapy

Approximately 60% of women with a diagnosis of gynecologic cancer receive radiation therapy. **Although there are differences in the experiences of patients receiving external radiation therapy and intracavitary radiation, most patients report confusion and negative emotions regarding these treatments.** Misinformation is common, with some patients fearing permanent contamination from treatment and others assuming that radiation attacks only “bad” cells, leaving others unaffected. A patient's prior knowledge of radiation therapy may be based on the experiences of a friend or relative, and if their treatment was unsuccessful or difficult, she may enter treatment believing it will be the same for her (27).

External Radiation

The initiation of external therapy brings fears or uneasiness about the size or the safety of treatment machines and distress from being in a radiation therapy department where other patients with cancer in obvious ill health are seen. For some women, disrobing and exposing the pelvic area can be a daily embarrassment, and field-marking tattoos are visible reminders of the disease. Such concerns are common early in treatment; in one study, roughly 80% of patients receiving radiation therapy expressed an unwillingness to discuss these concerns with their physicians (28). This occurs because patients may perceive their physicians as too busy, or they may have difficulty devising “intelligent” questions for their physicians.

As the procedures of radiation therapy become more routine, many patients report less emotional distress, but the side effects of fatigue, diarrhea, and anorexia appear by the second week. These side effects complicate living, requiring, for example, activity reductions and dietary modifications. Previously symptom-free patients may begin to feel and think of themselves as “ill,” doubting their positive prognosis. Premenopausal women experience hot flushes, a salient and distressing symptom of the loss of their fertility.

At the termination of treatment, these patients might be expected to report a drop in anxiety and fear, similar to the pattern exhibited by relatively healthy people undergoing surgery. Instead, gynecologic patients (29), as well as other patients with cancer (30), report a different pattern of anxiety responses. Women with high pretreatment anxiety are less anxious on the last treatment day than on the first, although they remain the most distressed. Those with moderate levels of pretreatment distress report little diminution in distress by the last treatment, and surprisingly, those with low levels of anxiety at the onset of treatment report significantly greater anxiety on the last treatment day. As expected, physical symptoms of fatigue, abdominal pain, anorexia, diarrhea, and skin irritation are significant for all patients at the conclusion of treatment.

Recovery from the physical and psychologic distress of radiation therapy is not rapid. Nail et al. (31) have documented an incidence of nausea in 5%, anorexia in 15%, diarrhea in 15%, and fatigue in 32% of gynecologic patients treated as long as 3 months previously. In addition, new long-term complications, such as radiation proctitis or fistulas, can emerge. Decreased lubrication and vaginal tenderness also result in significant sexual disruption during recovery, with dyspareunia a major problem for many women.

Intracavitary Radiation

In contrast to external-beam radiation, few patients have heard of intracavitary radiation. Worries about lengthy isolation and permanent contamination are common, and women may cope with the impending treatment by diverting their attention to less distressing thoughts (32). During intracavitary radiation, women report significant physical discomfort, even when there has been liberal analgesic medication (33). Gas pains, burning sensations, and lower backache are typical physical complaints, and emotional distress is also pervasive. The visitation restrictions limit contact with one's family and friends, and this may be frightening to a patient if it is perceived as isolation from nurses or physicians. It is not surprising that many women feel irritable and/or upset during treatment.

A second application is received by 50% to 75% of women. Whereas physicians see their patients as better adjusted during a second treatment, patients do not “get used to” this treatment. In fact, women report feeling more anxious and debilitated after their second treatment than after their first; women with lower levels of anxiety before their first intracavitary treatment experience reported elevated levels of anxiety after their second application (34).

Intervention

The patterns of emotional distress, as well as the patients' descriptions of themselves as anxious, confused, and uncomfortable about expressing such concerns, provide targets for intervention. **Patients most vulnerable to distress and most likely to need psychological assistance during treatment may include** (30,33,34):

1. **Those who exhibit relatively little emotional distress before treatment**
2. **Those with a history of emotional problems**
3. **Those with a disease causing chronic discomfort**
4. **Those who are socially isolated**

Several strategies may be useful to address the anxiety-based concerns of the patient undergoing radiation therapy. **General counseling focused on the patient's problems may be offered.** For example, Forrester et al. (35) provided weekly sessions in which women receiving external radiation could discuss any topic, although most sessions were supportive and informational. Improved functioning was found when these patients were compared with those receiving no intervention; intervention patients reported lower levels of emotional distress and less severe side effects.

Other interventions have focused primarily on provision of information. Topics worthy of discussion include simulation, radiation equipment, side effects of radiation, length of recovery, and strategies for managing side effects (e.g., diet modification, skin care, adequate rest). Research on patient preparation suggests that such information needs to be simplified and repeated. Instead of providing all information to patients on one occasion at the start of treatment, an alternative is to repeat portions of it as it becomes more relevant. For example, Israel and Mood (36) provided information about therapeutic procedures early in the treatment, about radiation side effects and their management at the midpoint of treatment, and about emotional issues and the length of recovery toward the end of therapy.

A special category of information for the gynecologic oncology patient is that of vaginal care and sexuality after radiation treatment. Dyspareunia is the most frequent complaint, and it appears to be most severe among women receiving both external and internal radiation, although patients receiving only external therapy also report this symptom (18). The magnitude of pain during intercourse appears to decrease during the months after treatment for women who maintain sexual activity.

A regimen of vaginal care is necessary for all patients to reduce pain and maintain, as much as possible, vaginal plasticity. Women who are not sexually active should be supplied with a vaginal dilator of sufficient length and width that, when lubricant is applied, it can be inserted comfortably and held in place. **They should be instructed to use their dilator regularly** (e.g., two to three times per week for 10 to 15 minutes). If the frequency of intercourse is low (i.e., less than once a week), women should use a dilator intermittently.

If not contraindicated, topical estrogen cream may promote healing and improve the vaginal epithelium (37). Despite these interventions, pain during intercourse may occur until sufficient healing of the vaginal epithelium has occurred.

Once any type of information has been delivered, patient understanding needs to be assessed inasmuch as many patients become confused or forgetful when too much information is given. One way to ensure understanding is to ask the patient to explain in her own words what she has been told, as if she were telling her husband or a close friend. This strategy provides an opportunity for reinforcement of her understanding as well as for correction of misconceptions.

Chemotherapy

Patients' reactions to learning that they need chemotherapy can range from extreme negativity (i.e., feeling angry or depressed) **to relief that some kind of treatment is available to them** (38). This mix of emotions reflects the distress at having to undergo a difficult treatment, which many patients believe is only for “hopeless” cancers, and they fear that it will not control the disease or prevent a recurrence.

To allay patients' concerns, medical personnel usually spend a session or two providing descriptions of, and written materials about, the effects and side effects of treatment. Yet, as many as 10% of such patients may still report uncertainty and lack of knowledge when beginning treatment (38). Others may approach chemotherapy optimistically and believe that they will belong to the small subset of people who do not experience any side effects.

Patients experience a significant and constant level of distress throughout chemotherapy. As treatment occupies more and more of a patient's life, worries become intrusive, and the intense and noxious side effects generate stronger feelings of illness. Women who attempt to control the side effects and fail become more distressed than those who report that they have coped successfully (38).

Anticipatory nausea and vomiting may complicate the course of chemotherapy for approximately 25% of patients. This refers to nausea and/or vomiting before the administration of chemotherapy. It is hypothesized that this disturbing situation develops because the stimuli surrounding the administration of chemotherapy (e.g., needles and smell of alcohol) become paired with posttreatment nausea and vomiting. With repeated cycles, the stimuli become conditioned and are able to evoke nausea or vomiting before the administration of chemotherapy. Once anticipatory reactions develop, they can become more general (e.g., alcohol-containing substances such as perfume may elicit the response), and they occur progressively earlier (e.g., on entering the hospital, rather than on entering the treatment room).

Factors that place a patient at risk for development of anticipatory nausea and vomiting include (39):

1. **Age under 50 years**
2. **Lengthy infusion of chemotherapy**
3. **Severe posttreatment nausea or vomiting in the early cycles**
4. **Extreme anxiety and/or depression**
5. **Previous susceptibility to motion sickness**

Another concomitant of some chemotherapy is confusion, a distressing symptom for the patient and her family. Pharmacologic effects of chemotherapeutic agents account for some cognitive changes (40), and such changes further emphasize the illness and its consequences to the patient.

Intervention

To the extent that posttreatment nausea and vomiting can be controlled or lessened with antinauseants from the start of a regimen, the likelihood of anticipatory problems developing is reduced. **Once anticipatory nausea and vomiting develop, behavioral interventions have demonstrated some effectiveness in breaking the chain of responses. These efforts include** (39):

1. **Hypnotic or biofeedback-assisted relaxation training**
2. **Systematic desensitization**
3. **Instruction in coping strategies**

Such problems can be reduced or eliminated within limits. Continuous intervention (i.e., relaxation instruction before the administration of each chemotherapy) is often necessary (39). “Live” rather than audiotaped relaxation training instruction is more effective.

Recovery

Psychological

For decades, there has been the clinical impression that psychological and behavioral outcomes after cancer diagnosis and treatment were unsatisfactory (41,42 and 43). **Data now indicate that most patients cope successfully; many former patients report renewed vigor in their approach to life, stronger interpersonal relationships, and a "survivor" adaptation** (44,45). Longitudinal data also confirm this scenario for gynecologic patients with cancer.

Lingering emotional distress from the trauma of diagnosis, treatment, and, more generally, life threat, may occur for a small subset, 5% to 10%, of patients with cancer. When pronounced, this long-term distress has been likened to *posttraumatic stress disorder*. In fact, residual distress from the diagnosis and treatment of a life-threatening illness is included as one of the circumstances that may precipitate a *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)* (46) diagnosis of Post Traumatic Stress Disorder. However, it is unlikely that such extreme distress occurs for the "average" patient with cancer. Instead, it may be a possibility only for those who have undergone the most difficult of treatment regimens (e.g., bone marrow transplantation) or those who undergo life-altering and/or disfiguring cancer treatments and are left with significant morbidity (e.g., pelvic exenteration). As is the case with anxiety disorders, patients with a prior history of traumatic stress might also be at heightened risk.

Some cancer survivors may need to cope with the expected but nevertheless troubling sequelae that may be consequences of the disease or treatment and be permanent. For example, coping with permanent changes in organ functions (e.g., infertility) may require adjustment that demands new behaviors or emotions. Others may have to cope with losses (e.g., a sexual relationship that does not include intercourse). Late side effects of cancer treatment, such as bowel dysfunction traceable to pelvic radiation therapy, can occur and change health status as well as affect mood and coping.

Despite these possibilities, **longitudinal data indicate that if the disease is controlled, by 1 year posttreatment the severe distress of diagnosis dissipates and emotions stabilize.** The first longitudinal studies conducted in the United Kingdom for patients with breast cancer indicated that by 12 (47) and 24 months (48), approximately 20% of the patients had problems with moderate to severe depression, compared with 8% of comparison subjects with benign disease. However, more recent, controlled, longitudinal studies of breast cancer (49,50), gynecologic cancer (4), and Hodgkin's disease and non-Hodgkin's lymphoma (51,52) have indicated no differences between the levels of emotional distress of patients with cancer and comparison subjects who either have benign disease or are healthy. The consistency of findings is important because it represents replications across site and, to some degree, treatment toxicity. Thus, we preface the remaining discussion by noting that **global adjustment problems do not occur for most cancer survivors; a more likely scenario is the occurrence of specific problem areas.**

An exception to this positive trajectory may be the circumstances of bone marrow transplantation survivors, who experience, in general, a somewhat slower recovery (53). Comparison of bone marrow transplantation survivors and other patients with cancer on maintenance chemotherapy indicated that psychological functioning was satisfactory for both groups when assessed 3 to 4 years postdiagnosis (54). However, when bone marrow transplant recipients were assessed sooner (2 to 4 years posttreatment), they reported poorer physical functioning, greater impaired personal functioning (e.g., need for self-care assistance), and more sexual difficulties than patients on maintenance chemotherapy (54). Also, data suggest a risk of neuropsychological impairment from bone marrow transplantation procedures. Andrykowski (55) found impairments in memory and higher cognitive processing, which may be a sequela of bone marrow transplantation *per se*, or of cancer treatments that precede bone marrow transplantation (e.g., cranial radiation, intrathecal chemotherapy). The many difficult aspects of bone marrow transplantation (e.g., intensive chemotherapy, possible whole-body irradiation, long recovery time, isolation) may contribute to a slower and more problematic recovery [see Winer et al. (56) and Andrykowski (57) for reviews].

Sexuality

Increased national attention has been given to the sexual difficulties of patients with cancer (58) and to women with gynecologic cancer in particular (59). **Of women treated for gynecologic disease, 30% to 90% experience significant sexual disruption, and much of the variability in this estimate can be accounted for by disease site or treatment.** When queried about sexuality, strategies for alleviating pain during intercourse, or the schedule for resuming sexual activity after treatment, all patients have indicated that these are important concerns that need to be addressed (23,24,60).

Female Sexual Response Cycle and Dysfunction

A conceptual model for understanding sexual response includes the phases of sexual desire, excitement, orgasm, and resolution.

Sexual Desire

Sexual desire is the least understood of all the phases. It has been conceptualized as a drive or motivation for sexual activity, and androgen is hypothesized as the hormonal basis for sexual desire in women. Data in support of the latter point come from a prospective, cross-over experiment in women with surgically induced menopause (61). Exogenous androgen enhanced the intensity of sexual desire and arousal, but estrogen had no effect.

The term *inhibited sexual desire* characterizes those people who report that they are usually uninterested in sexual activity. Such an attitude can be manifest by avoidance of sexual contacts, refusal of sexual activity, or infrequent initiation of sexual activity. Inhibited people report an absence or low frequency of sexual fantasy or other pleasant, arousing sexual thoughts. People with sexual desire dysfunction may experience sexual excitement and/or orgasm when engaging in sexual activity; however, disruption in the focus, intensity, or duration of sexual activity is typical, and excitement and/or orgasmic phase dysfunctions commonly occur.

Sexual Excitement

The phase of sexual excitement begins with psychological or physical stimulation. Physiologic responses that occur during the excitement phase include vaginal engorgement and lubrication. Maximal vasocongestion produces a congested orgasmic platform in the lower one third of the vaginal barrel.

Dysfunctional responses during the phase of sexual excitement would include insufficient response so that penetration during heterosexual intercourse would be difficult or uncomfortable. Psychologically, a woman may report that she does not feel aroused and/or that her body is not responding. As with desire phase difficulties, subsequent orgasmic disruption could easily result from lowered levels of excitement.

If such disruption occurs after treatment of gynecologic cancer, it is likely to be due to nerve damage or the structural changes imposed. Women report that their bodies do not feel aroused; concurrently, they report few arousing feelings or thoughts (18). Also, normal excitement responses can be disrupted with treatment side effects. For example, dyspareunia is a common problem after radiation therapy, particularly intracavitary treatment. It is likely that this pain results from the direct trauma to the vaginal epithelium, decreased vascular engorgement, and reduced vaginal lubrication.

Orgasm

Although the specific neurophysiologic mechanism of orgasm is not known, it has been proposed that orgasm is triggered when a plateau of excitement has been reached (62).

Subjectively, a woman's awareness of orgasm typically focuses on pelvic sensations, centered in the clitoris, vagina, and uterus. Orgasm is marked by rhythmic contractions of the uterus, the orgasmic platform, and the rectal sphincter. A woman's awareness of orgasm is reported to be similar, regardless of the manner in which it is achieved (63).

Among patients with cancer, the typical difficulty is a dramatic decline in frequency of orgasm or a failure of orgasm to occur. This problem is typically accompanied by the excitement difficulties described previously, so that the woman feels she does not become sufficiently aroused to approach the plateau necessary for orgasm.

Resolution

If effective stimulation ends and/or orgasm occurs, the anatomic and physiologic changes that occurred during excitement reverse. The orgasmic platform disappears, the uterus moves back into the true pelvis, and the vagina shortens and narrows. Such bodily responses after orgasm usually are accompanied by subjective feelings of tension release, relaxation, and contentment. If orgasm does not occur, the same physiologic processes are completed at a much slower rate.

Women with excitement or orgasmic dysfunctions typically report discontentment with the resolution period as well, with symptoms of continued pelvic vasocongestion, residual sexual tension, lack of satisfaction, and/or negative affect. Complaints with resolution after unimpaired excitement and orgasm are infrequent; when they occur, they may be prompted by inhibitory affects, such as guilt or marital discord, that are associated with sexual activity generally.

When all previous sexual responses are satisfactory for patients with cancer, resolution responses are similar to those of healthy women. When difficulties arise, problematic resolution responses among patients with cancer can be quite varied. Those with lowered desire and excitement and/or orgasmic disruption may have sexual tension, disappointment, and concern that their sexual responsiveness has been changed permanently. Those who experience pain during intercourse often have residual discomfort. Such outcomes, not unexpectedly, often lower a woman's interest in sexual activity.

Sexual Outcomes

Extensive data on sexual outcomes for patients with cervical cancer are available [see Andersen and van der Does (64) for a review]. Sexual outcomes have been reported for treatments ranging from cervical conization for *in situ* disease to pelvic exenteration for recurrence. In contrast, patients with endometrial and vulvar cancer have been less well studied. There has been no study of the sexual outcomes for patients with ovarian cancer.

Cervix

Preinvasive Lesions After conization of the cervix, there appears to be no significant decline in the frequency of sexual intercourse or in sexual satisfaction and no concomitant increase in sexual dysfunction (65).

Invasive Lesions In a prospective pretreatment study of patients with cervical and endometrial cancer, Andersen et al. (18) reported a surprisingly high frequency of major sexual disruption in the months immediately before diagnosis. This disruption seemed to be related to the appearance of disease symptoms (i.e., fatigue, postcoital bleeding, vaginal discharge, or pain). The difficulties were pervasive and included loss of desire, arousal problems, and orgasmic difficulties. For example, orgasm during intercourse occurred about half as often as usual.

Retrospective studies of posttreatment outcomes report diminished sexuality in up to 78% of patients after radical hysterectomy, 44% to 79% of patients after radiation therapy, and 33% to 46% of patients after combined treatment (18,64). Many oncologists believe that radiation therapy is significantly more disruptive to sexual functioning than surgery. However, prospective research has documented that surgery and radiation therapy produce comparable rates of disruption, with 30% to 40% of all patients experiencing significant sexual problems (66).

The most comprehensive descriptive study of sexual outcomes in women with gynecologic cancer comes from Andersen et al. (4,18). Women with clinical stage I or II gynecologic cancers (n = 47) were compared with two matched comparison groups: women treated for benign gynecologic disease (n = 18) and gynecologically healthy women (n = 57). All women were assessed after diagnosis but before treatment and then reassessed 4, 8, and 12 months after treatment. The frequency of intercourse declined for women treated for disease, whether malignant or benign. Considering the sexual response cycle, diminution of sexual excitement was pronounced for women with disease; however, this difficulty was more severe and distressing for the women with cancer, possibly because of significant coital and postcoital pain, premature menopause, and/or treatment side effects. Changes in desire, orgasm, and the resolution phase of the sexual response cycle also occurred. In approximately 30% of the women treated for cancer, a sexual dysfunction was diagnosed. Table 24.1 provides a summary of the rates of sexual dysfunction 12 months after treatment. The nature, early timing, and maintenance of sexual functioning morbidity suggest the instrumental role that cancer and cancer treatments play in these deficits (particularly arousal problems).

	Sexual Dysfunction (% Affected)			
Group	Desire	Excitement	Orgasm	Dyspareunia
Cancer	32%	29%	29%	29%
Benign	13%	30%	14%	14%
Healthy	9%	9%	6%	6%

[a]Twelve months posttreatment.
From Andersen BL, Anderson B, deProsse C. Controlled prospective longitudinal study of women with cancer: I. sexual functioning outcomes. J Consult Clin Psychol 1989;57:683-691.

Table 24.1 Sexual Dysfunction Diagnoses According to Gynecologic Condition[a]

Pelvic Exenteration Pelvic exenteration is clearly a radical and disfiguring operation. Not surprisingly, clinical studies have reported the cessation of sexual activity for 70% to 80% of patients after surgery (24,67,68 and 69). Although vaginal reconstruction offers the possibility that future sexual activity can include intercourse, it is not a panacea. Some women have specific difficulties related to the reconstruction (e.g., the cavity is too large or too small). Others have problems due to hampered healing (e.g., there may be a persistent vaginal discharge). In addition, some women avoid sexual intercourse because of the fear of vaginal bleeding or dyspareunia.

Endometrial Cancer

Limited information is available on sexual functioning after treatment for early-stage endometrial cancer. In the only retrospective study addressing this issue, 25% of the patients treated with surgery and 44% who had both surgery and radiation therapy experienced a decrease in the frequency of sexual activity (70). Most women who reported such a change also reported dyspareunia and diminished lubrication. Several women reported diminished arousal, but this factor was not influential in affecting the frequency of intercourse. These findings were replicated with data from the sexual partners. **Approximately one third of the sample reported the end of all sexual activity after treatment.**

Vulvar Cancer

Despite the mutilating nature of surgical procedures for vulvar cancer, there has been minimal study of the sexual outcomes for these patients. Carcinoma *in situ* of the vulva is increasing in frequency and occurring at an earlier age (71). The original treatment advocated for vulvar carcinoma *in situ* was wide local excision, but until recently many gynecologists removed the entire vulva, arguing that the disease was frequently multicentric. The main nonsurgical approaches for *in situ* disease have included the topical use of chemotherapy or CO_2 laser vaporization. The cosmetic and sexual results are thought to be optimal with these procedures, although confirming data have not yet been obtained. Patient tolerance of *5-fluorouracil* is low because of intense burning and pruritus (72).

Andersen et al. (60) retrospectively studied sexual outcomes after surgical treatment, vulvectomy versus wide local excision, for patients with *in situ* vulvar disease. A pattern of sexual disruption was found. The patients with *in situ* disease did not report diminished sexual desire despite excitement and orgasmic difficulties. There was a three- to fourfold increase in sexual dysfunction from pretreatment to posttreatment, and more than 30% of the sample were not sexually active at follow-up. Also, **the type of surgery was significantly correlated with the magnitude of sexual difficulties, with greater sexual problems among those who underwent total vulvectomy rather than wide local excision.**

Radical vulvectomy used to be the routine treatment for invasive vulvar cancer, but individualized treatment and less radical surgery is becoming the standard (73,74). **Radical vulvectomy causes substantial emotional and sexual disruption** (23). Such patients have a limited capacity for sexual arousal but little diminution in sexual desire. **As many as 50% stop all sexual activity except "friendly" kissing with their partner.** This may result from negative feelings by the woman or her partner about the changed bodily appearance or from the severe dyspareunia that can occur with a surgically narrowed introitus (75,76).

Intervention

If the sexual problems for women that occur as a result of gynecologic cancer treatment are to be minimized, a significant investment of time, energy, and resources is necessary. Such an effort must include additional time spent in consultation with patients, development of psychological interventions or written educational materials, and delivery of services by professionals or well trained and closely supervised paraprofessionals experienced in the assessment and treatment of difficult, medically related sexual problems. Because institutions differ in the services they are able to provide, a system for interventional development is described.

Preparation

Physicians and nurses need to be informed about the potential sexual outcomes for patients with gynecologic cancer that have been detailed here. It is best if this information is part of a broad understanding of normal female sexual function and response. **Patients make few inquiries, despite their concerns, so care providers need to initiate discussion of sexuality topics. When questions do arise, an informed and understanding response encourages future disclosure of questions and concerns.**

Departments caring for patients with gynecologic cancer need to determine how they will provide psychosexual help. For the individual patient, preventive rather than rehabilitative efforts are desirable. This should include the routine provision of sexual information to patients, particularly those at high risk for sexual problems (77). Longitudinal data indicate that if sexual difficulties develop, most are evidenced in the early months of recovery (18); therefore, information should be provided before and immediately after treatment, with a gradual decrease in the therapeutic efforts across time. **Women at greatest risk for problems include those with vulvar or vaginal cancer and those who have had a pelvic exenteration.**

In contrast to preventive services, rehabilitative services may be considered for women at less risk (e.g., a 55-year-old patient having a radical hysterectomy). With such a system, women would usually be seen only after sexual problems had developed. Although they might be more difficult to treat then, the positive benefit of having a readily available treatment program would be important to the patients. Patients returning for follow-up need to be informed of the availability of such a resource.

Assessment

A brief sexual history should be obtained from all patients before treatment. Obtaining a sexual assessment can achieve three goals:

1. **It identifies sexuality as an area of importance to the patient with gynecologic cancer.**
2. **It provides the healthy baseline data necessary to evaluate any future changes in sexual functioning.** Retrospective reports are subject to the patient's recollections of past sexual activity and responses.
3. **It provides an informed context for future discussions about sexuality with the medical team.**

Even for the older woman or the woman who is not currently sexually active, such information is desirable. **The most important determiner of the frequency of sexual activity for a woman is the presence of a healthy and interested sexual partner, not age *per se*** (78). Women who are not currently sexually active may wish to be so in the future and need to know how their functioning may be changed. A pretreatment sexual history is best obtained by questioning the patient directly. Questionnaires can be used to assess such topics as sexual behavior (79,80) or sexual arousal (81). The following areas can be briefly surveyed during a discussion with a patient:

1. Marital status and availability of current sexual partner(s)
2. Frequency of sexual activities (e.g., intercourse)
3. Presence of female sexual dysfunction (e.g., lack of desire, orgasmic difficulties)
4. Presence of sexual dysfunction in the partner (e.g., premature ejaculation, erectile difficulties)

Treatment

There have been few clinical (82,83) and empiric (16,84) reports of sexual intervention for female patients with cancer. Two investigations provided brief counseling to patients with gynecologic cancer on a variety of topics, such as causes of cancer, relaxation training, diet, exercise, and sexuality (16,85). Sexual function was significantly less disrupted among counseled patients than among uncounseled control patients.

Provision of Information

Information *per se* is an important component of sexual therapy interventions, even for healthy women (86). Patients should be well informed of the potential direct effects that the treatments may have on sexuality. Such effects include changed general health (e.g., chronic fatigue), structural changes to the genitals, hormonal changes, and direct interference with the physiologic components of the sexual response cycle. The range of sexual behaviors possible after treatment should be outlined.

Although sexual problems for most patients with gynecologic cancer are more difficult to treat than those of healthy people, such information may prevent problems resulting from ignorance or misconception and may decrease the severity of problems that arise from other factors.

Medical Therapy

Specific medical interventions may enhance sexual functioning for selected patients [see Berek and Andersen (87) for a complete discussion]. For example, hormonal medication may be used for menopausal symptoms; after vulvectomy the introitus may be narrowed, and the defect may be surgically correctable; the regular use of a sterile lubricant may be necessary for patients undergoing radiation therapy. Despite these efforts, certain sexual activities may remain impossible. For example, surgical modification of the introitus for a patient with vulvar cancer may not be successful, so the woman and her partner need to reorient themselves to a sexual lifestyle that does not include vaginal intercourse.

Behavioral Therapy

Although the sexual problems of the gynecologic patient with cancer are more difficult to treat than those of healthy women, behavioral techniques offer a useful place to begin. They should be conducted by a professional who is trained broadly in sexual therapy and familiar with the specific difficulties of the patient with gynecologic cancer.

Desire Problems In the treatment of desire problems, a careful determination of cause is important. Many women with cancer may experience direct disruption of excitement or orgasm from their treatments, which in turn may lead to loss of sexual desire. Women may report that the body does not respond or they do not feel the bodily sensations of arousal. Because interventions to enhance arousal or orgasm may, unfortunately, be met with limited success, such desire problems may remain and require direct intervention. **Desire problems commonly occur in the earliest months of recovery.** Therefore, a lack of desire may not be a problem but, rather, evidence of a normal, prolonged recuperative process. **Several interventions for desire problems can be considered, including:**

1. **Determining what conditions for sexual activity are more or less appealing** and encouraging sexual activity under the most desirable circumstances
2. **Increasing the frequency and variety of intimate activities** (not only sexual behaviors) that the woman might find pleasurable
3. **Increasing the frequency and variety of the woman's sexual fantasies** during sexual activity and on other occasions

Enhancing Arousal

Many desire-phase interventions have been used to enhance arousal, including the use of individual and couple body-touching exercises (i.e., sensate focus). Graduated steps for sexual activity are suggested to the woman or to the couple, with each stage using more intimate touching and higher levels of arousal. For example, the couple's sensate focus could involve steps that include caressing of hands, arms, and face; caressing the whole body without genitals, breasts, or buttocks; caressing whole body without genital stimulation; caressing the whole body; and, finally, caressing the whole body with focused stimulation. Individual masturbation activities can be designed according to the same principles. Although activities such as these are useful to all couples, they are particularly important for women who are unable to resume intercourse. **Such graduated activities have several potential benefits:**

1. **They can reintroduce relaxing and enjoyable sexual activity to a woman or a couple.** This is important because many patients come to sexual therapy after many frustrating, discouraging, or unsatisfactory sexual encounters.
2. **The activities are not strenuous,** which is helpful to the woman who is not fully recovered or who tires easily.
3. **The activities do not focus on a particular body part or area,** and one objective is to find new, previously unexplored areas or methods of stimulation.
4. **Touching of an area affected by treatment can be eliminated or introduced gradually.**

Such a strategy can be less anxiety provoking for a woman and her partner. Also, both partners can learn what sensitivity, if any, remains in affected areas. Some areas have sensations similar to those present before cancer treatment, whereas others may feel unpleasant to the touch. Some couples may prefer not to explore certain areas. When this is done in the context of sensate focus exercises, other areas remain for touching, and a loving, sexual relationship can prevail, rather than a rejecting or anxiety-provoking one.

Reducing Negative Sexual Reactions Women may react negatively to their changed bodies after radical surgery—such as vulvectomy or pelvic exenteration—although the same reactions can occur for any person with cancer (88). **Extreme responses may include disgust or anxiety when looking at the site, and fear of being seen by others.** Many healthy women with sexual difficulties or anxieties have similar feelings. For such women, anxiety-reducing techniques, particularly systematic desensitization (89,90) or individual sensate focus exercises (91,92), have proved effective. Although such activities may not change a woman's negative body feelings to positive, the feelings may become neutral, or at least nondisruptive, to her sexual activities and overall mood.

Resuming Sexual Intercourse The graduated sexual activities described here provide a relaxing and sensual context in which intercourse can be resumed. Although there is no “correct” intercourse position, there may be positions that are more or less comfortable for the woman recovering from cancer treatment. If the patient tires easily or needs body support, the male superior position is the least strenuous for the woman. In contrast, if a woman is having pain with intercourse (e.g., after intracavitary radiation), it is important that she have control over the depth of penetration and the rate of thrusting. In this case, the female superior position is often optimal. If this position does not provide relief from pain and a longer period of healing is necessary, it is important that couples be told to wait before resuming intercourse and to engage in other intimate activities if they wish.

During this period, the woman should be using a vaginal dilator regularly. **In addition to keeping the vagina “open,” the dilator exercises provide a source of feedback to the woman regarding her degree of persistent vaginal discomfort.** This information helps her to decide when it might be most comfortable to resume intercourse.

Orgasmic Dysfunction **Orgasmic dysfunction among women after gynecologic treatment is common.** The difficulty is typically acute, with disruption occurring immediately after treatment. It is also pervasive, with the woman who was regularly orgasmic with coital activity before treatment becoming nonorgasmic. With this pattern, it is likely that the difficulty is a result of altered structure or innervation. For some women, orgasm is more difficult to achieve, although it does occur intermittently. Before beginning a treatment program for orgasmic difficulties, it is important that other reasons for orgasmic difficulties be assessed, including insufficient arousal or dyspareunia.

The most successful treatment programs for healthy, nonorgasmic women include a series of individual sexuality and masturbation exercises. The early steps of such programs involve body touching, identification of genital anatomy, actual body and genital self-examination to identify pleasurable sensations, and focused genital stimulation. Even though pelvic or genital anatomy after cancer treatment is changed, it is possible that orgasm can still be experienced through other means, because women can experience orgasm without genital stimulation or without specific organs such as the clitoris, once believed critical to the response.

If the woman is motivated to undertake treatment, the exercises are completed with conscientious effort, and orgasm does not occur, the change in orgasmic ability may be long-standing. Even in this case, the exercises may help the woman to take a more active role in her sexuality, give her an improved body concept, and allow her to discover new modes of experiencing sexual pleasure (92,93).

Resolution Disruption Sexual dysfunction or difficulty during resolution is seldom noted in healthy women. However, in view of the kinds of sexual difficulties that occur for women with gynecologic cancer, disruption during this phase is common. **Sources of difficulty may include residual pain if there has been dyspareunia or continued arousal from lack of orgasm.** The most straightforward remedy to such problems is enhanced functioning during earlier phases of the sexual response cycle so that the resolution period is satisfactory. However, for those women with permanent sexual changes, efforts should be made to counteract feelings of discouragement, “letdown,” or continued tension that might predominate a woman's view of her sexual functioning during the resolution phase. The woman should be reoriented to focus on the positive aspects of her sexual life, such as the continued ability to engage in sexual activity, the experience of physical closeness and intimacy with her partner, and the sharing of alternative sexual activities with her partner.

New Strategies

Although sexual difficulties for the patient with gynecologic cancer may have a different cause, be of greater magnitude, and be more resistant to successful treatment, they do not differ in principle from the sexual problems of many healthy women. The first step in treating these sexual difficulties should be a consideration of medically based interventions. For many women, however, consideration of behaviorally oriented techniques is necessary. In addition to those discussed here, new strategies undoubtedly will be necessary. For example, biofeedback has had some use in the treatment of sexual dysfunctions and has been important in the area of physical rehabilitation. It has been used with healthy women to enhance sexual arousal (94) and as an aid to masturbation training for patients with secondary orgasmic dysfunction (95). It may have some role, for example, in providing feedback during masturbation treatment of women who have had radical genital surgery. Structural or neural changes may be such that women are not able to perceive the low level of genital sensation generated, and biofeedback may provide the necessary amplification. Techniques will also have to be developed to overcome common and troublesome difficulties such as dyspareunia (96). At present, however, there are sufficient behaviorally oriented techniques available that preventive and rehabilitative efforts can begin.

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